TITLE PAGE

Division: Worldwide Development
Information Type: Protocol Amendment

Title:	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

Development Phase: I

Effective Date: 20-MAR-2017

Protocol Amendment Number: 5

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Revision Chronology

GlaxoSmithKline Document Number	Date	Version
2012N149024_00	2013-JUL-11	Original
2012N149024_01	2013-OCT-23	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 Added a QTc stopping criterion that patients will be withdrawn if they experience an increase in QTc 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	2013-OCT-30	Amendment No.: 02
applies to all study sites. Following review of the protocol by the 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 Added a QTc stopping criterion that subjects will be withdrawn if they experience		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	2015-APR-03	Amendment No. 03

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	2016-MAR-17	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).

2012N149024_05	2017-MAR-20	Amendment No. 5

Amendment 5 applies to all global sites. Updates were made throughout the protocol to correct minor inconsistencies, spelling errors and provide further clarification. The following updates have been made to the this amendment to align with updated GSK SOPs and Guidance documents, as well as, to include expansion cohorst in Part 1 of the study to explore further efficacy and safety data:

- Updates made to the Part 1 and Part 2 Objectives, Endpoints and study hypothesis to align with the added Part 1 expansion cohorts of GCB DLBCL and solid tumors containing EZH2 inhibitor sensitizing mutations or prostate cancer to support MTD/RP2D and initiation of planned part 2 analysis
- Study design and number of subjects updated to include the added Part 1 expansion cohorts and update Part 2 expansion cohort
- Inclusion and exclusion criteria updated to define eligibility of GCB DLBCL and solid tumor subjects in Part 1 expansion cohort. Exclusion for Central nervous system metastases, invasive malignancy other than disease under study and prior allogeneic transplant added.
- Male and female contraception use and pregnancy information updated in inclusion criteria and Section 10 to align with GSK written standards
- Statistical methods/Section 12 updated to include Part 1 interim analysis of futility and efficacy for GCB DLBCL subjects. Part 2 updated to further clarify that expansion design is planned based on predictive probability methodology. Rather than early stop for either futility or efficacy, Part 2 allows early stop for futility only. Number of subjects to be enrolled into the Part 2 expansion cohorts updated accordingly
- Risk Assessment updated to include: updated list of medications with risk and possible risk of tpd that are prohibited or to be used with caution; drugs that are to be used with caution will require additional ECG monitoring; clarify instructions for the treatment of infusion reactions; new drug interaction data; additional data and instructions for phototoxicity; and data and mitigation strategy for increased ALT levels seen in higher doses.
- PK/PD cohort moved from Part 1 to Part 2
- Study rationale updated to include supporting rationale for inclusion of GCB-DLBCL and solid tumor subjects (to include prostate cancer)
- Safety management guidelines updated to clarify QTcF to be used for eligibility

and stopping criteria

- Time and Events tables updated to clarify required assessments. Added clarification that brain scans are required for all subjects at screening and bone scans should be completed as clinically indicated. Collection of Blood for PD biomarkers removed and collection of whole blood for biomarkers added
- Response criteria added for subjects with prostate cancer in Appendix 7 of the protocol
- Adverse event and serious adverse event Section 8 updated to align with latest GSK written standards, to include: further definition of events which would meet liver stopping and monitoring criteria, as well as, definition and process for study treatment restart and rechallenge after a liver event and removal of Section 8.4 addressing disease related event
- Section 9 updated with latest list of prohibited medications and those to be used with caution

SPONSOR SIGNATORY

PPD

20 Mar 2017

Li Yan, MD, PhD
Vice President, Head Un[PPD]cian
Oncology R&D

Date

PPD

SPONSOR/MEDICAL MONITOR INFORMATION PAGE

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In some countries, the clinical trial sponsor may be the local GlaxoSmithKline affiliate company (or designee). Where applicable, the details of the Sponsor and contact person will be provided to the relevant regulatory authority as part of the clinical trial submission.

Regulatory Agency Identifying Number(s):

Compound Number	IND Number	EudraCT Number
GSK2816126	118286	2013-001585-42

INVESTIGATOR PROTOCOL AGREEMENT PAGE

For protocol EZH117208

I confirm agreement to conduct the study in compliance with the protocol, as amended by this protocol amendment.

