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

Title	:	Reporting and Analysis Plan: A phase I open-label, dose escalation study to investigate the safety, pharmacokinetics, pharmacodynamics and clinical activity of GSK2879552 given orally in subjects with relapsed/refractory small cell lung carcinoma.
Compound Number	:	GSK2879552
Effective Date	:	23-JAN-2018

Description:

The purpose of this RAP is to describe the planned analyses and output to be included in the Clinical Study Report for Protocol 2013N173386_05

This RAP is intended to describe the safety, tolerability, pharmacokinetic and pharmacodynamic analyses required for the study.

This RAP will be provided to the study team members to convey the content of the Statistical Analysis Complete (SAC) deliverable.

RAP Author(s):

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1. INTRODUCTION

The purpose of this reporting and analysis plan (RAP) is to describe the analyses to be included in the Clinical Study Report for Protocol:

GlaxoSmithKline Document Number	Date	Version
2013N173386_01	09-OCT-2013	Original
2013N173386_02	20-NOV-2013	Amendment No. 01
The starting dose, DLT criteria and safety management criteria are revised according to the regulatory input. One of the eligibility criteria is also modified to allow enrolment of patients without tumor tissues at baseline. Other changes are to clarify one of the exploratory objectives and endpoints, correct the investigational product storage conditions, clarify the definition of subject completion and allow flexibility in the timing of assessments.		
2013N173386_03	06-MAR-2015	Amendment No. 02
The protocol is amended to add two new dose strengths that will reduce the pill burden for subjects.		
2013N173386_04	27-MAY-2015	Amendment No. 03
Additional eligibility criteria and safety monitoring measures are put in place to address recent safety findings. Primary end point and futility criteria for Part 2 are modified based on the compound's mechanism of action. Other changes include additional urine and plasma sample collection for metabolite profiling (at the highest dose cohort in Part 1 PK/PD expansion), update in concomitant medications, clarification on the timing for pre- and post-dose optional biopsies, and addressing the inconsistencies in the definition of febrile neutropenia.		
2013N173386_05	22-NOV-2016	Amendment No. 4
Appendix 5 country specific IP label requirements for Korea have been modified. Fetal hemoglobin testing requirement has also been removed for Korea.		

2. SUMMARY OF KEY PROTOCOL INFORMATION

2.1. Changes to the Protocol Defined Statistical Analysis Plan

Due to the business decision of terminating study MID200858, this RAP is developed for an abbreviated CPSR. Since Part 2 cohort expansion was not initiated prior to study closure, no statistical analysis will be performed for Part 2.

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

Table 1 Changes to Protocol Defined Analysis Plan

Protocol	Reporting & Analysis Plan	
Statistical Analysis Plan	**Statistical Analysis Plan**	**Rationale for Changes**
• Interim Analysis and CSR for Part 2	• No Statistical Analysis for Part 2	• Part 2 was not implemented
• Full CSR	• Abbreviated CSR	• Study terminated

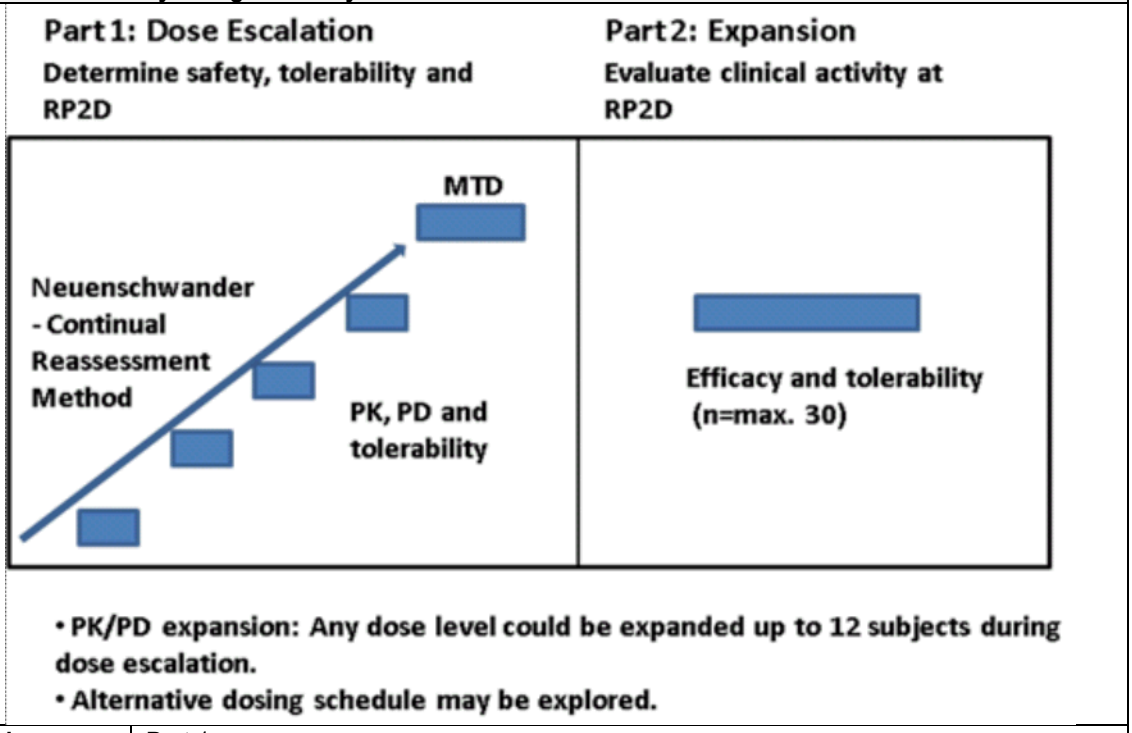
2.2. Study Objective(s) and Endpoint(s)

Part 1 Objectives	Part 1 Endpoints
Primary Objectives	**Primary Endpoints**
• To determine the safety, tolerability and Recommended Phase 2 Dose(s) (RP2D) and regimen of GSK2879552 given orally in adult subjects with SCLC.	• AEs, SAEs, dose limiting toxicities, dose reductions or delays, withdrawals due to toxicities and changes in safety parameters (e.g., laboratory values, vital signs, ECGs, physical examinations).
• **Secondary Objectives**	• **Secondary Endpoints**
• To characterize the pharmacokinetics of GSK2879552 after single- and repeat-dose oral administration.	• GSK2879552 PK parameters following single-(Day 1) and repeat-dose (Day 15) administration of GSK2879552, including AUC, Cmax, tmax, t½ (terminal phase and/or effective half-life), accumulation ratio, and time invariance.
• To evaluate clinical response after treatment with GSK2879552.	• Disease Control Rate (DCR) (CR + PR + SD) at week 16 based on Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.
• To evaluate the relationship between GSK2879552 exposure and safety/ efficacy/PD parameters	• Relationship between GSK2879552 exposure markers (e.g. dose, Cmax, Cmin or AUC (0-tau)), and ProGRP, platelet levels in blood, and safety/efficacy parameters.
Exploratory Objectives	**Exploratory Endpoints**
• To assess feasibility of a select gene panel for use as a PD assay for GSK2879552	• Change from baseline expression in select genes in whole blood and tumor
• To investigate the impact of GSK2879552 on the RNA expression profile in tumor and blood to identify mechanisms of rational combination and potential resistance.	• Transcriptomic (RNA) profile of tumor and whole blood pre- and post-treatment with GSK2879552
• To investigate relationship between tumor baseline genomic profile and response or resistance to GSK2879552	• Tumor DNA, RNA and protein markers at baseline.
• To discover circulating response and resistance biomarkers	• Circulating biomarkers (e.g. cfDNA, protein and RNA)
• To investigate the impact of GSK2879552 on fetal haemoglobin	• Pre- and post-treatment fetal haemoglobin levels
• To characterize the metabolite profile of GSK2879552 after oral single and/or repeat-dosing in some subjects	• GSK2879552 metabolites in plasma and/or urine
• To determine the amount of GSK2879552 excreted in urine after	• Concentration of GSK2879552 in urine measured with an investigational bioanalytical method and extrapolated to

