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

Title	:	Reporting and Analysis Plan for A Phase I Open-label, Dose Escalation Study to Investigate the Safety, Pharmacokinetics, Pharmacodynamics and Clinical Activity of GSK2816126 in Subjects with Relapsed/Refractory Diffuse Large B cell Lymphoma, Transformed Follicular Lymphoma, Other Non-Hodgkin's Lymphomas, Solid Tumors and Multiple Myeloma
Compound Number	:	GSK2816126
Effective Date	:	01-MAR-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 EZH117208 Amendment 04.
- This RAP is intended to describe the safety, tolerability, efficacy and pharmacokinetic 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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RAP Team Approvals:

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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**
2012N149024_00	11-JUL-2013	Original
2012N149024_01	23-OCT-2013	Amendment No. 1
Applies only to sites in the UK. Following review of the protocol by the MHRA, the following changes were made: 1. Removed wording from the protocol stating that GSK2816126 treatment will continue until commercial availability. 2. The stopping criterion based on QTc will be changed to ≥ 500 msec. 3. Added a QTc stopping criterion that patients will be withdrawn if they experience an increase in QTc > 60msec from baseline following dose reduction and re-challenge.		
2012N149024_02	30-OCT-2013	Amendment No.: 02
Applies to all study sites. Following review of the protocol by the Food and Drug Administration (FDA), the following changes were made: 1. The starting dose of GSK2816126 is reduced from 125 mg/dose to 50 mg/dose 2. Updated Dose Limiting Tox language 3. Revised 100% dose escalation wording 4. Decreased QTc baseline exclusion criterion 5. Added regular ECG monitoring timings 6. Added blood glucose testing to our list of clinical lab tests 7. Removed any wording pertaining to the use of central labs 8. Removed wording from the protocol stating that GSK2816126 treatment will continue until commercial availability 9. Clarify that PET scans are optional 10. Elaborated on CT scan timings		

11. The stopping criterion based on QTc will be changed to ≥ 500 msec 12. Added a QTc stopping criterion that subjects will be withdrawn if they experience an increase in QTc > 60 msec from baseline following dose reduction and re-challenge 13. Added explanatory language to T&E Table around coagulation, CT and standalone PET assessments 14. Changed corticosteroid exclusion criteria		
2012N149024_03	03-APR-2015	Amendment No. 03
Amendment 03 applies to all study sites and includes the addition of solid tumor malignancies and other NHLs to Part 1 of the study, transformed follicular lymphoma subjects to Part 2 and multiple myeloma subjects to both Part 1 and 2. The protocol title, study rationale, objectives, endpoints, hypotheses, inclusion/exclusion criteria, background, preclinical pharmacology and safety, risk/benefits, investigational plan, population rationale, T&E table, tumor biomarker analysis have all been updated to reflect these changes. RECIST criteria and multiple myeloma response criteria have also been added. A description of genetic research has been added to the appendix. To accommodate these changes we have also augmented the number of subjects, evaluation of futility, organ function table, data management and statistical analysis. Other additions include dose adjustment for hematologic and non-hematologic toxicity, description of the investigational product and time windows for the PK sample collection table. Additions were also made to the Pharmacodynamics and Translational Research sections to cover potential studies in a surrogate tissue. Updated the Prohibited Meds Table 13 and Table 14. Removed PD analysis from Part 2.		
2012N149024_04	17-MAR-2016	Amendment No. 4
Amendment 04 applies to all study sites and includes the following updates: 1. Updated primary and secondary medical monitor contact information 2. Extend the period of post treatment contraception for women to 2 weeks (14 days) (previously 1 week). 3. Updated requirement for pregnancy test to within 7 days of first dose (previously within 14 days of first dose) and added requirements for repeat testing every 4 weeks. 4. Added requirement that any female subject who becomes pregnant while on study be withdrawn from the study. 5. Added that subjects be instructed to avoid excess exposure to sunlight and UV and to use protective measures if outdoors. 6. Modified the storage period for diluted investigational product prior to infusion to 12 hours (previously 48 hours). 7. Updated prohibited medications to clarify exclusion of IV ondansetron and palonosetron (oral doses up to 8mg TID are permitted).		

2. SUMMARY OF KEY PROTOCOL INFORMATION

2.1. Changes to the Protocol Defined Statistical Analysis Plan

There were changes to the originally planned statistical analysis specified in the Protocol Amendment 4 (Dated: 17-MAR-2016).

Due to the termination of study EZH117208 resulting from no evidence of efficacy, this RAP is developed for an abbreviated CPSR. Since Part 2 cohort expansion was not performed before the study closed, 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**
• Statistical Analysis for Part 2	• No Statistical Analysis for Part 2	• Part 2 was not implemented
• Full CSR	• Abbreviated CSR	• Study terminated
• To evaluate the relationship between GSK2816126 exposure and safety/efficacy/PD parameters	• Not to be performed	• Abbreviated CSR
• To determine the amount of GSK2816126 excreted in urine after dosing at steady state	• Not to be performed	• Abbreviated CSR

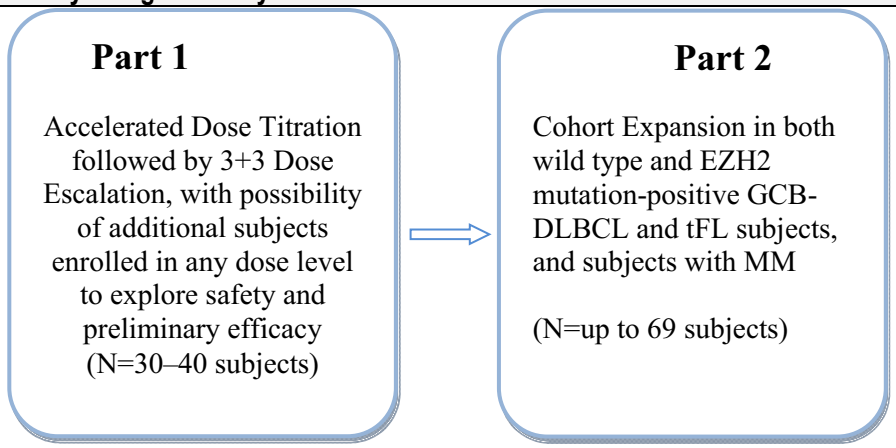
2.2. Study Objective(s) and Endpoint(s)