I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described study.

I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure that site staff receives the appropriate information throughout the study.

Investigator Name:	
Investigator Address:	
Investigator Phone Number:	

Investigator Signature	Date

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LIST OF ABBREVIATIONS

AE(s)	Adverse Event(s)
ALT	Alanine aminotransferase
ALP	Alkaline phosphatase
ANC	Absolute Neutrophil Count
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
AUC_{0-24h}	Area under the concentration-time curve from time zero (pre-dose) up to 24 hours
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
β-HCG	Beta-Human Chorionic Gonadotropin
BP	Blood pressure
BUN	Blood urea nitrogen
Cav	Averaged observed concentration
cfDNA	Circulating cell free DNA
CI	Confidence Interval
CL	Systemic clearance of parent drug
Cmax	Maximum observed concentration
CR	Complete response
CRPC	Castration resistant prostate cancer
CRU	Clinical Research Unit
CT	Computed Tomography
CV	Coefficient of variance
CYP	Cytochrome P450
DLBCL	Diffuse Large B Cell Lymphoma
DLT	Dose-limiting toxicity
DMPK	Drug Metabolism and Pharmacokinetics
DNA	Deoxyribonucleic acid
DoR	Duration of Response
EC	Ethics committee
EC_{50}	Exposure producing 50% of the maximum effect
ECG(s)	Electrocardiogram(s)
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EZH2	Enhancer of Zeste Homolog 2
FACTS	Fixed and Adaptive Clinical Trial Simulator
FDG	[18F]fluorodeoxyglucose
FL	Follicular Lymphoma
FSH	Follicle Stimulating Hormone
GC	Germinal Center

GCB	Germinal Center B-cell like
GCB-DLBCL	Germinal Center B-cell-like Diffuse Large B-cell Lymphoma
GCP	Good Clinical Practice
GEP	Gene Expression Profile
GLP	Good Laboratory Practices
GSK	GlaxoSmithKline
H3K27me3	Tri-methylated Histone H3 lysine 27
HIV	Human Immunodeficiency Virus
h/hr	Hour(s)
HNSTD	Highest non-severely toxic dose
HR	Heart rate
HRT	Hormone replacement therapy
IB	Investigator's Brochure
IC_{50}	Half maximal inhibitory concentration
ICH	International Council on Harmonization
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IHC	Immunohistochemistry
IND	Investigational New Drug
INR	International normalization ratio
IP	Investigational Product
IRB	Institutional Review Board
IV	Intravenous
IVRS	Interactive voice response system
kg	Kilogram
L	Liter
LDH	Lactate dehydrogenase
LFTs	Liver function tests
LHRH	luteinizing hormone releasing hormone
LSLV	Last subject's last visit
LVEF	Left Ventricular Ejection Fraction
µg	Microgram
µM	Micromolar
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
mg	Milligrams
MFD	Maximum Feasible Dose
min	Minute
mL	Milliliter
MM	Multiple Myeloma
MRI	Magnetic Resonance Imaging
mRNA	Messenger RNA
MSDS	Material Safety Data Sheet
msec	Milliseconds