Part 1 Objectives	Part 1 Endpoints
oral single and/or repeat-dosing	total amount excreted in urine over time

Part 2 Objectives	Part 2 Endpoints
Primary Objectives	**Primary Endpoints**
• To evaluate clinical activity of GSK2879552 given orally in adult subjects with SCLC.	• Disease Control Rate (DCR) (CR + PR + SD) at week 16 based on Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.
• Secondary Objectives	• Secondary Endpoints
• To evaluate the safety and tolerability of RP2D of GSK2879552	• AEs, SAEs, dose limiting toxicities, dose reductions or delays, withdrawals due to toxicities and changes in safety assessments (e.g., laboratory parameters, vital signs, physical examinations).
• To characterize the population PK of GSK28795522.	• Population PK parameters for GSK2879552 such as clearance (CL/F) and volume of distribution (V/F), and relevant covariates which may influence exposure (e.g., age, weight, or disease associated covariates).
• To evaluate the relationship between GSK2879552 exposure and safety/efficacy/PD parameters.	• Relationship between GSK2879552 exposure markers (e.g. dose, Cmin, Cmax or AUC (0-tau)), and ProGRP, platelet levels in blood, and safety/efficacy parameters.
• To evaluate duration of response and progression free survival (PFS)	• Duration of response and PFS
• To evaluate objective response rate (ORR)	• % of subjects achieving response and partial response
Exploratory Objectives	**Exploratory Endpoints**
• To assess feasibility of a select gene panel for use as a PD assay for GSK2879552	• Change from baseline expression in select genes in whole blood
• To investigate the impact of GSK2879552 on the RNA expression profile in blood to identify mechanisms of rational combination and potential resistance.	• Transcriptomic (RNA) profile of whole blood pre- and post-treatment with GSK2879552.
• To investigate relationship between tumor baseline genomic profile and response or resistance to GSK2879552	• Tumor DNA, RNA and protein markers at baseline.
• To discover circulating response and resistance biomarkers	• Circulating biomarkers (e.g. cfDNA, protein and RNA).
• To investigate the impact of GSK2879552 on fetal haemoglobin	• Pre- and post-treatment fetal haemoglobin levels

2.3. Study Design

Overview of Study Design and Key Features	
 • PK/PD expansion: Any dose level could be expanded up to 12 subjects during dose escalation. • Alternative dosing schedule may be explored.	
Design Features	Part 1 Dose Escalation Phase • In Cohort 1, a single subject will receive a dose of GSK2879552 0.25 mg once daily. The subject in Cohort 1 must complete a full 28 days of dosing, and the safety and PK data will be reviewed prior to starting Cohort 2. If the first subject becomes inevaluable for reasons other than toxicity, another subject will be recruited. The dose-escalation decision and rationale will be documented in writing with copies maintained at each study site and in the master study files at GlaxoSmithKline (GSK). • Starting with Cohort 2 the dose escalation will continue using the Neuenschwander - continuous reassessment method (N-CRM) [Neuenschwander, 2008]. A sufficient number of subjects will be enrolled in each cohort to ensure that data from at least one subject that has completed the first 28 days of dosing is available prior to defining a new dose and starting the next cohort. In addition, subjects who fail to take at least 75% of their scheduled doses in the first 28 days for reasons other than toxicity (e.g., dose limiting toxicities) will be replaced. • Upon review of the safety, tolerability, clinical activity, PK, PD data, the RP2D or doses will be selected. PK/PD Expansion Cohort • Any dose level(s) in Part 1 may be expanded up to 12 subjects in order to collect adequate data on safety, PK or PD. Pre-dose and post-dose tumor biopsies may be required from a subset of subjects in PK/PD expansion cohorts. A minimum of five pairs of evaluable pre- and post-dose biopsies may be collected at selected doses based on emerging PK/PD data.

Overview of Study Design and Key Features	

	• Subjects may be enrolled at previously completed dose levels for the purpose of obtaining additional PK or PD data. A reduced PK schedule may be used in subjects enrolled to obtain additional PD samples. These subjects may have the dose escalated to a higher completed dose level (not exceeding the maximum tolerated dose [MTD]) once the necessary PK/PD procedures have been completed.
	
	<u>Part 2</u>
	
	Expansion Cohort
	
	• Once the RP2D has been determined, a minimum of 10 and a maximum of 30 subjects will be enrolled at the RP2D, assuming futility criteria, as defined below, are not met.
	
	• Definition of Clinical Benefit – Stopping Guidelines
	
	  • Clinical benefit will be defined as objective response rate (ORR) (CR + PR) based on RECIST 1.1. The null hypothesis is:
	
	  o H0: RR ≤10%
	
	  • The alternative hypothesis is:
	
	  o HA:RR ≥25%
	
	• After 10 subjects have been enrolled to examine safety and efficacy, the number of observed unconfirmed objective responses will guide further enrolment. In order to stop for futility as quickly as possible as long as there is no sign of efficacy, the responses don't need to be confirmed. A maximum of 30 subjects will be enrolled in Part 2 expansion cohort. All available data will be considered in making enrollment decisions. The futility boundaries (inclusive) for subjects having clinical benefit are 0/10, 1/17, 2/22, 3/27, and 4/30 subjects.

Dosing	• In Part 1, in Cohort 1, a single subject will receive a dose of GSK2879552 0.25 mg once daily. The subject in Cohort 1 must complete a full 28 days of dosing, and the safety and PK data will be reviewed prior to starting Cohort 2. • Starting with Cohort 2 the dose escalation will continue using the Neuenschwander - continuous reassessment method (N-CRM). • Upon review of the safety, tolerability, clinical activity, PK, PD data, the RP2D or doses will be selected. • Subjects may be enrolled at previously completed dose levels for the purpose of obtaining additional PK or PD data. • In Part 2, once the RP2D has been determined, subjects will be enrolled at the RP2D and will be evaluated for safety and efficacy while monitoring the futility stopping rules.
Time & Events	• Refer to Protocol Amendment 4 Section 7.1 Time and Event Table(s)
Treatment Assignment	• This is a non-randomized open-label study. • RAMOS was used for treatment assignment.
Interim Analysis	• For dose escalation in Part 1, there is no interim analysis. • For Part 2, interim analysis of futility for each cohort will be conducted continually once a minimum number of subjects for futility analysis complete the response evaluation. These interim analyses will not be formal analyses, but will be used to support the

Overview of Study Design and Key Features	
	decision of early termination of study MID200858.

NOTES:

- Due to the business decision of study termination, Part 2 was not implemented. As a result, the remainder of this document contains no content related to Part 2 and will only provide information related to Part 1.

2.4. Statistical Hypotheses

No formal statistical hypotheses are being tested for the dose escalation in Part 1. Analysis of the data obtained from dose escalation of Part 1 will only utilize descriptive methods.

3. PLANNED ANALYSES

As this is an open-label study, the treatment allocation (dose) is collected in the eCRF and this will be the treatment information used for interim and final analyses.

3.1. Interim Analyses

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

3.1.1. Part 1: Dose Escalation Phase

Review of preliminary safety and available pharmacokinetic data will be performed after completion of each dosing cohort in Part 1. Preliminary safety and study population data may include a demographic summary, AE summary, AE summary by maximum toxicity category, SAE listing, listing of AEs that are reported to be DLT's, and listing of AEs leading to dose modification. Spreadsheets containing relevant study data will also be supplied by the study data manager.

The GSK study team, in collaboration with study investigators, will review PK and safety data to support:

- whether the current dose had acceptable toxicity,
- the next dose level(s), and
- whether the pharmacodynamic cohort should be opened to enrollment at the current dose

3.2. Final Analyses

The final planned primary analyses will be performed after the completion of the following sequential steps:

1. All subjects have either permanently discontinued study treatment or have been enrolled in the study at least 12 months (starting from Day 1)
2. All required database cleaning activities have been completed and final database release and database freeze has been declared by Data Management.