Part 1 Objectives	Part 1 Endpoints
Primary Objectives	**Primary Endpoints**
• To determine the safety and tolerability, and establish the recommended Phase 2 dose (RP2D) of IV administered GSK2816126	• Adverse Events (AEs), Serious Adverse Events (SAEs), Dose Limiting Toxicity (DLT), withdrawals due to AEs, dose interruptions and reductions, and changes in safety assessments (e.g., clinical laboratory parameters, vital signs, and cardiac parameters)

Part 1 Objectives	Part 1 Endpoints
Secondary Objectives	**Secondary Endpoints**
• To describe the pharmacokinetics of GSK2816126 after single- and repeated administration	• GSK2816126 PK parameters following single- (Day 1) and repeat-dose administration of GSK2816126, including area under the concentration-time curve (AUC), pre-dose (trough) concentration at the end of the dosing interval ($C\tau$), maximum observed concentration (Cmax), time of occurrence of Cmax (tmax), terminal phase half-life ($t_{1/2}$), time invariance and accumulation ratio
• To evaluate the relationship between GSK2816126 exposure and safety/efficacy/PD parameters	• GSK2816126 exposure markers (dose, concentration, Cmax or AUC) and safety/efficacy/PD responses. Pharmacodynamic response assessed by change from baseline in tri-methylation of Histone H3K27 (H3K27me3)
• To determine clinical activity of GSK2816126	• Response rate (complete response [CR] + partial response [PR])
• To generate samples (data reported separately) with which to characterize the metabolic profile of GSK2816126 after repeat-dosing (In the PK/PD expansion cohort only)	• Samples to characterize the metabolites in blood, bile and/or urine
• To determine the amount of GSK2816126 excreted in urine after dosing at steady state	• Concentration of GSK2816126 in urine measured with an investigational bio-analytical method and extrapolated to total amount excreted in urine over time using urine volume
Exploratory Objectives	**Exploratory Endpoints**
• To confirm tumor EZH2 and GCB-DLBCL status	• IHC for confirmation of GCB-DLBCL status
• To investigate the mechanism of action and additional indicators of sensitivity and resistance to GSK2816126	• Tumor baseline genetic profiles, response
• To generate samples (data reported separately) with which to investigate the potential for GSK2816126 to affect cytochrome P450 (CYP) 3A4 enzyme activity	• Samples to assess a potential change in 4b-OH cholesterol to cholesterol ratio in plasma following repeat dosing of GSK2816126 (data reported separately)

Part 2 Objectives	Part 2 Endpoints
Primary Objectives	**Primary Endpoints**
• To determine clinical activity of GSK2816126 in cohorts of subjects with EZH2 mutant and wild type GCB-DLBCL and tFL and subjects with MM	• Objective response rate (% of subjects achieving CR and PR per response criteria)
Secondary Objectives	**Secondary Endpoints**
• To determine the safety, tolerability of the selected IV dose of GSK2816126	• AEs, SAEs, DLTs, withdrawals due to AEs, dose interruptions and reductions, and changes in safety assessments (e.g., clinical laboratory parameters, vital signs, and cardiac parameters)
• To characterize the population PK of GSK2816126	• Population PK parameters for GSK2816126 including clearance (CL), and volume of distribution (Vd) and relevant covariates which may influence exposure (e.g. age, weight, or disease related covariates)
• To evaluate the relationship between exposure and safety/efficacy parameters	• GSK2816126 exposure markers (e.g. dose, concentration, Cmax, or AUC) and safety/efficacy/ responses
• To begin to characterize the durability of response and progression free survival with GSK2816126	• Duration of response (DoR) • Progression-free survival (PFS)
Exploratory Objectives	**Exploratory Endpoints**
• To identify biomarkers predictive of response or resistance to GSK2816126	• Evaluation of wild-type (WT) subject tumors for the presence of additional, undefined, mutations in the EZH2 gene
• To investigate the mechanism of action of GSK2816126 by evaluating changes in gene expression profiles	• Deoxyribonucleic acid (DNA), ribonucleic acid (RNA) and protein markers in tumor and blood

2.3. Study Design

Overview of Study Design and Key Features	
	
Design Features	• This study consisted of 2 parts; Part 1 of the study was a dose escalation phase with cohort expansion to select the recommended Phase 2 dose (RP2D) based on the safety, PK, and PD profiles observed after IV administration of GSK2816126. Eligible subjects with relapsed/refractory DLBCL, transformed FL malignancies, other non-Hodgkin lymphomas (NHL), Multiple Myeloma (MM) and solid tumors would be enrolled in the dosing cohorts until a RP2D was determined or until a maximum tolerated dose (MTD) or a dose of 3000 mg was established. • In Part 1, an accelerated dose titration was employed with one subject per dose level until the first instance of a ≥ Grade 2 drug related non-haematological toxicity or dose limiting toxicity (DLT) occurs. After the accelerated dose titration, subjects would be enrolled in a standard 3+3 dose escalation design. • Any dose level during Part 1 could be expanded to explore safety and preliminary efficacy. At RP2D, cohort may be expanded to enroll more GCB-DLBCL subjects or subjects with solid tumor containing EZH2-sensitive mutations to explore safety and preliminary efficacy. Subjects may continue treatment in the study until disease progression, unacceptable toxicity, or withdrawal of consent. • Part 2 expansion cohorts were planned in subjects with MM, and in subjects with both EZH2 mutant positive and wild type GCB-DLBCL and tFL to further explore clinical activity at the RP2D.
Dosing	• In Part 1 dose escalation, the starting dose was 50 mg, IV, twice weekly. Subsequent cohorts would allow up to 100% dose escalations up to 500 mg, then up to 50% dose escalation at each step thereafter. The maximum dose was 3000mg. Dose adjustments were allowed to address tolerability and safety issues. Alternative schedules would be evaluated if emerging data suggest that twice weekly administration with 2 hour infusions would result in excessive toxicity. • In Part 2, patients would be IV dosed RP2D twice weekly, 3 weeks on / 1 week off for each 28-day cycle.
Time & Events	• Refer to Protocol Amendment 4 Section 7.1 Time and Event Table(s)
Treatment Assignment	• This was a non-randomized open-label study. • Randomization & Medication Ordering System (RAMOS) was used for

Overview of Study Design and Key Features	
	treatment assignment.
Interim Analysis	• For dose escalation in Part 1, there was no interim analysis. • For Part 2, interim analysis of futility for each cohort would be conducted continually once a minimum number of subjects for futility analysis complete response evaluation. These interim analyses would not be formal analyses, but would be used to support the decision of early termination of study EZH117208.