MTD	Maximum Tolerated Dose
MUGA	Multigated (radionuclide) angiogram
N-CRM	Neuenschwander-Continuous Reassessment Method
NCI-CTCAE	National Cancer Institute - Common Terminology Criteria for Adverse Events
NHL	Non-Hodgkin's Lymphoma
NOAEL	No-observed-adverse-effect-level
NYHA	New York Heart Association
ORR	Overall Response Rate
PBMC	Peripheral blood mononuclear cell
PD	Progressive disease or pharmacodynamic
PET	Probability of early termination or positron emission tomography
PFS	Progression-free survival
PICC	Peripherally Inserted Central Catheter
PK	Pharmacokinetic
PO_4	Phosphate
PPD	Product of the perpendicular diameters
PR	Partial response
PRC2	Polycomb Repressive Complex 2
PT	Prothrombin time
PTT	Partial Prothromboplastin time
QTc	Corrected QT interval duration
QTcB	QT interval corrected for heart rate by Bazett's formula
QTcF	QT interval corrected for heart rate by Fridericia's formula
R-CHOP	Rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone
RAP	Reporting and Analysis Plan
RBC	Red blood cells
RNA	Ribonucleic acid
RP2D	Recommended Phase 2 Dose
RT-PCR	Reverse transcription-polymerase chain reaction
SAE	Serious adverse event(s)
SAS	Statistical Analysis Software
SCID	Severe Combined Immodeficiency
SD	Stable disease
SPD	Sum of the products of the diameters
SPM	Study Procedures Manual
STD10	Severely toxic dose 10%
t	Time of last observed quantifiable concentration
t1/2	Terminal phase half-life
TdP	Torsades de Pointe
tFL	Transformed Follicular Lymphoma
τ	Dosing interval
tmax	Time of occurrence of Cmax
ULN	Upper limit of normal
UK	United Kingdom
US/USA	United States/United States of America

Vd	Volume of distribution after IV administration
WBC	White blood cells
WT	Wild-type

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PROTOCOL SYNOPSIS

- **PROTOCOL TITLE:** 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

- **PROTOCOL NO.:** EZH117208

- **U.S. Investigational New Drug (IND) NO.:** 118286

- **CLINICAL PHASE:** I

- **COMPOUND:** GSK2816126

STUDY RATIONALE: Enhancer of zeste homolog 2 (EZH2), a component of the Polycomb Repressive Complex 2 (PRC2), mediates transcriptional repression of target genes through tri-methylation of histone H3 on lysine 27 (H3K27me3). EZH2 and H3K27me3 are dysregulated in many cancers through diverse pathways. While EZH2 mutation plays a significant role in progression of certain lymphomas, data from prostate, breast, and several other tumors have demonstrated that increased EZH2 expression correlates with increased aggressiveness of tumors and poor prognosis.

GSK2816126 is a selective and potent inhibitor of wild-type and mutant EZH2 capable of decreasing H3K27me3 levels in all cell types examined. EZH2 inhibition has been shown to decrease the growth of several cell lines derived from EZH2 wild type (WT) and mutant lymphomas, SNF5-mutant malignant rhabdoid tumors, multiple myeloma, AML, neuroblastoma, prostate, breast, skin and colon cancers.

Most of these cancers have an overall poor outlook either because of lack of any effective therapy or standard therapies do not result in a durable remission. This first study of this agent will be conducted in subjects with non-Hodgkin lymphomas, especially germinal center B-cell diffuse large B-cell lymphoma (GCB-DLBCL) and transformed follicular lymphoma (t-FL), and subjects with solid tumors (including castrate resistant prostate cancer) and multiple myeloma (MM) who have relapsed or are refractory to prior therapies and have a high degree of unmet medical need in terms of available treatment options.

- **STUDY OBJECTIVES, ENDPOINTS AND HYPOTHESES:**

	Part 1 Objectives	Part 1 Endpoints
Primary	• 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)
Secondary	• 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 (t1/2), 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. PD response assessed by change from baseline in tri-methylation of Histone H3K27 (H3K27me3)
	• To determine clinical activity of GSK2816126 in GCB DLBCL and solid tumors containing EZH2 inhibitor sensitizing mutations or prostate cancer	• Best Overall Response rate (complete response [CR] + partial response [PR])

Part 1 Objectives		Part 1 Endpoints
Exploratory	• To confirm tumor EZH2 and GCB-DLBCL status • To investigate the mechanism of action of GSK2816126 • To identify biomarkers predictive of response or resistance to GSK2816126	• Immunohistochemistry (IHC) for confirmation of GCB-DLBCL status • PCR or NGS to determine EZH2 mutation status • Evaluate transcriptional and/or protein changes upon GSK2816126 treatment • Correlate baseline tumor genomic [deoxyribonucleic acid (DNA)], protein and/or transcription [ribonucleic acid (RNA)] profiles with response
Hypothesis	No formal statistical hypotheses are being tested for the dose escalation in Part 1. Analysis of the data obtained from dose escalation in Part 1 will utilize descriptive methods only. The cohort expansion of GCB-DLBCL subjects in Part 1 will assess the overall response rate (p) of GCB-DLBCL patients. The null and alternative hypotheses for the overall response rate are detailed below: The null hypothesis is: H_0: p≤20% The alternative hypothesis is: H_A: p≥40% For cohort expansion of solid tumor subjects in Part 1, there is no formal statistical hypothesis being tested. Analysis of the data obtained from solid tumor expansion cohort will utilize descriptive methods only.	