4. ANALYSIS POPULATIONS

Population	Definition / Criteria	Analyses Evaluated
All Randomized Subjects	All participants assigned a randomization number.	Subject accountability, Subject Disposition
All Treated Subjects	All subjects who receive at least one dose of study treatment.	Dose escalation cohort reviews, Efficacy, Safety
PK	All subjects in the All Treated Subjects Population for whom a PK sample is obtained and analyzed.	Pharmacokinetic
Pharmacodynamic	All subjects in the All Treated Subjects Population and who contributed PD/Biomarker samples.	Change from baseline levels of pharmacodynamic

Population	Definition / Criteria	Analyses Evaluated
		markers and tumor DNA, RNA, and protein, cell proliferation markers.

NOTES:

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

Protocol deviations will be tracked by the study team throughout the conduct of the study in accordance with the Protocol Deviation Management Plan.

- Data will be reviewed prior to freezing the database to ensure all important deviations and deviations which may lead to exclusion from the analysis are captured and categorised on the protocol deviations dataset.
- This dataset will be the basis for the listing of protocol deviations.

5. CONSIDERATIONS FOR DATA ANALYSES AND DATA HANDLING CONVENTIONS

5.1. Study Treatment & Sub-group Display Descriptors

Treatment Group Descriptions			
RandAll NG		Data Displays for Reporting	
Code	Description	Description	Order
A	GSK2879552	0.25 mg Daily	1
		0.5 mg Daily	2
		1.0 mg Daily	3
		1.5 mg Daily	4
		2.0 mg Daily	5
		3.0 mg Daily	6
		3.0 mg 4 days on/3 days off	7
		3.0 mg 4 days on/10 days off	8
		4.0 mg 4 days on/10 days off	9

5.2. Baseline Definitions

Baseline is defined as the most recent, non-missing value prior to or on the first study treatment dose date. For laboratory data, baseline values will be defined as the most recent, non-missing value from a central laboratory prior to or on the first dose of study treatment.

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

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

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

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

5.3. Multicentre Studies

Data from all participating centres will be pooled prior to analysis. The number of subjects by County and Centre will be summarized.

5.4. 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
13.3	Appendix 3: Assessment Windows
13.4	Appendix 4: Study Phases and Treatment Emergent Adverse Events
13.5	Appendix 5: Data Display Standards & Handling Conventions
13.6	Appendix 6: Derived and Transformed Data
13.7	Appendix 7: Reporting Standards for Missing Data
13.9	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 Subjects population, unless otherwise specified.

Study population analyses will be based on GSK Core Data Standards. Details of the planned displays are presented in Appendix 10: List of Data Displays.

6.2. Disposition of Subjects

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

6.3. Protocol Deviations

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

6.4. Demographic and Baseline Characteristics

The demographic characteristics (e.g., age, race, ethnicity, sex, baseline 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. In addition, age will also be categorized and summarized by <18, 18-64, 65-74, and >74. The count and percentage will be computed for sex and ethnicity. A separate summary of age ranges will be produced for study disclosure requirements.

Race and racial combinations will be summarized.

Current and past medical conditions will be summarized.

Prior anti-cancer therapy will be coded using GSK Drug coding dictionary. A listing of prior anti-cancer therapy will show ATC Level 1, Ingredient, and verbatim text. Prior anti-cancer therapy and prior cancer related surgeries will be listed.

6.5. Concomitant Medications

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

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

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

Blood products or blood supportive care products with onset date within the on-therapy window will be included in the summary tables. The frequency and percentage of subjects using blood products and blood supportive care products after the start of study medication will be provided.

7. SAFETY ANALYSES

The safety analyses will be based on the All Treated Subjects population, unless otherwise specified. All summaries will be presented by dose level and overall.

Study population analyses will be based on GSK Core Data Standards. Details of the planned displays are presented in Appendix 10: List of Data Displays.

7.1. Extent of Exposure

Extent of exposure to GSK2879552 will be summarized and listed by dose level.

The duration of exposure to study treatment in weeks (from first day to last day of treatment) will be summarised. Descriptive statistics including mean, median, standard deviation, minimum, and maximum will be calculated for time on study treatment.

The subject's average daily dose, defined as the cumulative dose divided by the duration of exposure for each subject, will be summarized.

Dose reductions will be summarized by number of reductions and reasons for reductions. Dose escalations will be summarized by number of escalations and reasons for escalation. Dose interruptions will be summarised by number of interruptions, reasons for the interruptions, and interruption duration (days). The mean, standard deviation, median, minimum value, and maximum value will be computed for the duration of interruptions as well as the number and percentage of the interruptions ≤7, 8-14, 15-21 and >21 days.

All the dose reductions, dose escalations and dose interruptions will be listed separately.

7.2. Adverse Events Analyses

Adverse events analyses including the analysis of adverse events (AEs), serious AEs (SAEs) and other significant AEs will be based on GSK Core Data Standards. The details of the planned displays are provided in Appendix 10: List of Data Displays.

AEs will be graded according to the CTCAE, Version 4.0. Adverse events will be coded to the PT level using the MedDRA dictionary. The relationship of AE system organ, preferred term, and verbatim text will be listed. The subject numbers for individual AEs will be listed.

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

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

In addition, the frequency and percentage of AEs (all grades) will be summarized and displayed in descending order of total frequency. The common (>=5%) non-serious adverse events by system organ class and preferred term (number of participants and occurrences) will also be summarized.

The relationship between MedDRA SOC, PT, and Verbatim Text will be listed.

Summary tables will be provided for study treatment-related AEs. A study treatment-related AE is defined as an AE for which the investigator classifies the relationship to study treatment as "Yes". A worst-case scenario approach will be taken to handle missing relatedness data, i.e. the summary table will include events with the relationship to study treatment as 'Yes' or missing. Two summary tables for treatment-related AEs will be provided:

- Summary of treatment-related AE by maximum toxicity grade. For each toxicity grade, treatment-related AEs will be displayed in descending order of total incidence by PT only.

- Summary of treatment-related AE by frequency. Treatment-related AEs will be displayed in descending order of total incidence by PT only.

A listing of All AEs will be provided.

Serious adverse events by system organ class and preferred term (number of participants and occurrences) will be summarized. All serious adverse events (SAEs) will be tabulated based on the number and percentage of subjects who experienced the event. The summary tables will be displayed in descending order of total incidence.

Separate listings will be generated for all fatal SAEs and non-fatal SAEs. A listing will also be created for dose-limiting toxicities.

7.3. Adverse Events of Special Interest

A comprehensive list of MedDRA terms based on clinical review will be used to identify each of the AESI.

The events of special interest include:

- Encepalopathy
- Thrombocytopenia
- Hemorrhages
- Diarrhea
- Nausea & Vomiting
- Constipation
- Infections
- Neutropenia

- Fatigue
- Anemia

Separate summaries of the number and percentage of subjects with each of these AESI will be provided by maximum grade. The number and percentage of subjects with each of the preferred terms defining a given AESI will also be provided. The worst case approach will be applied at subject level for the event outcome and maximum grade, i.e. a subject will only be counted once as the worst case from all the events experienced by the subject.

7.4. Clinical Laboratory Analyses

Laboratory evaluations will be based on GSK Core Data Standards. The details of the planned displays are in Appendix 10: List of Data Displays.

The assessment of laboratory toxicities will examine the following laboratory tests as specified in Table 2 below.