NOTES:

- Part 2 was not implemented, due to the business decision of study termination.

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

3.1. Interim Analyses

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

No formal interim analysis will be performed in Part 1. Dose escalation and stopping rules are guidelines for decision-making and the totality of the data will be considered by the team when making decision. Clinical trial data used in these decisions will be in-stream data only; that is, the data will not necessarily be cleaned in advance of decision making.

3.1.1. Part 1: Dose Escalation Phase

In the accelerated dose escalation cohorts and the 3+3 dose escalation cohorts of Part 1, prior to making decision of the GSK2816126 dose for the next cohort, exploratory analyses will be conducted to assess the relationship of GSK2816126 dose levels with safety, PK parameters (if data permits) using all data from available cohorts.

3.1.1.1. Displays To Be Created For Dose Escalation Review

Review of preliminary data will be performed after completion of each dosing cohort in Part 1. Preliminary safety and study population data may include a demographic summary, adverse event (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 may also be supplied by the study data manager.

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

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

3.2. Final Analyses

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

1. All subjects have completed the study, i.e. discontinued study treatment or receiving study treatment at the time of Sponsor's decision of closing the study.

   For Part 1 dose escalation phase, a completed subject is one who has completed the DLT observation period, has discontinued study treatment and completed a post-treatment follow-up visit, or has died while receiving study treatment or is receiving ongoing study treatment at the time of Sponsor's decision to close the study.
2. All required database cleaning activities have been completed and final database release and database freeze has been declared by Data Management.
3. Randomization codes have been distributed according to RandAll NG procedures.

4. ANALYSIS POPULATIONS

Population	Definition / Criteria	Analyses Evaluated
Enrolled	All participants who passed screening and signed the Informed Consent Form.	Study Population
All Subjects	Consists of all subjects that received at least one dose of study treatment	• Efficacy • Safety
PK	Consists of all subjects in the All Subject population for whom a blood sample for pharmacokinetics is analyzed and at least 1 non-missing values is obtained	Pharmacokinetic
Pharmacodynamics	Consists of subjects in the All Subjects population for whom a pharmacodynamics/biomarkers sample was obtained and analyzed	Translational/Exploratory analysis, e.g. Somatic mutation, DNA and (or) RNA analysis, H3K27me3

NOTES:

- 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 summarised and listed.

Protocol deviations will be tracked by the study team throughout the conduct of the study in accordance with the Protocol Deviation Management Plan (Version 2.0, 25-MAY-2017).

- Data will be reviewed prior to freezing the database to ensure all important 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
B	GSK2816126 Twice-weekly by IV	50 mg	1
		100 mg	2
		200 mg	3
		400 mg	4
		800 mg	5
		1200 mg	6
		1800 mg	7
		2400 mg	8
		3000 mg	9

5.2. Baseline Definitions

For laboratory data, baseline values are defined as the most recent, non-missing value from a local laboratory prior to the first dose of study treatment.

For ECG analyses, subject level baseline is defined as the mean of triplicate Cycle 1 Day 1 (C1D1) pre-dose QTc results.

Parameter	Study Assessments Considered as Baseline			Baseline Used in Data Display
	Screening	Day -1	Day 1 (Pre-Dose)	
Efficacy				
Disease Assessment	X			Screening
Safety				
Vital Signs	X		X	Day 1 Pre-dose if collected, otherwise, use screening
ECG	X		X	Mean of triplicate pre-dose measurements on Day 1, if not available, use mean values at screening
Clinical Chemistry, Hematology	X		X	Day 1 Pre-dose if collected, otherwise, use screening

Parameter	Study Assessments Considered as Baseline			Baseline Used in Data Display
	Screening	Day -1	Day 1 (Pre-Dose)	
Coagulation	X			Screening
PK/PD				
PK Concentration			X	Day 1 Pre-dose
PD Biomarker			X	Day 1 Pre-dose

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

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

5.3. Multicentre Studies

In this multicentre global study, enrolment will be presented by country and investigative site.

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
Section 12.3	Appendix 3: Assessment Windows
Section 12.4	Appendix 4: Study Phases and Treatment Emergent Adverse Events
Section 12.5	Appendix 5: Data Display Standards & Handling Conventions
Section 12.6	Appendix 6: Derived and Transformed Data
Section 12.7	Appendix 7: Reporting Standards for Missing Data
Section 12.8	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 Subjects population, unless otherwise specified.

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

All summary tables for study population analyses will be summarized by dose cohort and overall, unless otherwise specified.

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 have completed the study or have withdrawn from the study, including primary and secondary (if any) reasons for study withdrawal. Reasons for study withdrawal will be presented in the order they are displayed in the eCRF (Electronic Case Report Form). Subjects who die for any reason during on-treatment period will be considered to be complete.

Number of subjects based on the Enrolled population will be summarized by country and site for each dose cohort.

A listing of treatment discontinuation will be generated. The listing will include last dose date, and primary reasons for study treatment discontinuation.

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, height, and baseline body weight) will be listed and summarized. Age, height and weight will be summarized using the mean, standard deviation, minimum, median, and maximum. In addition, age will also be categorized and summarized by <18, 18-64, 65-74 and >74. The count and percentage will be computed for race, ethnicity and sex. The summary of demographic data will be displayed for each dose level and overall.

A separate summary of age ranges based on the Enrolled population will be provided. Age will be summarized in categories: 18-64, 65-74, 75-84 and ≥85. Race and racial combinations will also be summarized.

6.5. Prior Medications

Disease history and characteristics (primary tumor type, lesion status, time since initial diagnosis in weeks, stage at initial diagnosis and screening, time since last progression in weeks) will be summarized for solid tumors and lymphoma separately. Medical conditions present at screening will be summarized by past and current categories.