Part 2 Objectives		Part 2 Endpoints
Primary	• To determine clinical activity of GSK2816126 in cohorts of subjects with EZH2 mutant and wild type GCB-DLBCL and tFL and subjects with MM	• Overall response rate (% of subjects achieving CR and PR per response criteria)
Secondary	• 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 GSK2816126 exposure and PD parameters	• GSK2816126 exposure markers (dose, concentration, Cmax or AUC) and PD responses. PD response assessed by change from baseline in tri-methylation of Histone H3K27 (H3K27me3)
	• 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
	• 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)
	• 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)
Exploratory	• To identify biomarkers predictive of response or resistance to	• Evaluation of wild-type (WT) subject

Part 1 Objectives		Part 1 Endpoints
	GSK2816126. • To investigate the mechanism of action of GSK2816126 • To investigate the relationship between genetic variants in candidate genes and the pharmacokinetics (PK) and safety profile of GSK2816126 based on Part 1 and 2 data combined	tumors for the presence of additional, undefined, mutations in the EZH2 gene • Correlate baseline tumor genomic (DNA), protein and/or transcription (RNA) profiles with response • Evaluate transcriptional and/or protein changes upon GSK2816126 treatment • Pharmacogenomic (PGx) analysis of whole blood
Hypothesis	In Part 2, the overall response rate (p) of GCB-DLBCL and tFL patients will be assessed for each EZH2 mutation status cohort (wild type and mutant), and also for MM patients. • For each of the GCB-DLBCL and tFL cohort, the null and alternative hypotheses of the overall response rate are as following: The null hypothesis is: H_0: p≤20% The alternative hypothesis is: H_A: p≥40% • For MM cohort: The null hypothesis is: H_0: p≤10% The alternative hypothesis is: H_A: p≥25%	

- **STUDY DESIGN:** This study is divided into 2 parts; Part 1 of the study is a dose escalation phase to identify MTD and 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 will be enrolled in the dosing cohorts until a RP2D is established. One or more dose level/s during Part 1 escalation may be expanded up to 12 subjects to explore safety and preliminary efficacy. At the identified MTD, approximately 27 GCB-DLBCL subjects and approximately 15 subjects with solid tumors containing EZH2-inhibitor sensitizing mutations or metastatic castrate resistant prostate cancer (mCRPC, regardless of mutation status), may be enrolled to explore safety and preliminary efficacy. Subjects may continue treatment in the study until disease progression, unacceptable toxicity, or withdrawal of consent. Expansion cohorts

(Part 2) are planned in subjects with MM, and in subjects with both EZH2 mutant positive and EZH2 WT GCB-DLBCL and tFL to further explore clinical activity at the RP2D.

- **STUDY DURATION:** Duration of study will depend on recruitment rates, and timing of subjects' duration on study (withdrawal rates due to toxicity or progression).

- **NUMBER OF SUBJECTS:** Up to approximately 250 subjects worldwide (inclusive both Parts 1 and 2).
- **INCLUSION/EXCLUSION CRITERIA:**

Part I: Inclusion Criteria

Deviations from inclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

Subjects eligible for enrollment in the study must meet all of the following criteria:

1. Provided signed written informed consent.
2. Males and females ≥18 years of age (at the time consent is obtained).
3. Tumor type criteria:
    - Relapsed/refractory NHL that meets the following criteria:
        - Germinal Center B cell Diffuse large B cell lymphoma (GCB-DLBCL) relapsed, or refractory to at least one prior regimen (e.g., rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone [R-CHOP]) AND not a candidate for standard salvage regimens or autologous or allogeneic stem cell transplant. Local confirmation of lymphoma subtype GCB-DLBCL is allowed for enrollment but must be confirmed through central laboratory testing.