Table 2 Laboratory Tests

Hematology
Platelet count
White blood cell (WBC) Count (absolute)
Hemoglobin
Automated WBC Differential:
Neutrophils
Lymphocytes
Monocytes
Eosinophils
Basophils
Red blood cell (RBC) Indices (at screening and if Hemoglobin decrease ≥2 g/dL compared to baseline):
Mean corpuscular volume (MCV)
Mean corpuscular hemoglobin(MCH)
Mean corpuscular hemoglobin concentration (MCHC)
Reticulocytes
RBC

Clinical Chemistry			
Blood urea nitrogen	Potassium	Aspartate aminotransferase (AST)	Total and Direct bilirubin[1]
Creatinine	Chloride	Alanine aminotransferase (ALT)	
Glucose, random	Total CO2	Albumin	
Sodium	Calcium[2]	Alkaline phosphatase (ALP)	
Magnesium	Phosphorus	Lactate dehydrogenase (LDH)	
Fasting Lipid panel including fractionated serum cholesterol, triglycerides, total cholesterol, HDL and LDL			
Estimated glomerular filtration (Modification of Diet in Renal Disease) or 24 hr urine creatinine clearance[3]			
Beta-hCG pregnancy test for appropriate females (serum or urine)			
Coagulation			
Prothrombin time/International normalized ratio (PT/INR)			
Partial prothrombin time (PTT)			
Urinalysis			
Specific gravity			
pH – dipstick			
Glucose – dipstick			
Protein – dipstick			
Blood – dipstick			
Ketones – dipstick			
Microscopic examination required (if blood or protein by dipstick ≥1+)			
Urine total protein to creatinine ratio (UPC ratio) – (if protein by dipstick ≥2+)			

1. Bilirubin fractionation is required if total bilirubin >2x ULN
2. For screening ionized calcium is acceptable
3. The Modification of Diet in Renal Disease Equation will be used to determine an estimated glomerular filtration rate.

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

For hematology, RBC is not gradable by CTCAE v4.0.

For clinical chemistry, BUN, LDH and estimated creatinine clearance are not gradable by CTCAE v4.0. For sodium, potassium, calcium, glucose, and magnesium there will be two bi-directional parameters (hyper and hypo) created and the tests will be graded by CTCAE v4.0 in both directions.

For coagulation tests, INR and partial thromboplastin time are gradable by CTCAE v4.0 but prothrombin time is not.

For all laboratory results, displays for hematology, clinical chemistry, and liver function tests will be separately produced.

Summaries of worst case grade increase from baseline grade will be provided for all the lab tests that are gradable by CTCAE v4.0. These summaries will display the number and percentage of subjects with a maximum post-baseline grade increasing from their baseline grade. Any increase in grade from baseline will be summarized along with any increase to a maximum grade of 3 and any increase to a maximum grade of 4. Missing baseline grade will be assumed as grade 0. For laboratory tests that are graded for both

low and high values, summaries will be done separately and labeled by direction, e.g., sodium will be summarized as hyponatremia and hypernatremia.

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

A supporting listing of all chemistry and haematology laboratory data will be provided.

Detailed derivation of baseline assessment is specified in Section 5.2.

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

7.4.1. Liver Function Analyses

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

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

7.5. Other Safety Analyses

The analyses of non-laboratory safety assessment results will be based on GSK Core Data Standards, unless otherwise specified. The details of the planned displays are presented in Appendix 10: List of Data Displays.

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.

ECG

A summary of the number and percentage of subjects who had normal and abnormal (clinically significant and not clinically significant) ECG findings will be displayed by scheduled visits as well as for the worst case post-baseline. The summaries for the QTc will use the collected value based on Bazett's formula (QTcB).

The QTcB values will be rounded to the integer and the values will be categorized into the following ranges: Grade 0 (<450), Grade 1 (450-480), Grade 2 (481-500), and Grade 3 (≥501). Summaries of grades will display the number and percentage of subjects by

grade at each scheduled assessment time and in the worst case post-baseline. Similarly, grade changes relative to baseline grade will also be generated.

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

Vital Signs

Vital Signs will be listed.

Left Ventricular Ejection Fraction

A listing of the left ventricular ejection fraction results will be generated.

ECOG Performance Status

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

A supporting listing will also be provided.

Montreal Cognitive Assessment (MOCA)

A listing of the Montreal Cognitive Assessment will be generated.

8. EFFICACY ANALYSES

All efficacy analyses will be based on the All Treated Subjects population unless otherwise specified. All analyses will be presented by dose of study treatment. Details of the planned displays are provided in Appendix 10: List of Data Displays.

Efficacy assessments are based on RECIST 1.1 criteria to assess clinical activity and disease status for all subjects and also on the modified RECIST criteria. The investigator-assessed best response with confirmation will be summarized by dose of study treatment.

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

The investigator assessment of target lesion and non-target lesion will be listed, separately. A listing of investigator-assessed confirmed tumor response and baseline target lesions previously irradiated will be provided. Also, a listing of subject accountability and best response (with and without confirmation) will be generated.

9. PHARMACOKINETIC ANALYSES

9.1. Primary Pharmacokinetic Analyses

Pharmacokinetic analysis will be the responsibility of the Clinical Pharmacology Modeling and Simulation (CPMS) Department, GSK.

The results of the pharmacokinetic analysis may be provided in a report separate from the main CSR.

9.1.1. Endpoint / Variables

9.1.1.1. Drug Concentration Measures

The GSK2879552 concentration-time data will be summarized by planned time point and dose cohort. Standard summary statistics will be calculated (i.e. mean, standard deviation, median, minimum and maximum).

Refer to Appendix 5: Data Display Standards & Handling Conventions (Section 13.5.3 Reporting Standards for Pharmacokinetic)

9.1.1.2. Derived Pharmacokinetic Parameters

Pharmacokinetic analysis of GSK2879552 in Part 1 will be conducted by noncompartmental methods using WinNonlin (Version 6.3 or higher). The following pharmacokinetic parameters will be determined if data permit:

- maximum observed plasma concentration (Cmax)
- time to Cmax (tmax)
- area under the plasma concentration-time curve (AUC[0-t] and/or AUC[0-∞]) after single dose and AUC(0-t) and AUC(0-τ) after repeated administration
- apparent terminal phase elimination rate constant (λz)
- apparent terminal phase half-life (t½)

Trough concentration (Cτ) samples collected on the specified days. To estimate the extent of accumulation after repeat dosing, the observed accumulation ratio (Ro) may be determined from the ratio of AUC(0-τ) in Day 15/ AUC(0-τ) in Day 1. The ratio of AUC(0-τ) on Day 15/ Day 1 AUC(0-∞) will be calculated to assess time invariance.

GSK2879552 concentrations may be determined in urine samples to determine urinary recovery of unchanged drug and renal clearance.

9.1.2. Population of Interest

All pharmacokinetic analyses will be based on the PK population, unless otherwise specified.

9.1.3. 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 9.1.1 will be summarised using descriptive statistics and listed.

GSK2879552 concentration-time data will be listed for each subject and summarized by planned time point and dose cohort.

Pharmacokinetic parameters will be listed and summarized descriptively (mean, standard deviation, median, minimum, maximum, geometric mean, and the standard deviation, CV% and 95% confidence interval (CI) of log-transformed parameters) by dose cohort.

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

If data permits, dose proportionality will be assessed using power model for:

- AUC(0-∞) and Cmax on Day 1
- AUC(0-τ) and Cmax on Day 15

Dose proportionality of GSK2879552 AUC(0-∞) and Cmax following single dose administration and AUC(0-τ) and Cmax following repeat dose administration will be evaluated 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.

Only dose cohorts with repeat daily dosing will be analysed (i.e. 0.25 mg – 3.0 mg daily dose cohorts).

9.1.3.2. Accumulation

If data permits, accumulation using ANOVA will be performed for AUC(0-τ) on Day 15 vs AUC(0-τ) on Day 1 by dose cohort. Only dose cohorts with repeat daily dosing will be analysed (i.e. 0.25 mg – 3.0 mg daily dose cohorts).

To estimate the extent of accumulation after repeat dosing, the observed accumulation ratio (Ro) based on AUC data will be determined as follows:

$$Ro = AUC(0\text{-}\tau)_{D15} / AUC(0\text{-}\tau)_{D1}$$

Assuming both linear and time-invariant pharmacokinetics, the Ro at steady-state should be unity.

An ANOVA with a random effect term for subject and fixed effect terms for day will be performed by dose on the $\log_e$-transformed PK parameters AUC(0-τ). Day will be treated as a class variable in the model. The accumulation ratio of GSK2879552 will be estimated by calculating the ratio of the geometric least squares (GLS) means of the PK parameter between Day 15 and Day 1 for all dose levels and the corresponding 90% CI for each ratio.

The accumulation ratio will be summarized by dose.