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

Prior anti-cancer therapy will be coded using GSK Drug coding dictionary and listed. A listing of prior anti-cancer therapy will show the relationship between Anatomical Therapeutic Chemical (ATC) Level 1, ingredient, and verbatim text.

Prior anti-cancer radiotherapy and prior anti-cancer surgeries will be listed.

6.6. 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 listing or 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.

6.7. Treatment Compliance

Summary of study treatment exposure and dose modifications (e.g., number of dose reductions, number of dose interruptions) will be provided. For the study treatment exposure, the number of cycles administered, dose intensity (dose delivered per cycle), and the cumulative dose received will be summarized with mean, median, standard deviation, minimum, and maximum. Listing of study treatment exposure will also be provided.

7. SAFETY ANALYSES

The safety analyses will be based on the All Subjects population, unless otherwise specified. All safety displays will use treatment labels as specified in Section 5.1. All summaries will be presented by dose level and overall.

7.1. Extent of Exposure

Dose reductions will be summarised by number of reductions and reasons for reductions. Dose escalations will be summarised by number of escalations and reasons for escalation. Dose interruptions will be summarised by number of interruptions and reasons for interruptions

All the dose reductions, dose escalations and dose interruptions will be listed separately and will be based on GSK data standards and statistical principles.

Dose reductions, interruptions and escalations will be listed by dose level and subjects.

7.2. Adverse Events Analyses

Adverse events analyses including the analysis of adverse events (AEs), Serious (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.

Adverse events (AEs) will be graded according to the Common Terminology Criteria for Adverse Events (CTCAE v4.0). Adverse events will be coded to the PT level using the MedDRA dictionary. The relationship of AE system organ class, preferred term, and verbatim text 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 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.

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 summary of non-serious AEs that occurred in strictly 5% of the subjects or above will be provided (no rounding for the percentage will be used in terms of 5% threshold, e.g., event with 4.9% incidence rate should not be included in this table). The summary will be displayed by System Organ Class (SOC) and Preferred Term (PT) in descending order of total incidence.

A listing of all AEs will be provided. A listing of adverse events recorded as dose-limiting toxicities will be provided.

A listing of deaths will be generated to provide subject-specific details on subjects who died.

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 by SOC and PT in descending order of total incidence.

Separate supportive listings with subject-level details will be generated for fatal and non-fatal SAEs, respectively. The fatal and non-fatal SAEs will be listed by dose level and subjects, including the relationship with treatment. A study treatment-related SAE is defined as an SAE for which the investigator classifies the relationship to study treatment as "Yes".

7.3. Clinical Laboratory Analyses

Laboratory evaluations including the analyses of Chemistry laboratory tests, Haematology laboratory tests, and liver function tests 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:

Hematology			
Platelet Count	*RBC Indices*:		*Automated WBC Differential:*
Red Blood Cell (RBC) Count	Mean Corpuscular Volume (MCV)		Neutrophils
White Blood Cell (WBC) Count (absolute)	Mean Corpuscular Hemoglobin (MCH)		Lymphocytes
Reticulocyte Count	Mean Corpuscular Hemoglobin Concentration (MCHC)		Monocytes
Hemoglobin			Eosinophils
Hematocrit			Basophils
Clinical Chemistry			
Blood Urea Nitrogen (BUN)	Potassium	Alanine Aminotransferase (AST)	Total and direct bilirubin
Creatinine	Chloride	Aspartate Aminotransferase (ALT)	Uric Acid
Sodium	Calcium	Alkaline phosphatase	Total Protein
Magnesium	Glucose	Lactate Dehydrogenase (LDH)	
Follicle Stimulating Hormone (FSH) and estradiol (as needed in women of non-child bearing potential and all peri menopausal women) Pregnancy test for females (serum B-HCG at screening, Urine or serum B-HCG during Continuation Phase)			

Laboratory grades will be evaluated using CTCAE v4.0. However, some tests are not graded using CTCAE.

For hematology, Red Blood Cell (RBC) is not gradable by CTCAE v4.0.

For clinical chemistry**,** BUN and 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.

Separate summary tables for hematology and chemical chemistry will be produced as detailed below. Liver function and pancreatic laboratory tests will be included with chemical chemistry.

Summary of worst case toxicity grade of lab values increase from baseline grade across all scheduled visits will be generated by dose level for all the lab tests that are gradable by CTCAE v4.0. Any increase to a higher grade from baseline will be summarized. 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 change 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 same time interval, then the subject is counted in both the “Decrease to Low” categories and the “Increase to High” categories.

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 visit.

Supporting listings of haematology and chemistry laboratory tests will be provided.

A character lab value starting with '<X' or '>X' will be displayed in listings, but will not be imputed with a numeric value thus will not be included for summaries.

7.3.1. 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 overall** bilirubin ≥2×ULN (with direct bilirubin ≥35% of total bilirubin, if direct bilirubin is measured) **OR** (ALT ≥3×ULN **and** INR >1.5, if INR is measured). Note that INR measurement is not required and the threshold value stated will not apply to patients receiving anticoagulants.

A listing of liver function tests for subjects meeting Hy's law will be generated. A listing of subjects with liver function test toxicity grade >=3 will also be provided.

7.4. Other Safety Analyses

The analyses of non-laboratory safety test results including ECGs and vital signs 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.

Vital Signs

Listing of vital signs including Systolic BP, diastolic BP, heart rate, body temperature, height and weight at each scheduled visit will be provided.

ECOG (Eastern Cooperative Oncology Group) Performance Status

A summary of worst case post-baseline ECOG status shift from baseline among all visits by dose level will be provided. A supporting listing including performance status and change from baseline will also be provided.

ECG

A summary of the number and percentage of subjects who had normal and abnormal ECG findings will be displayed by scheduled visits as well as for the worst case post-baseline for each dose level. A listing of abnormal ECG findings will be provided. ECG interval values will also be listed.

The mean of ECG values at each collection point will be used for ECG analyses

Summary of the worst case QTc (QTcF and QTcB) post-baseline values relative to baseline will be provided by dose level. The QTc values (QTcF and QTcB) 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).