    - Solid tumors that meet the following criteria:
        - Measurable disease by RECIST 1.1 in at least 1 site
            - For Castrate Resistant Prostate Cancer (CRPC) measurable disease can also include PSA level (see below)
        - Disease progression with the last line of therapy and at least one prior standard of care regimens, or tumor for which there is no approved therapy, or for which standard therapy is unsuitable or refused.
        - Mutation Status:
            - Solid tumor types, other than prostate, must have one of the following EZH2 inhibitor sensitizing mutations as determined via local testing:

- An activating mutation in EZH2 (Y641F/C/S/H/N, A677V/G, and/or A687V
- Loss of a component of the SWI/SNF complex, including, but not limited to, ARID1A, SMARCB1 (aka SNF5/INI1/BAF47), SMARCA4 (aka BRG1), or PBRM1 (aka PB1) as determined by molecular testing (bi-allelic loss or mutation) or immunohistochemistry
- Loss of BAP1 (ubiquitin carboxy-terminal hydrolase) as determined by molecular testing (bi-allelic loss or mutation) or immunohistochemistry

- CRPC subjects:
  - Must have measurable disease by either:
    - RECIST1.1 (Appendix 5), or
    - a minimum PSA of 5 ng/mL
  - Disease progression on last line of therapy and must have progressed on abiraterone, enzalutamide, or taxane chemotherapy
  - Subjects may continue GnRH agonists
  - Small cell prostate cancer is eligible

4. For all subjects: Availability of archival tissue, or willingness to undergo fresh biopsy if archival tissue is not available, as described in Section 7.6.1.1, Section 7.6.1.2, and Section 7.6.5.
5. Must have a pre-existing central venous access such as a port, Hickmann catheter, or a peripherally inserted central catheter (PICC line) or be willing and able to have one inserted.
6. Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1 (see Appendix 2).
7. Men with a female partner of childbearing potential must have either had a prior bilateral vasectomy with resultant azoospermia, bilateral orchiectomy, or must agree to use one of the contraception methods listed in Section 10.1 from the time of the first dose of study medication until at least 2 weeks (14 days) after the last dose of study treatment due to the long elimination phase of study drug.
8. A female subject is eligible to participate if she is of:
   - Non-child bearing potential as defined in Section 10.1.1.
   - Child bearing potential as defined in Section 10.1.1 and agrees to use effective contraception, as defined in Section 10.1, for an appropriate period of time (as determined by the product label) prior to the start of dosing to sufficiently minimize the risk of pregnancy and for at least 2 weeks (14 days) following the last dose of study treatment. Women of

childbearing potential must have a negative serum pregnancy test within 7 days of first dose of study treatment followed by negative urine or serum pregnancy test once every 4 weeks (prior to next dose cycle) thereafter.

9. Adequate organ system function as defined below:

System	LABORATORY VALUES
Hematologic	
ANC	≥1.2 x 10 ^{9}/L
Hemoglobin	≥9 g/dL
Platelets	≥75x 10^{9}/L
PT/INR and PTT	≤1.5 x ULN
Hepatic	
Albumin	≥2.5 g/dL
Total bilirubin	≤1.5 times ULN
AST and ALT	≤2.5 times ULN without liver metastases ≤5 times ULN if documented liver metastases
Renal	
Calculate Creatinine Clearance[a, b]	≥50 mL/min
Reproductive/Endocrine for CRPC only	
Testosterone	<50 ng/dL (only for subjects with CRPC)
Cardiac	
Left Ventricular Ejection Fraction (LVEF)	≥LLN (minimum of 50% LVEF) by ECHO or MUGA[c]

Abbreviation(s): ANC, absolute neutrophil count; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ECHO, echocardiogram; INR, international normalization ratio, MUGA, multigated (radionuclide) angiogram; PT, prothrombin time, PTT, partial thromboplastin time, ULN, upper limit of normal , LLN, lower limit of normal.

a. Calculated by Cockcroft-Gault formula
b. For MM subjects, adequate renal function is defined as calculated creatinine clearance ≥30 mL/min.
c. ECHO is the preferred method and should always be used if available.