9.1.3.3. Time Invariance

To evaluate whether the pharmacokinetics remains unaltered after repeat dosing a similar analysis to that described above will be carried out after $\log_e$-transformation of AUC(0-∞) for D1 and AUC(0-τ) for D15, the difference of which provides the steady-state ratio (Rs).

A mixed effect model will be fitted with day as a fixed effect and subject as a random effect for each treatment (dose) separately. AUC(0-τ) on D15 will be compared to AUC(0-∞) on D1 in order to assess time invariance for each dose. The Kenward & Roger (KR) degrees of freedom approach will be used. The ratio and 90% confidence interval will be calculated by back-transforming the difference between the least square means for the two days and associated 90% confidence interval, for each dose. Assuming both linear and time-invariant pharmacokinetics, the Rs at steady-state should be one.

The time invariance ratio will be summarized by dose.

Only dose cohorts with repeat daily dosing will be analysed (i.e. 0.25 mg – 3.0 mg daily dose cohorts).

10. PHARMACODYNAMIC AND BIOMARKER ANALYSES

10.1. Pharmacodynamic Analyses

As LSD1 inhibition results in a blockage of platelet maturation, platelet count changes can be viewed as a PD effect. From the time course of platelet, the platelet nadir and time to nadir will be computed for each subject. This analysis will only take into account the platelet data observed at the initial dose level and during the first 60 days on treatment. The platelet nadir will also be expressed as percent change from baseline platelet count.

Pharmacodynamic parameters will be listed and summarized descriptively (mean, standard deviation, median, minimum, maximum, geometric mean, and the standard deviation, CV% and 95% confidence interval (CI) of log-transformed parameters) by dose cohort.

If a subject has received the planned doses for at least 7 days out of first 10 days on study, this subject will be included in the descriptive statistics summary. Otherwise the subject will not be included.

10.2. Biomarker Analyses

If this data is analysed, it will be summarized in a separate report.

11. PHARMACOKINETIC / PHARMACODYNAMIC ANALYSES

The primary goal of this analysis is to characterize the pharmacokinetic / pharmacodynamic relationship of GSK2879552 administered orally in participants with SCLC.

11.1. Statistical Analyses / Methods

Quantitative safety parameters and biomarkers of interest, as available, will be plotted graphically against summary exposure measures (e.g.; Cmax, AUC obtained on Day 1) as well as against dose. Only dose cohorts with repeat daily dosing will be included in the analysis of platelet as a PD effect (i.e. 0.25 mg – 3.0 mg daily dose cohorts). Where evidence of a signal is seen, linear and/or non-linear mixed effect models will be fitted to the data to estimate PK/PD parameters of interest; e.g. slope, baseline (E0), or exposure producing 50% of the maximum effect (EC50), and maximum effect (Emax).

12. REFERENCES

GUI_137354 (2.0): Information for Authors: Reporting and Analysis Plans

GUI_51487: Non-compartmental Analysis of Pharmacokinetic Data, CPMS Global

Kenward, M. and Roger, J. (1997). Small Sample Inference for Fixed Effects from Restricted Maximum Likelihood. Biometrics 53, 983-997.

SOP_54838 (6.0): Development, Review and Approval of Reporting and Analysis Plans

13. APPENDICES

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

13.1.1. Exclusions from Per Protocol Population

There will be no Per Protocol population used for any displays or statistical analysis.

13.2. Appendix 2: Schedule of Activities

13.2.1. Protocol Defined Schedule of Events

Refer to Protocol Amendment 4 Section 7.1.

13.3. Appendix 3: Assessment Windows

No assessment windows will be applied.

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

13.4.1. Study Time Periods

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

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

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

13.4.1.1. Study Phases for Concomitant Medication

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

NOTES:

- Refer to Appendix 7: Reporting Standards for Missing Data for handling of missing and partial dates for concomitant medication. Use the rules in this table if concomitant medication date is completely missing.

13.5. Appendix 5: Data Display Standards & Handling Conventions

13.5.1. Reporting Process

Software	
• The currently supported versions of SAS software will be used.	
Reporting Area	
HARP Server	: US1SALX00259
HARP Compound	: Compound: GSK2879552, Study:200858
Analysis Datasets	
• Analysis datasets will be created according to Legacy GSK A&R dataset standards	
Generation of RTF Files	
• RTF files will be generated for SAC.	

13.5.2. 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.
  • Visits outside the protocol defined time-windows (i.e. recorded as protocol deviations) will be included in listings but omitted from figures, summaries and statistical analyses.

Unscheduled Visits
• Unscheduled visits will not be included in summary tables. • Unscheduled visits will be included in figures. • All unscheduled visits will be included in listings.

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

13.5.3. 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 [Insert document name]. Note: Concentration values will be imputed as per GUI_51487
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 summarized graphical displays only.
Pharmacokinetic Parameter Data	
Is NQ impacted PK Parameters Rule Being Followed	Yes, refer to GUI_51487
Descriptive Summary Statistics, Graphical Displays and Listings	Refer to IDSL PK Display Standards. Refer to GUI_51487

13.6. Appendix 6: Derived and Transformed Data

13.6.1. 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 there are two values within a time window the value closest to the target day for that window will be used. If values are the same distance from the target, then the mean will be taken. • Participants having both High and Low values for Normal Ranges at any post-baseline visit for safety parameters will be counted in both the High and Low categories of "Any visit post-baseline" row of related summary tables. This will also be applicable to relevant Potential Clinical Importance summary tables.
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

13.6.2. Study Population

Extent of Exposure
• Number of days of exposure to study drug will be calculated based on the formula: Duration of Exposure in Days = Treatment Stop Date – (Treatment Start Date) + 1 • Participants who were randomized but did not report a treatment start date will be categorised as having zero days of exposure.

13.7. Appendix 7: Reporting Standards for Missing Data

13.7.1. Premature Withdrawals

Element	Reporting Detail
General	• A subject will be considered to have completed the study if they complete screening assessments, at least 28 days of study treatment(s) and the post-treatment follow-up visit. • If subjects which prematurely discontinue, additional subjects may be enrolled as replacement subjects at the discretion of the Sponsor in consultation with the investigator. • Subjects who fail to take at least 75% of their scheduled doses in the first 28 days for reasons other than toxicity (e.g., dose limiting toxicities) will be replaced • 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. • Withdrawal visits will be summarised as withdrawal visits.

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

13.7.2.1. Handling of Missing and Partial Dates

Imputed partial dates will not be used to derive study day, duration (e.g. duration of adverse events), or elapsed time variables.

With the exception of exposure end date on the Exposure analysis dataset, imputed dates will not be stored on datasets.

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

Dataset	Date	Missing Element	Rule
Adverse Events (AE)	Start Date	day, month, and year	• No Imputation for completely missing dates

Dataset	Date	Missing Element	Rule
		day, month	• If study treatment start date is missing (i.e. subject did not start study treatment), then set start date = January 1. • Else if study treatment start date is not missing: o If year of start date = year of study treatment start date then • If stop date contains a full date and stop date is earlier than study treatment start date then set start date = January 1. • Else set start date = study treatment start date. o Else set start date = January 1.
		Day	• If study treatment start date is missing (i.e. subject did not start study treatment), then set start date = 1st of month. • Else if study treatment start date is not missing: o If month and year of start date = month and year of study treatment start date then • If stop date contains a full date and stop date is earlier than study treatment start date then set start date= 1st of month. • Else set start date = study treatment start date. o Else set start date = 1st of month.
	End Date		• No imputation for partial end dates will be performed

Anti-Cancer Therapy and Radiotherapy:

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), the rules for imputation will be defined within the algorithm of the derived covariate. Additionally, post treatment anti-cancer therapy and radiotherapy start dates may be imputed to determine date of new anti-cancer therapy. In this case only, the date of new anti-cancer therapy (not all anti-cancer therapy and radiotherapy start dates) will be stored on appropriate efficacy datasets. Imputed partial dates will not be used to derive time since most recent prior therapy. In addition, the cancer therapy treatment status variable, and not any variables that use imputed partial dates, will be used to differentiate prior and follow-up anti-cancer therapy and radiotherapy.