Summary of the worst case QTc (QTcF and QTcB) increase from baseline by dose level will be provided. The categories of 'Increase of <=30 msec' 'Increase of 31-60 msec' and 'Increase of >60 msec' will be used. A summary of change in QTc value will display the number and percentage of subjects with a change within each category in the worst case post-baseline among all visits.

Baseline results are defined by the nearest timepoint prior to first dose. The baseline QTc value is determined by the mean of the triplicate Cycle 1 Day 1 (C1D1) pre-dose QTc results. If these results are not available, then the mean of QTc of the screening triplicate QTc results would be used. Subjects with a missing baseline value will be assumed to have a normal baseline value.

LVEF (Left Ventricular Ejection Fraction)

LVEF results will be listed with subject level details including absolute change from baseline. Only the post-baseline assessments that used the same method (ECHO or MUGA) as the baseline assessments will be used to derive the change from baseline.

8. EFFICACY ANALYSES

The efficacy analyses will be based on the All Subjects population. All efficacy analyses will be descriptive, graphically presented (where appropriate) and listed. All summaries and data listings will use treatment labels as specified in Section 5.1. All summaries will be presented by dose level and overall.

A summary of investigator-assessed best response with confirmation will be presented by tumor types (solid tumors and Lymphoma). Subjects with Not Evaluable or missing response will be treated as non-responders; and they will be included in the denominator when calculating the percentage. To be assigned a status of complete response or partial response, all responses must be confirmed by repeat assessments performed no less than four weeks after the criteria for CR or PR were met (Protocol Appendix 4 (Revised Response Criteria for Malignant Lymphoma (RRCML) and Appendix 5 (RECIST 1.1)).

The investigator assessment of target lesion, non-target lesion and new lesion will be listed, separately. A listing of investigator-assessed confirmed tumor response will be provided. Waterfall plots of maximum investigator-assessed tumor size reduction from baseline will be generated for solid tumor subjects including prostate cancer and lymphoma subjects, respectively.

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

9. PHARMACOKINETIC ANALYSES

9.1. Primary Pharmacokinetic Analyses

9.1.1. Endpoint / Variables

9.1.1.1. Drug Concentration Measures

The GSK2816126 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 12.5.3 Reporting Standards for Pharmacokinetic)

9.1.1.2. Derived Pharmacokinetic Parameters

Pharmacokinetic parameters will be calculated by standard non-compartmental analysis according to current working practices and using the currently supported version of WinNonlin Version 6.3. All calculations of non-compartmental parameters will be based on actual sampling times.

Pharmacokinetic parameters listed will be determined from the plasma concentration-time data, as data permits.

Parameter	Parameter Description
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 Cycle 1 Day 1 only
AUC(0-tau)	Area under the concentration-time curve from time zero to the predose of the next dose.
Cmax	Maximum observed concentration, determined directly from the concentration-time data.
tmax	Time to reach Cmax, determined directly from the concentration-time data.
t½	Apparent terminal half-life will be calculated as: **t½ = ln2 / lambda_z**
λz	Apparent terminal phase elimination rate constant
C_τ	Trough (pre-dose) concentration at the end of dosing interval on the specified days (Days 8, 15 and 22 where available).
CL	Clearance
V	Volume

NOTES:

Additional parameters may be included as required.

9.1.2. Summary Measure

AUC(0-∞) and Cmax following single dose, and AUC(0- τ) and Cmax following repeat dose will be 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.

Tmax will be summarized descriptively using non-transformed values.

In addition, the following assessments will be performed:

9.1.3. Population of Interest

All pharmacokinetic analyses will be based on the PK population, unless otherwise specified. All summaries, figures and data listings will use treatment labels specified in Section 5.1.

9.1.4. 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, graphically presented (where appropriate) and listed.

GSK2816126 plasma concentration-time data will be listed for each subject and summarized by planned time point and dose cohort. It is noted that the urine and bile concentration data will not be analysed due to unavailability of data.

Pharmacokinetic parameters will be listed and summarized descriptively (mean, standard deviation, median, minimum, maximum, geometric mean (excluding tmax and %AUCex), 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).

9.1.4.1. Dose proportionality

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

- AUC(0-∞) and Cmax on Cycle 1 Day 1 (C1D1)
- AUC(0- τ) and Cmax on Cycle 1 Day 1 and Cycle 1 Day 15 (C1D15)

Dose proportionality of GSK2816126 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.

10. PHARMACODYNAMIC ANALYSES

The statistical analysis for Tri-methylated Histone H3 lysine 27 (H3K27me3) biomarker will be detailed and reported in a separate document and may not be included in the main clinical study report.

11. REFERENCES

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

GUI_51487 (5.0): 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

12. APPENDICES

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

12.1.1. Exclusions from Per Protocol Population

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

12.2. Appendix 2: Schedule of Activities

12.2.1. Protocol Defined Schedule of Events

Refer to Protocol Amendment 4 Section 7.1.

12.3. Appendix 3: Assessment Windows

No assessment windows will be applied.

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

12.4.1. Study Phases

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 + 30 days
Post-Treatment	Date > Study Treatment Stop Date + 30 days

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.

12.4.1.1. 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.

12.4.2. Treatment Emergent Flag for Adverse Events

Flag	Definition
Treatment Emergent	If AE onset or worsening date is on or after treatment start date & on or before treatment stop date plus 30 days.

NOTES:

- If the study treatment stop date is missing, then the AE will be considered to be On-Treatment.

12.5. Appendix 5: Data Display Standards & Handling Conventions

12.5.1. Reporting Process

Software	
• The currently supported versions of SAS software will be used.	
Reporting Area	
HARP Server	: US1SALX00259
HARP Compound	: Compound: GSK2816126, Study:117208
Analysis Datasets	
• Analysis datasets will be created according to Legacy GSK Analysis and Reporting (A&R) dataset standards	
Generation of RTF Files	
• RTF files will be generated for SAC.	

12.5.2. 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.	

12.5.3. 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 GUI_51487: Non-compartmental Analysis of Pharmacokinetic Data. 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

12.6. Appendix 6: Derived and Transformed Data

12.6.1. 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 (PCI) 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

12.6.2. 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**

12.7. Appendix 7: Reporting Standards for Missing Data

12.7.1. Premature Withdrawals

Element	Reporting Detail
General	• A subject will be considered to have completed the study after they have completed their end of study visit or if the subject dies or is still in follow-up at the time the study is closed or terminated, whichever is sooner. • Withdrawn subjects may be replaced in the study at the discretion of the Sponsor in consultation with the investigator. • 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.