NOTE: Laboratory results obtained during Screening should be used to determine eligibility criteria. In situations where laboratory results are outside the permitted range, the investigator may opt to retest the subject and the subsequent within range screening result may be used to confirm eligibility.

Part 2: Inclusion Criteria

1. In addition to inclusion criteria listed for Part 1, Part 2 will enroll **GCB-DLBCL, tFL and MM subjects only.**
    a. Relapsed and/or refractory MM or tFL that have failed prior standard therapy and for which there is no standard salvage regimen
2. Lymphoma subjects will be required to undergo EZH2 mutation testing. This will require availability of archival tissue, or willingness to undergo fresh biopsy, for central testing of EZH2 mutation status.

3. Based on the results of the mutation test, lymphoma subjects may be enrolled in one of four cohorts:
    - GCB-DLBCL EZH2 mutant cohort:
        - Tumors must contain one, or more, of the following EZH2 activating mutations: Y641F; Y641N; Y641S; Y641H; Y641C; A677G; and/or A687V
    - GCB-DLBCL EZH2 wild type cohort:
        - Tumors that do not contain one of the above mutations
        - Subjects with tumors harboring EZH2 mutations other than the seven outlined above will be enrolled in the EZH2 wild type cohort
    - tFL EZH2 mutant cohort:
        - Tumors must contain one, or more, of the following EZH2 activating mutations: Y641F; Y641N; Y641S; Y641H; Y641C; A677G; and/or A687V
    - tFL EZH2 wild type cohort:
        - Tumors that do not contain one of the above mutations
        - Subjects with tumors harboring EZH2 mutations other than the seven outlined above will be enrolled in the EZH2 wild type cohort

Part 1 and 2: Exclusion Criteria

Deviations from exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

Subjects meeting any of the following criteria must not be enrolled in the study:

1. Receiving any cancer therapy within 2 weeks of first dose (including surgery and/or tumor embolization)

    Note: the following are allowed:

    - Corticosteroids to control systemic or local symptoms, up to a dose of 10 mg prednisone or equivalent daily and stable for at least 7 days prior to enrollment.
    - Subjects with prostate cancer may remain on GnRH agonists. Other hormonal therapies (e.g., bicalutamide, abiraterone and enzlutimide) for prostate cancer must be stopped 4 weeks prior to enrolment

    Note: the following are NOT allowed:

    - Chemotherapy regimens with delayed toxicity within the last 3 weeks

- Nitrogen mustards, Melphalan, Monoclonal antibody or Nitrosourea within the last 6 weeks

2. Any major surgery, radiotherapy or immunotherapy within the 4 weeks prior to first dose of study drug, or palliative radiotherapy to a single symptomatic lesion within the 2 weeks prior to first dose of study drugs.
3. Subjects with prior allogeneic transplant are excluded: however, subjects who have previously received an autologous stem cell transplant are allowed if a minimum of 100 days has elapsed from the time of transplant and the subject has recovered from transplant-associated toxicities prior to the first dose of GSK2816126
4. Received an investigational anti-cancer drug within 6 weeks, or within 5 half-lives (whichever is shorter) of the first dose of study drug. A minimum of 14 days must have passed between the last dose of prior investigational agent and the first dose of study drug.
5. Current use of a prohibited medication or expected to require any of these medications during treatment with study drugs (Section 9).
6. Known human immunodeficiency virus (HIV), or serological evidence for Hepatitis B (positive HBsAg), or chronic Hepatitis C infection.
    - For subjects who are negative for HBsAg, but HBcAb positive, a HBV DNA (viral load) test will be performed and if negative are eligible.
    - Subjects with positive Hepatitis C antibody serology with a negative HCV RNA test results are eligible.
7. Concurrent use of therapeutic warfarin is allowed. However, anticoagulants that do not have reversal agents available are prohibited (see Section 9.2).
8. Unresolved toxicity greater than Grade 1 National Cancer Institute – Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4 from previous anti-cancer therapy, with the exception of alopecia and peripheral neuropathy [NCI-CTCAE, 2009].
    - Lymphoma subjects with ≤Grade 3 lymphopenia can be enrolled at the discretion of the investigator
9. Packed red blood cell or platelet transfusion within 7 days of screening laboratory tests.
10. Psychological, familial, sociological or geographical conditions that do not permit compliance with the protocol.
11. Cardiac exclusion criteria:
    - History of acute coronary syndromes (including myocardial infarction and unstable angina), coronary angioplasty, or stenting within the past 6 months prior to first dose of study drug.
    - QT interval corrected for heart rate by Fridericia's formula (QTcF) interval >450msec.