Dataset	Date	Missing Element	Rule
Anti-Cancer Therapy	Start Date	day, month,	• No Imputation for completely missing dates

Dataset	Date	Missing Element	Rule
Radiotherapy		and year	
		day, month	• If partial date contains a year only set to January 1st.
		day	• If partial date contains a month and year set to the 1st of the month.
	End Date		• No imputation for partial end dates will be performed

Surgery:

The date of surgery or procedure is generally not imputed. If the date of surgery or procedure needs to be imputed for an analysis (e.g., to calculate duration or elapsed time as covariates for efficacy analyses), the rules for imputation will be defined within the algorithm of the derived covariate. Additionally, post treatment surgery or procedure dates maybe imputed (where applicable) to determine date of new anti-cancer therapy. In this case only, the date of new anti-cancer therapy (not specific surgery or procedure date) will be stored on appropriate efficacy datasets. The category for surgical procedure variable, and not any variables that use imputed partial dates, will be used to differentiate prior, on, and follow-up surgical procedure data. The derived time in relation to treatment variables are not needed for reporting of data because the category for surgical procedure variable can be used. Therefore, imputed dates are not needed for derivation of time in relation to treatment.

Dataset	Missing Element	Rule
Surgical Procedures	day, month, and year	• No Imputation for completely missing dates
	day, month	• If partial date contains a year only set to January 1st.
	day	• If partial date contains a month and year set to the 1st of the month

Concomitant Medication and Blood and Blood Supportive Care Products:

Start and end dates may be imputed for use in derivation of the reference variables concomitant medication start and end relative to treatment and blood and blood supportive care start and end relative to treatment, but should not be permanently stored in the analysis datasets. The reference variables will be used to differentiate before,

during and after for the concomitant medication or blood or blood supportive care start and end dates. The derived time in relation to treatment variables are not needed for reporting of these data.

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

Dataset	Date	Missing Element	Rule
		month	
		day	• If partial end date contains month and year, set end date = earliest of last day of the month or date of last contact (MSTONE.LCONTDT).

Overall Response Rate and Duration of Response:

Start dates for follow-up anti-cancer therapy, radiotherapy (where applicable), and surgical procedures (where applicable) will be temporarily imputed in order to define overall response rate or duration of response (i.e. start date for new anti-cancer therapy). Dates will only be imputed when a month and year are available but the day is missing. The imputed date(s) will not be stored on the anti-cancer therapy, radiotherapy, or surgical procedure datasets. The following rules will be used to impute the date when partial start dates are present on anti-cancer therapy radiotherapy, and/or surgical procedures datasets:

Dataset	Date	Missing Element	Rule
Anti-Cancer Therapy Where applicable: Radiotherapy Surgical Procedures	Start Date	day, month, and year	• No Imputation for completely missing dates
		day, month	• No imputation for missing day and month (note the eCRF should only allow for missing day)
		day	• If partial date falls in the same month as the last dose of study treatment, then assign to earlier of (date of last dose of study treatment+1, last day of month). • If partial date falls in the same month as the subject's last assessment and the subject's last assessment is PD, then assign to earlier of (date of PD+1, last day of month). • If both rules above apply, then assign to

Dataset	Date	Missing Element	Rule
			latest of the 2 dates • Otherwise, impute missing day to the first of the month.
	End Date		• No imputation for partial end dates will be performed

The date of new anti-cancer therapy is derived as the earliest date of new anti-cancer therapy (e.g., chemotherapy), radiotherapy (where applicable), or cancer related surgical procedure (where applicable) and will include imputed dates.

13.8. Imputation of Missing Exposure End Dates

For subjects who have missing end dates in their last exposure record potentially due to being lost to follow-up, the last contact date will be imputed as the last exposure date (i.e. date of last dose). This imputation will only be used when needed, e.g. TBD.

13.9. Appendix 8: Values of Potential Clinical Importance

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.

To identify laboratory values of potential clinical importance, National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE v4.0) will be used to assign grades to the relevant laboratory parameters.

13.10. Appendix 9: Abbreviations & Trade Marks

13.10.1. Abbreviations

Abbreviation	Description
ADaM	Analysis Data Model
AE	Adverse Event
AIC	Akaike's Information Criteria
ALT	Alanine aminotransferase
ALP	Alkaline phosphatase
ANC	Absolute Neutrophil Count
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
AUC(0-∞)	Area under the concentration-time curve from time zero (pre-dose) extrapolated to infinite time
AUC(0-t)	Area under the concentration-time curve from time zero (pre-dose) to last time of quantifiable concentration within a subject across all treatments
AUC(0-τ)	Area under the concentration-time curve over the dosing interval
A&R	Analysis and Reporting
BUN	Blood urea nitrogen
CI	Confidence Interval
Cmax	Maximum observed concentration
CPMS	Clinical Pharmacology Modelling & Simulation
CR	Complete response
CS	Clinical Statistics
CSR	Clinical Study Report
CTR	Clinical Trial Register
CV_b / CV_w	Coefficient of Variation (Between) / Coefficient of Variation (Within)
C1D1	Cycle 1 Day 1
C1D15	Cycle 1 Day 15
DBF	Database Freeze
DBR	Database Release
DLBCL	Diffuse Large B Cell Lymphoma
DLT	Dose-limiting toxicity
DOB	Date of Birth
DP	Decimal Places
ECG(s)	Electrocardiogram(s)
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Record Form
EMA	European Medicines Agency
EZH2	Enhancer of Zeste Homolog 2
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Clinical Results Disclosure Requirements
GCB	Germinal Center B-cell like
GCB-DLBCL	Germinal Center B-cell-like Diffuse Large B-cell Lymphoma
GSK	GlaxoSmithKline

Abbreviation	Description
H3K27me3	Tri-methylated Histone H3 lysine 27
IA	Interim Analysis
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
IDSL	Integrated Data Standards Library
IMMS	International Modules Management System
INR	International normalization ratio
IP	Investigational Product
ITT	Intent-To-Treat
LDH	Lactate dehydrogenase
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MM	Multiple Myeloma
MMRM	Mixed Model Repeated Measures
msec	Millisecond
NCI-CTCAE	National Cancer Institute - Common Terminology Criteria for Adverse Events
NHL	Non-Hodgkin's Lymphoma
PCI	Potential Clinical Importance
PD	Pharmacodynamic
PDMP	Protocol Deviation Management Plan
PK	Pharmacokinetic
PopPK	Population PK
PP	Per Protocol
PR	Partial response
QC	Quality Control
QTc	Corrected QT interval duration
QTcB	Bazett's QT Interval Corrected for Heart Rate
RAP	Reporting & Analysis Plan
RAMOS	Randomization & Medication Ordering System
RBC	Red blood cells
SAC	Statistical Analysis Complete
SAE	Serious adverse event(s)
SD	Stable disease
SDSP	Study Data Standardization Plan
SDTM	Study Data Tabulation Model
SOP	Standard Operation Procedure
t1/2	Terminal phase half-life
τ	Dosing interval
TA	Therapeutic Area
tFL	Transformed Follicular Lymphoma
TFL	Tables, Figures & Listings
tmax	Time of occurrence of Cmax
WBC	White blood cells

Abbreviation	Description
WT	Wild-type

13.10.2. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
NONE

Trademarks not owned by the GlaxoSmithKline Group of Companies
SAS
WinNonlin

13.11. Appendix 10: List of Data Displays

13.11.1. Data Display Numbering

The following numbering will be applied for RAP generated displays:

Section	Tables	Figures
Study Population	1.1 to 1.7	N/A
Efficacy	2.1	N/A
Safety	3.1 to 3.32	N/A
Pharmacokinetic	4.1 to 4.6	N/A
Pharmacodynamic	5.1	N/A
PK/PD	6.1 to 6.6	6.1 to 6.6
Section	**Listings**	
ICH Listings	1 to 29	
Other Listings	30 to 35	

13.11.2. Mock Example Shell Referencing

Non IDSL specifications will be referenced as indicated and if required example mock-up displays provided in a separate document.