12.7.2. 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.

12.7.2.1. 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 new anti-cancer start date on the Oncology time to event analysis dataset and 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.

Element	Reporting Detail
General	• Partial dates will be displayed as captured in subject listing displays.
Adverse Events	• The eCRF allows for the possibility of partial dates (i.e., 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: ○ Missing Start Day: First of the month will be used unless this is before the start date of study treatment; in this case the study treatment start date will be used and hence the event is considered On-treatment as per Appendix 4: Study Phases and Treatment Emergent Adverse Events. ○ Missing Stop Day: Last day of the month will be used, unless this is after the stop date of study treatment; in this case the study treatment stop date will be used. • Completely missing start or end dates will remain missing, with no imputation applied. Consequently, time to onset and duration of such events will be missing.
Concomitant Medications/ Medical History	• Partial dates for any concomitant medications recorded in the CRF will be imputed using the following convention: ○ If the partial date is a start date, a '01' will be used for the day and 'Jan' will be used for the month ○ If the partial date is a stop date, a '28/29/30/31' will be used for the day (dependent on the month and year) and 'Dec' will be used for the month. The recorded partial date will be displayed in listings.

12.8. 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. Clinical laboratory test results outside of the reference range will be flagged in the listings.

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.

12.9. Appendix 9: Abbreviations & Trade Marks

12.9.1. Abbreviations

Abbreviation	Description
AE	Adverse Event
ALT	Alanine aminotransferase
ANOVA	Analysis of Variance
A&R	Analysis and Reporting
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
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
CL	Clearance
Cmax	Maximum observed concentration
CPMS	Clinical Pharmacology Modelling & Simulation
CR	Complete response
CS	Clinical Statistics
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
C_{tau} or Cτ	Pre-dose (trough) concentration at the end of the dosing interval
C1D1	Cycle 1 Day 1
C1D15	Cycle 1 Day 15
DLBCL	Diffuse Large B Cell Lymphoma
DLT	Dose-limiting toxicity
DoR	Duration of response
DP	Decimal Places
ECG(s)	Electrocardiogram(s)
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
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
GLS	Geometric least squares
GSK	GlaxoSmithKline
H3K27me3	Tri-methylated Histone H3 lysine 27
ICH	International Conference on Harmonization

Abbreviation	Description
IDMC	Independent Data Monitoring Committee
IDSL	Integrated Data Standards Library
IHC	Immunohistochemistry
INR	International normalization ratio
LDH	Lactate dehydrogenase
LVEF	Left ventricular ejection fraction
λz	Apparent terminal phase elimination rate constant
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MM	Multiple Myeloma
msec	Millisecond
MTD	Maximum tolerated dose
NCI-CTCAE	National Cancer Institute - Common Terminology Criteria for Adverse Events
NHL	Non-Hodgkin's Lymphoma
PCI	Potential Clinical Importance
PD	Pharmacodynamic
PFS	Progression-free survival
PK	Pharmacokinetic
PR	Partial response
PT	Preferred Term
QTc	Corrected QT interval duration
QTcF	Frederica's QT Interval Corrected for Heart Rate
QTcB	Bazett's QT Interval Corrected for Heart Rate
RAP	Reporting & Analysis Plan
RAMOS	Randomization & Medication Ordering System
RBC	Red blood cell
REML	Restricted maximum likelihood
RP2D	Recommended Phase 2 dose
SAC	Statistical Analysis Complete
SAE	Serious adverse event(s)
SOC	System Organ Class
SOP	Standard Operation Procedure
t1/2	Terminal phase half-life
Tau or τ	Dosing interval
tFL	Transformed Follicular Lymphoma
TFL	Tables, Figures & Listings
tmax	Time of occurrence of Cmax
V	Volume
WBC	White blood cell
WT	Wild-type

12.9.2. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
None

Trademarks not owned by the GlaxoSmithKline Group of Companies
SAS
WinNonlin

12.10. Appendix 10: List of Data Displays

12.10.1. Data Display Numbering

The following numbering will be applied for RAP generated displays:

Section	Tables	Figures
Study Population	1.1 to 1.12	N/A
Efficacy	2.1	2.2
Safety	3.1 to 3.17	N/A
Pharmacokinetic	4.1 to 4.3	4.1
Section	**Listings**	
ICH Listings	1 to 22	
Other Listings	23 to 31	

12.10.2. Mock Example Shell Referencing

Non IDSL specifications will be referenced as indicated and example mock-up displays are provided in Appendix 11: Example Mock Shells for Data Displays.

Section	Figure	Table	Listing
Safety	N/A	SAFE_T1	SAFE_L2
Pharmacokinetic	N/A	PK_T1	PK_L1

NOTES:

- Non-Standard displays are indicated in the 'IDSL / Example Shell' or 'Programming Notes' column as '[Non-Standard] + Reference.'

12.10.3. 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

12.10.4. Study Population Tables

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition					
1.1.	All Subjects	ES1	Summary of Subject Disposition	ICH E3, FDAAA, EudraCT	SAC [1]
1.2.	Enrolled	NS1	Summary of Number of Participants by Country and Site ID	EudraCT/Clinical Operations	SAC [1]
Protocol Deviation					
1.3.	All Subjects	DV1	Summary of Important Protocol Deviations	ICH E3	SAC [1]
Demographic and Baseline Characteristics					
1.4.	All Subjects	DM1	Summary of Demographic Characteristics	ICH E3, FDAAA, EudraCT	SAC [1]
1.5.	Enrolled	DM11	Summary of Age Ranges	EudraCT Age categories: 18-64, 65-74, 75-84 and ≥85	SAC [1]
1.6.	All Subjects	DM5	Summary of Race and Racial Combinations	ICH E3, FDA, FDAAA, EudraCT	SAC [1]
Prior and Concomitant Medications					
1.7.	All Subjects	MH1	Summary of Current/Past Medical Conditions	ICH E3	SAC [1]
1.8.	All Subjects	CM1	Summary of Concomitant Medications	ICH E3	SAC [1]
1.9.	All Subjects	LA1	Summary of Disease Burden at Screening		SAC [1]
1.10.	All Subjects	DC2	Summary of Disease Characteristics at Screening for Subjects with Solid Tumors Including Prostate Cancer		SAC [1]
1.11.	All Subjects	DC2	Summary of Disease Characteristics at Screening for Subjects with Lymphomas		SAC [1]
Exposure and Treatment Compliance					
1.12.	All Subjects	OEX5	Summary of Exposure to Study Treatment	ICH E3 Calculate dose intensity per cycle.	SAC [1]