- Uncontrolled arrhythmias. Subjects with rate controlled atrial fibrillation for >1 month prior to first dose of study drugs may be eligible.
- Class II, III or IV heart failure as defined by the New York Heart Association (NYHA) functional classification system.

12. Known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to the study drug or their excipients.
13. Pregnant or lactating female.
14. Unwillingness or inability to follow the procedures outlined in the protocol.
15. Uncontrolled diabetes or other medical condition that may interfere with assessment of toxicity.
16. Central nervous system (CNS) metastases, with the following exception:
    - Subjects who have previously treated CNS metastases, are asymptomatic, and have no requirement for steroids at least 14 days prior to first dose of study drug.
    - Subjects with carcinomatous meningitis are excluded regardless of clinical stability.
17. Invasive malignancy or history of invasive malignancy other than disease under study, except as noted below:
    - Any other invasive malignancy from which the subject has been disease-free for more than 2 years and, in the opinion of the principal investigator and GSK Medical Monitor, will not affect the evaluation of the effects of this clinical trial treatment on currently targeted malignancy, can be included in this clinical trial.
    - Curatively treated non-melanoma skin cancer and any carcinoma-in-situ.

- **STUDY TREATMENT DOSAGE/DOSAGE FORM, ROUTE, AND DOSE REGIMEN**: Starting dose will be 50 mg, IV, twice weekly, with one 28 day cycle being defined as twice weekly dosing for three consecutive weeks and one week off. Dose escalations will be performed in Part 1 and dose adjustments are allowed to address tolerability and safety issues. Alternative schedules may be evaluated if emerging data suggest that twice weekly administration with 2 hour infusions will result in excessive toxicity. In addition, alternative dosing schedules may be considered if the safety, pharmacokinetic (PK), and pharmacodynamic (PD) data suggest that a sufficient therapeutic exposure cannot be achieved using the initial schedule and after a protocol amendment.
- **SAFETY ASSESSMENTS**: Routine physical examinations, vital sign measurements, echocardiograms, and monitoring of adverse events. Cardiac safety monitoring will be required, consisting of triplicate 12-lead electrocardiograms (ECGs) pre-infusion of drug, at the end of infusion of drug, one at night prior to going to sleep (*e.g.*, 10 pm) and one prior to discharge from the unit for Day 1, dose one only. The subject will not be discharged from the unit unless the QTcF is <500 msec. In addition, 24 hours of high fidelity 12-lead Holter monitoring will be performed for dose one. Tracings from this will be used for concentration QT analysis as well. Pre-infusion and end of infusion ECGs will be recorded for all

other ECG timepoints. Laboratory testing includes at least hematology and clinical chemistry. Additional safety assessments may be necessary based on emerging data.

- **PHARMACOKINETIC/PHARMACODYNAMIC MEASUREMENTS:** There will be extensive serial blood sampling for PK and PD measurements in Part 1 of this study with limited blood sampling performed on all subjects in Part 2. Urine and bile may be collected in some subjects in the Part 2 PK/PD expansion cohort. Single safety PK blood draws may be collected for subjects with severe adverse events or adverse events of concern. Mandatory collection of pre-treatment and post-treatment biopsies will be implemented in Part 2 PK/PD cohorts.

- **CLINICAL ACTIVITY ASSESSMENTS**: CR, PR, PFS, DoR.