Section	Figure	Table	Listing
Pharmacokinetic	N/A	PK_T1	PK_L1
Pharmacodynamic	N/A	PD_T1	PD_L1
PKPD	PKPD_F1	PKPD_T1	N/A

13.11.3. Deliverables

Delivery [Priority] [1]	Description
SAC [1]	Final Statistical Analysis Complete

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

13.11.4. Study Population Tables

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition					
1.1.	All Treated Subjects	ES1	Summary of Subject Disposition (Part 1)		SAC [1]
1.2.	Enrolled	NS1	Summary of Number of Participant by Country and Site ID (Part 1)		SAC [1]
Demographic and Baseline Characteristics					
1.3.	All Treated Subjects	DM1	Summary of Demographic Characteristics (Part 1)		SAC [1]
1.4.	Enrolled	DM11	Summary of Age Ranges (Part 1)		SAC [1]
1.5.	All Treated Subjects	DM5	Summary of Race and Racial Combinations (Part 1)		SAC [1]
Medical History and Concomitant Medications					
1.6.	All Treated Subjects	MH1	Summary of Current/Past Medical Conditions (Part 1)		SAC [1]
1.7.	All Treated Subjects	CM1	Summary of Concomitant Medications (Part 1)		SAC [1]

13.11.5. Efficacy Tables

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Clinical Response					
2.1.	All Treated Subjects	RE1a	Summary of Independent Radiologist-Assessed and Investigator-Assessed Best Response With Confirmation (RECIST 1.1 Criteria) (Part 1)		SAC [1]

13.11.6. Safety Tables

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Exposure					
3.1.	All Treated Subjects	OEX5	Summary of Exposure to GSK2879552 (Part 1)		SAC [1]
3.2.	All Treated Subjects	ODMOD1	Summary of Dose Reductions (Part 1)		SAC [1]
3.3.	All Treated Subjects	ODMOD8	Summary of Dose Escalations (Part 1)		SAC [1]
3.4.	All Treated Subjects	ODMOD2	Summary of Dose Interruptions (Part 1)		SAC [1]
Adverse Events (AEs)					
3.5.	All Treated Subjects	OAE7	Summary of All Adverse Events by Maximum Grade by System Organ Class and Preferred Term (Part 1)		SAC [1]

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.6.	All Treated Subjects	AE3	Summary of All Adverse Events by Frequency (Part 1)		SAC [1]
3.7.	All Treated Subjects	AE15	Summary of Common (>=5%) Non-serious Adverse Events by System Organ Class and Preferred Term (Number of Participants and Occurrences) (Part 1)		SAC [1]
3.8.	All Treated Subjects	OAE7	Summary of Encephalopathy Adverse Event of Special Interest by Maximum Grade by System Organ Class and Preferred Term (Part 1)		SAC [1]
3.9.	All Treated Subjects	OAE7	Summary of Thrombocytopenia Adverse Event of Special Interest by Maximum Grade by System Organ Class and Preferred Term (Part 1)		SAC [1]
3.10.	All Treated Subjects	OAE7	Summary of Hemorrhages Adverse Event of Special Interest by Maximum Grade by System Organ Class and Preferred Term (Part 1)		SAC [1]
3.11.	All Treated Subjects	OAE7	Summary of Diarrhea Adverse Event of Special Interest by Maximum Grade by System Organ Class and Preferred Term (Part 1)		SAC [1]
3.12.	All Treated Subjects	OAE7	Summary of Nausea & Vomiting Adverse Event of Special Interest by Maximum Grade by System Organ Class and Preferred Term (Part 1)		SAC [1]
3.13.	All Treated Subjects	OAE7	Summary of Constipation Adverse Event of Special Interest by Maximum Grade by System Organ Class and Preferred Term (Part 1)		SAC [1]
3.14.	All Treated Subjects	OAE7	Summary of Infections Adverse Event of Special Interest by Maximum Grade by System Organ Class and Preferred Term (Part 1)		SAC [1]

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.15.	All Treated Subjects	OAE7	Summary of Neutropenia Adverse Event of Special Interest by Maximum Grade by System Organ Class and Preferred Term (Part 1)		SAC [1]
3.16.	All Treated Subjects	OAE7	Summary of Fatigue Adverse Event of Special Interest by Maximum Grade by System Organ Class and Preferred Term (Part 1)		SAC [1]
3.17.	All Treated Subjects	OAE7	Summary of Anemia Adverse Event of Special Interest by Maximum Grade by System Organ Class and Preferred Term (Part 1)		SAC [1]
3.18.	All Treated Subjects	OAE7	Summary of Treatment-Related Adverse Events by Maximum Grade by System Organ Class and Preferred Term (Part 1)		SAC [1]
3.19.	All Treated Subjects	AE3	Summary of Treatment-Related Adverse Events by Frequency (Part 1)		SAC [1]
Serious and Other Significant Adverse Events					
3.20.	All Treated Subjects	AE16	Summary of Serious Adverse Events by System Organ Class and Preferred Term (Number of Participants and Occurrences) (Part 1)		SAC [1]
3.21.	All Treated Subjects	AE3	Summary of Serious Adverse Events by Frequency (Part 1)		SAC [1]
Laboratory: Chemistry					
3.22.	All Treated Subjects	OLB9C	Summary of Clinical Chemistry Toxicity Grade Change from Baseline Grade (Part 1)	For gradable Clinical chemistry tests. By dose, and overall. Include Worst-case.	SAC [1]
3.23.	All Treated Subjects	OLB11B	Summary of Clinical Chemistry Laboratory Changes from Baseline With Respect to the Normal Range (Part 1) (Part 1)	For non-gradable lab tests. By dose, and overall.	SAC [1]

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Laboratory: Hematology					
3.24.	All Treated Subjects	OLB9C	Summary of Haematology Toxicity Grade Change from Baseline Grade (Part 1)	For gradable Haematology tests. By dose, and overall. Include Worst-case.	SAC [1]
3.25.	All Treated Subjects	OLB11B	Summary of Clinical Chemistry Laboratory Changes from Baseline With Respect to the Normal Range (Part 1)	For non-gradable lab tests. By dose, and overall.	SAC [1]
Laboratory: Hepatobiliary (Liver)					
3.26.	All Treated Subjects	OLB9C	Summary of Clinical Liver Function Test Toxicity Grade Change from Baseline Grade (Part 1)	For gradable Clinical chemistry tests. By dose, and overall. Include Worst-case.	SAC [1]
3.27.	All Treated Subjects	OLB11B	Summary of Clinical Liver Function Test Laboratory Changes from Baseline With Respect to the Normal Range (Part 1)	For non-gradable lab tests. By dose, and overall.	SAC [1]
3.28.	All Treated Subjects	OLIVER10	Summary of Hepatobiliary Laboratory Abnormalities (Part 1)		SAC [1]
ECG					
3.29.	All Treated Subjects	EG1	Summary of ECG Findings (Part 1)		SAC [1]
3.30.	All Treated Subjects	EG10	Summary of Maximum QTc Values Post-Baseline Relative to Baseline by Category (Part 1)		SAC [1]
3.31.	All Treated Subjects	EG11	Summary of Maximum Increase in QTc Values Post-Baseline Relative to Baseline by Category (Part 1)		SAC [1]
ECOG					
3.32.	All Treated Subjects	PS4A	Summary of Change in ECOG 'Performance Status' from Baseline (Part 1)		SAC [1]

13.11.7. Pharmacokinetic Tables

Pharmacokinetic: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
4.1.	PK	PK01	Summary of GSK2879552 Plasma Pharmacokinetic Concentration-Time Data (Part 1)		SAC [1]
4.2.	PK	PK06	Summary of Derived GSK2879552 Plasma Pharmacokinetic Parameters (non-transformed and log-transformed) (Part 1)		SAC [1]
4.3.	PK	PK_T1	Summary of Statistical Analysis to Assess the Dose Proportionality for AUC(0-∞) and Cmax Using Power Model – Day 1 (Part 1)		SAC [1]
4.4.	PK	PK_T1	Summary of Statistical Analysis to Assess the Dose Proportionality for AUC(0-τ) and Cmax Using Power Model – Day 15 (Part 1)		SAC [1]
4.5.	PK	PK_T2	Summary of Statistical Analysis to Assess the Accumulation for AUC(0-τ) on Day 15 vs AUC(0-τ) on Day 1 by Dose (Part 1)		SAC [1]
4.6.	PK	PK_T2	Summary of Statistical Analysis to Assess the Time Invariance based on AUC(0-∞) on D1 and AUC(0-τ) on Day 15 by Dose (Part 1)		SAC [1]