12.10.5. Efficacy Tables

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Clinical Response					
2.1.	All Subjects	RE1a	Summary of Investigator-Assessed Best Response with Confirmation	By dose and disease types (solid tumor and lymphoma). no p-values.	SAC [1]

12.10.6. Efficacy Figures

Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.1.	All Subjects	RE8b	Plot of Investigator-Assessed Percent Change at Maximum Reduction from Baseline in Tumor Measurement for Subjects with Solid Tumors Including Prostate Cancer		SAC [1]
2.2.	All Subjects	RE8b	Plot of Investigator-Assessed Percent Change at Maximum Reduction from Baseline in Tumor Measurement for Subjects with Lymphomas		SAC [1]

12.10.7. Safety Tables

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Adverse Events (AEs)					
3.1.	All Subjects	OAE1	Summary of All Adverse Events by Maximum Grade by System Organ Class and Preferred Term	ICH E3 By dose, and overall. For each SOC, sort PT in descending order of incidence	SAC [1]
3.2.	All Subjects	AE3	Summary of All Adverse Events by Frequency	ICH E3	SAC [1]
3.3.	All Subjects	AE15	Summary of Common (>=5%) Non-serious Adverse Events by System Organ Class and Preferred Term (Number of Participant and Occurrences)	FDAAA, EudraCT For each SOC, sort Preferred Terms by highest incidence rate	SAC [1]
3.4.	All Subjects	OAE1	Summary of Treatment-Related Adverse Events by Maximum Grade by System Organ Class and Preferred Term	ICH E3 For each SOC, sort PT in descending order of incidence	SAC [1]
3.5.	All Subjects	AE3	Summary of Treatment-Related Adverse Events by Frequency		SAC [1]
Serious and Other Significant Adverse Events					
3.6.	All Subjects	AE16	Summary of Serious Adverse Events by System Organ Class and Preferred Term (Number of Participants and Occurrences)	FDAAA, EudraCT For each SOC, sort PT in descending order of incidence	SAC [1]
3.7.	All Subjects	AE3	Summary of Serious Adverse Events by Frequency		SAC [1]
Laboratory: Chemistry					
3.8.	All Subjects	LB16	Summary of Worst Case Clinical Chemistry Toxicity Grade Change from Baseline Grade	ICH E3 For gradable Clinical chemistry tests. By dose, and overall.	SAC [1]

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Laboratory: Haematology					
3.9.	All Subjects	LB16	Summary of Worst Case Haematology Toxicity Grade Change from Baseline Grade	ICH E3 For gradable Haematology tests. By dose, and overall.	SAC [1]
Laboratory: Hepatobiliary (Liver)					
3.10.	All Subjects	OLIVER10	Summary of Hepatobiliary Laboratory Abnormalities	IDSL	SAC [1]
All Laboratory					
3.11.	All Subjects	LB15	Summary of Worst Case Laboratory Changes from Baseline with Respect to the Normal Range	ICH E3 For non-gradable lab tests. By dose, and overall.	SAC [1]
ECG					
3.12.	All Subjects	EG1	Summary of ECG Findings	IDSL	SAC [1]
3.13.	All Subjects	EG10	Summary of Maximum QTc Values Post-Baseline Relative to Baseline by Category	IDSL	SAC [1]
3.14.	All Subjects	EG11	Summary of Maximum Increase in QTc Values Post-Baseline Relative to Baseline by Category	IDSL	SAC [1]
ECOG					
3.15.	All Subjects	SAFE_T1	Summary of Worst-Case ECOG Performance Status Shifts from Baseline		SAC [1]
Exposure					
3.16.	All Subjects	ODMOD1	Summary of Dose Reductions		SAC [1]
3.17.	All Subjects	ODMOD2	Summary of Dose Interruptions		

12.10.8. Pharmacokinetic Tables

Pharmacokinetic: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
4.1.	PK	PK01	Summary of GSK2816126 Plasma Pharmacokinetic Concentration-Time Data		SAC [1]
4.2.	PK	PK06	Summary of Derived GSK2816126 Plasma Pharmacokinetic Parameters (non-transformed and log-transformed), Subjects with Extensive PK Sampling		SAC [1]
4.3.	PK	PK_T1	Summary of Results of Dose Proportionality Assessment for AUC(0- τ) and Cmax Using Power Model – C1D1 and C1D15		SAC [1]

12.10.9. Pharmacokinetic Figures

Pharmacokinetic: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
4.1.	PK	PK17	Mean GSK2816126 Plasma Concentration-Time Plots (Linear and Semi-log) for C1D1 and C1D15, Subjects with Extensive PK Sampling		SAC [1]

12.10.10. ICH Listings

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition					
1.	All Subjects	SD2	Listing of Study Treatment Discontinuation	ICH E3	SAC [1]
Protocol Deviations					
2.	All Subjects	DV2	Listing of Important Protocol Deviations	ICH E3	SAC [1]
Demographic and Baseline Characteristics					
3.	All Subjects	DM2	Listing of Demographic Characteristics	ICH E3	SAC [1]
Exposure and Treatment Compliance					
4.	All Subjects	OEX8b	Listing of Exposure to Study Treatment	ICH E3	SAC [1]
Adverse Events					
5.	All Subjects	AE2	Listing of Relationship Between Adverse Event System Organ Classes, Preferred Terms, and Verbatim Text	IDSL	
6.	All Subjects	OAE4	Listing of All Adverse Events	ICH E3	SAC [1]
Serious and Other Significant Adverse Events					
7.	All Subjects	OAE4	Listing of Fatal Serious Adverse Events	ICH E3	SAC [1]
8.	All Subjects	OAE4	Listing of Non-Fatal Serious Adverse Events	ICH E3	SAC [1]