13.11.8. Pharmacodynamic Tables

Pharmacodynamic: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
5.1.	All Treated Subjects	PD_01	Summary of Platelet Nadir by Dose (Part 1)		SAC [1]

13.11.9. PK/PD Tables

PD/PD: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
6.1.	PD	PKPD_T1	Summary of Emax model parameters describing the relationship between Platelet Nadir and Dose (Part 1)		SAC [1]
6.2.	PD	PKPD_T1	Summary of Emax model parameters describing the relationship between Platelet Nadir as Percent Change from Baseline and Dose (Part 1)		SAC [1]
6.3.	PD	PKPD_T1	Summary of Emax model parameters describing the relationship between Platelet Nadir and D1 Cmax (Part 1)		SAC [1]
6.4.	PD	PKPD_T1	Summary of Emax model parameters describing the relationship between Platelet Nadir as Percent Change from Baseline and D1 Cmax (Part 1)		SAC [1]
6.5.	PD	PKPD_T1	Summary of Emax model parameters describing the relationship between Platelet Nadir and D1 AUC(0-inf) (Part 1)		SAC [1]
6.6.	PD	PKPD_T1	Summary of Emax model parameters describing the relationship between Platelet Nadir as Percent Change from Baseline and D1 AUC(0-inf) (Part 1)		SAC [1]

13.11.10. PK/PD Figures

PK/PD: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
6.1.	PD	PKPD_F1	Relationship between Platelet Nadir and Dose (Individual Data and Emax model) (Part 1)	S&P to provide dataset to CPMS, who will then be able to produce these plots	SAC [1]
6.2.	PD	PKPD_F1	Relationship between Platelet Nadir as Percent Change from Baseline and Dose (Individual Data and Emax model) (Part 1)	S&P to provide dataset to CPMS, who will then be able to produce these plots	SAC [1]
6.3.	PD	PKPD_F1	Relationship between Platelet Nadir and Day 1 Cmax (Individual Data and Emax model) (Part 1)	S&P to provide dataset to CPMS, who will then be able to produce these plots	SAC [1]
6.4.	PD	PKPD_F1	Relationship between Platelet Nadir as Percent Change from Baseline and Day 1 Cmax (Individual Data and Emax model) (Part 1)	S&P to provide dataset to CPMS, who will then be able to produce these plots	SAC [1]
6.5.	PD	PKPD_F1	Relationship between Platelet Nadir and Day 1 AUC(0-inf) (Individual Data and Emax model) (Part 1)	S&P to provide dataset to CPMS, who will then be able to produce these plots	SAC [1]
6.6.	PD	PKPD_F1	Relationship between Platelet Nadir as Percent Change from Baseline and Day 1 AUC(0-inf) (Individual Data and Emax model) (Part 1)	S&P to provide dataset to CPMS, who will then be able to produce these plots	SAC [1]

13.11.11. ICH Listings

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Study Population					
1.	All Treated Subjects	SD2	Listing of Study Treatment Discontinuation (Part 1)		SAC [1]
2.	All Treated Subjects	DV2	Listing of Important Protocol Deviations (Part 1)		SAC [1]
3.	All Treated Subjects	DM2	Listing of Demographic Characteristics (Part 1)		SAC [1]
Safety					
4.	All Treated Subjects	OEX8b	Listing of Exposure to Study Treatment (Part 1)		SAC [1]
5.	All Treated Subjects	ODMOD10A	Listing of Dose Reductions (Part 1)		SAC [1]
6.	All Treated Subjects	ODMOD11A	Listing of Dose Interruptions (Part 1)		SAC [1]
7.	All Treated Subjects	ODMOD15A	Listing of Dose Escalations (Part 1)		SAC [1]
8.	All Treated Subjects	AE2	Listing of Relationship Between Adverse Event System Organ Classes, Preferred Terms, and Verbatim Text (Part 1)		SAC [1]
9.	All Treated Subjects	OAE3	Listing of Subject Numbers for Individual Adverse Events (Part 1)		SAC [1]
10.	All Treated Subjects	OAE4	Listing of All Adverse Events (Part 1)		SAC [1]

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
11.	All Treated Subjects	OAE4	Listing of Fatal Serious Adverse Events (Part 1)		SAC [1]
12.	All Treated Subjects	OAE4	Listing of Non-Fatal Serious Adverse Events (Part 1)		SAC [1]
13.	All Treated Subjects	OAE4	Listing of Dose-Limiting Toxicity (Part 1)		SAC [1]
14.	All Treated Subjects	OLB7	Listing of Clinical Chemistry Laboratory Data (Part 1)		SAC [1]
15.	All Treated Subjects	OLB7	Listing of Haematology Laboratory Data (Part 1)		SAC [1]
16.	All Treated Subjects	EG3	Listing of ECG Values (Part 1)		SAC [1]
17.	All Treated Subjects	EG5	Listing of Abnormal ECG Findings (Part 1)		SAC [1]
18.	All Treated Subjects	VS4	Listing of Vital Signs (Part 1)		SAC [1]
19.	All Treated Subjects	OLVEF2A	Listing of Left Ventricular Ejection Fraction Results (Part 1)		SAC [1]
20.	All Treated Subjects	PS5A	Listing of ECOG Performance Status (Part 1)		SAC [1]
21.	All Treated Subjects	DM2	Listing of Montreal Cognitive Assessment (MOCA) (Part 1)		SAC [1]
PK					
22.	PK	PK07	Listing of GSK2879552 Plasma PK Concentration-Time Data (Part 1)		SAC [1]

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
23.	PK	PK13	Listing of GSK2879552 Plasma PK Parameters Data (Part 1)		SAC [1]
Efficacy					
24.	All Treated Subjects	LA2	Listing of Investigator/Independent Radiologist/etc.-Assessed Target Lesion Assessments (RECIST 1.1 Criteria) (Part 1)		SAC [1]
25.	All Treated Subjects	LA3	Listing of Investigator/Independent Radiologist/etc.-Assessed Non Target Lesion Assessments (RECIST 1.1 Criteria) (Part 1)		SAC [1]
26.	All Treated Subjects	RE5	Listing of Investigator/Independent Radiologist/etc.-Assessed Tumour Responses with confirmation (RECIST1.1 Criteria) (Part 1)		SAC [1]
27.	All Treated Subjects	RE12	Listing of Subject Accountability and Best Response (With and Without Confirmation) (RECIST1.1 Criteria) (Part 1)		SAC [1]
28.	All Treated Subjects	LA2	Listing of Investigator/Independent Radiologist/etc.-Assessed Lesion Assessments (RECIST 1.1 Criteria) (Part 1)		SAC [1]
29.	All Treated Subjects	LA6	Listing of Investigator/Independent Radiologist/etc.-Assessed Baseline Target Lesions Previously Irradiated (RECIST 1.1 Criteria) (Part 1)		SAC [1]

13.11.12. Non-ICH Listings

Non-ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Study Population					
30.	All Treated Subjects	AC6	Listing of Prior Anti-Cancer Therapy (Part 1)		SAC [1]
31.	All Treated Subjects	OSP3	Listing of Prior Anti-Cancer Surgical Procedures (Part 1)		SAC [1]
Safety					
32.	All Treated Subjects	SAFE_L1	Listing of Echocardiogram Scan Results (Part 1)		SAC [1]
33.	All Treated Subjects	SAFE_L2	Listing of Liver Function Tests for Subjects Meeting Potential Hy's Law (Part 1)		SAC [1]
PD					
34.	All Treated Subjects	PD_L1	Listing of Platelet PD Parameters		SAC [1]
Efficacy					
35.	All Treated Subjects	LA5	Listing of Investigator-Assessed Lesion Assessments (Part 1)		SAC [1]