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
9.	All Subjects	OAE4	Listing of Dose-Limiting Toxicity		SAC [1]
10.	All Subjects	DTH3	Listing of Deaths		SAC [1]
All Laboratory					
11.	All Subjects	OLB7	Listing of Clinical Chemistry Laboratory Data		SAC [1]
12.	All Subjects	OLB7	Listing of Haematology Laboratory Data		SAC [1]
ECG					
13.	All Subjects	EG3	Listing of ECG Interval Data		SAC [1]
14.	All Subjects	EG5	Listing of Abnormal ECG Findings	IDSL	
Vital Signs					
15.	All Subjects	VS4	Listing of Vital Signs	IDSL	SAC [1]
ECOG					
16.	All Subjects	PS5A	Listing of ECOG Performance Status		SAC [1]
PK					
17.	All Subjects	PK07	Listing of GSK2816126 Plasma PK Concentration-Time Data		SAC [1]
18.	All Subjects	PK13	Listing of GSK2816126 Plasma PK Parameters Data – C1D1 and C1D15		SAC [1]
Efficacy					
19.	All Subjects	LA2	Listing of Investigator-Assessed Target Lesion Assessments		SAC [1]
20.	All Subjects	LA3	Listing of Investigator-Assessed Non Target Lesion Assessments		SAC [1]
21.	All Subjects	LA4	Listing of Investigator-Assessed New Lesions		SAC [1]

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
22.	All Subjects	RE5	Listing of Investigator-Assessed Tumor Responses with confirmation		SAC [1]

12.10.11. Non-ICH Listings

Non-ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Study Population					
23.	All Subjects	AC6	Listing of Prior Anti-Cancer Chemotherapy, Hormonal, Immunotherapy, Small Molecule Target Therapy, and Biologic Therapy		SAC [1]
24.	All Subjects	AC7	Listing of Prior Anti-Cancer Radiation Therapy		SAC [1]
25.	All Subjects	OSP3	Listing of Prior Anti-Cancer Surgery		SAC [1]
Safety					
26.	All Subjects	SAFE_L1	Listing of Echocardiogram Scan Results		SAC [1]
27.	All Subjects	OAE4	Listing of Subjects with Grade 3 and Higher Adverse Events		SAC [1]
28.	All Subjects	SAFE_L2	Listing of Subjects with Liver Function Test Toxicity Grade >=3		SAC [1]
29.	All Subjects	SAFE_L2	Listing of Liver Function Tests for Subjects Meeting Potential Hy's Law		SAC [1]
Efficacy					
30.	All Subjects	LA5	Listing of Investigator-Assessed Lesion Assessments		SAC [1]
PK					
31.	PK	PK_L1	SAS Output of Results of Dose Proportionality Assessment for AUC(0- τ) and Cmax Using Power Model – C1D1 and C1D15		SAC [1]

12.11. Appendix 11: Example Mock Shells for Data Displays

Example: SAFE_T1

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Population: All Treated

Table 3.14
Summary of Worst-case ECOG Performance Status Shifts from Baseline

Dose: 50mg

Baseline Performance Status	Worst-Case Performance Status						
	0	1	2	3	4	5	Total
0	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
1	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
2	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
Total	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (100%)

Example: PK_T1

Protocol: EZH117208
Population: PK

Table 4.3
Summary of Results of Dose Proportionality Assessment for AUC(0-inf) and Cmax Using Power Model - C1D1 and C1D15

Parameter	Number of Subjects	Estimated Mean Slope	90% Confidence Interval	
			90% CI Low	90% CI High
AUCinf (unit)	xx	xx.xxx	xx.xxx	xx.xxx
Cmax (unit)	xx	xx.xxx	xx.xxx	xx.xxx

Example: SAFE_L1

Protocol: EZH117208
Population: All Subjects

Listing 26
Listing of Echocardiogram Scan Results

Dose	Cent./ Subj.	Age(y)/ Sex/ Race	Visit	Date/ Study Day	Ejection Fraction %	Ejection Fraction Range Lower Limit	Change from Baseline	Scan Results
50mg	xxxxxx/ xxxx	xx/ F/ White - White/Caucasian/European Heritage	SCREENING	DDMMMYYYY/ xx	66	55		Normal
			CD-WEEK12	DDMMMYYYY/ xx	61	55	-5.00	Abnormal, not Clinically Significant
			CD-WEEK21	DDMMMYYYY/ xx	66	45	0.00	Abnormal, not Clinically Significant
			CD-WEEK24	DDMMMYYYY/ xx	65	45	-1.00	Normal

Example: SAFE_L2

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Population: All Subjects

Listing 28
Listing of Subjects with Liver Function Test Toxicity Grade >=3

Dose: 50 mg

Inv./ Subj.	Age(y)/ Sex/ Race	Lab Test	Date of Collection/ Study Day	Visit	Converted Data Result	Converted Data Normal Range	NR Flag [1]	Tox Gr.
xxxxxx/ xxxx	47/ M/ White - White/Caucasian/ European Heritage	Alanine Amino Transferase (IU/L)	DDMMMYYYY/-10	SCREENING	xx	0 - 34		0
			DDMMMYYYY /-1	C1D1	xx	0 - 34	H	1
			DDMMMYYYY /4	C1D4	xx	0 - 34	H	1
			DDMMMYYYY /8	C1D7	xx	0 - 34	H	1
				UNSCHEDULED				
			DDMMMYYYY /8	Worst-case on-therapy	xx	0 - 34	H	1
		Albumin (G/L)	DDMMMYYYY /-10	SCREENING	xx	35 - 50		0
			DDMMMYYYY /-1	C1D1	xx	35 - 50	L	1
			DDMMMYYYY /4	C1D4	xx	35 - 50	L	1

[1] Normal Range flag; H=Above range, L=Below range, M=Missing reference range, U=Unconverted lab value

Example: PK_L1

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Population: PK

Listing 31
SAS Output of Results of Dose Proportionality Assessment for AUC(0-inf) and Cmax Using Power Model
C1D1

Power Model For AUCINF Parameter

(SAS output)

Power Model For Cmax Parameter

(SAS output)