- **TRANSLATIONAL RESEARCH:** Translational or biomarker research may be performed on archival tissue, tumor biopsies and blood samples collected on study, to better understand DLBCL, transformed FL, and the mechanism of action and response to GSK2816126. Performance of these investigations may be conditional on the results of the clinical trial principally, but not exclusively, on the primary measures of the clinical trial outcome and samples may be selected for analysis on the basis of the clinical outcome. Unless stated otherwise, these investigations may be performed irrespective of whether a response to GSK2816126 is observed and will be categorized as exploratory. Findings may be reported independently of any final clinical study report.

- **STATISTICAL METHODS**: Subject demographic and safety data will be collected on electronic case report forms (eCRFs). All data will be pooled and descriptive safety analyses summarized and listed by cohort at study conclusion.
  - Part 1 in GCB-DLBCL subjects is designed to evaluate preliminary efficacy at the MTD/RP2D or other dose level. Futility and efficacy assessments will be conducted after 13 GCB-DLBCL subjects are enrolled, using overall response rate (ORR) as the efficacy endpoint, until up to 27 subjects are enrolled. The design allows interim analysis (IA) of futility and efficacy to be performed at any point in between. The futility and efficacy stopping rules are defined based on pre-specified type I error rate and power of the hypothesis testing of ORR. If the thresholds for futility are met, enrollment to Part 1 cohort/s may be stopped based upon the evaluation of the totality of the data. If the efficacy thresholds are reached, and the totality of the data support opening Part 2, then Part 2 will start. If neither futility nor efficacy thresholds are met at an interim analysis, and the totality of the data does not support continuation of the trial, then Part 1 may be stopped.

  For the cohort expansion of solid tumor subjects in Part 1, there is no formal statistical hypothesis testing. Analysis of the data obtained from the solid tumor expansion cohort will only utilize descriptive methods.
- Part 2 expansion phase of the study is designed to investigate clinical activity of GCB-DLBCL and tFL patients with EZH2 mutant and wild type, and MM patients, using ORR as the primary endpoint. Secondary endpoints such as PFS, TTR, TTP, DOR and OS will be evaluated. In Part 2, for patients with GCB-DLBCL and tFL, futility assessment will be conducted on an ongoing basis after data are available

from the first 10 subjects and until up to 32 patients. For patients with MM, futility assessment will be conducted on an ongoing basis after data are available from the first 14 subjects and until up to 40 subjects.

1. INTRODUCTION

1.1. Background

Enhancer of zeste homolog 2 (EZH2) is the catalytic subunit of the Polycomb Repressive Complex 2 (PRC2) responsible for maintaining transcriptional repression of target genes through tri-methylation of histone H3 on lysine 27 (H3K27me3). PRC2 activity is essential for maintaining the self-renewal capacity of embryonic and adult stem cells, and the dynamic regulation of this activity is critical for proper development and differentiation.

EZH2 and H3K27me3 are dysregulated in nearly all cancers through numerous pathways including 1) recurrent gain-of-function heterozygous mutations in germinal center B-cell (GCB) diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), melanoma, and parathyroid adenoma, 2) EZH2 over-expression in numerous other aggressive tumors including those from prostate, breast, lung, liver, bladder, head and neck, skin, and kidney, and 3) inactivating mutations in UTX, an H3K27 demethylase that acts in opposition to EZH2, described in numerous tumor types including transitional cell bladder carcinoma, esophageal squamous cell carcinoma, renal cell carcinoma, multiple myeloma, and subgroup 4 medulloblastoma (McCabe, 2014). Furthermore, data from prostate, breast, and several other tumor types have demonstrated that increased EZH2 expression correlates with increased aggressiveness of tumors and poor prognosis.

In the B-cell lineage, EZH2 is required by germinal center B-cells, which are the cells of origin of the most common forms of Non-Hodgkin's Lymphomas (NHL). GC derived DLBCLs are mostly addicted to EZH2 and require its histone methyltransferase activity for their survival. Recently, somatic activating mutations in EZH2 have been identified in follicular lymphoma (FL) and GCB-DLBCL [Morin, 2010; Morin, 2011; Pasqualucci, 2011; Ernst, 2010]. The frequency of the most prevalent mutation, Y641, is 7-27% in FL and 22% in DLBCL [Bodor, 2013]. Biochemical studies have demonstrated that Y641, A677 and A687 mutants exhibit an altered substrate preference and catalytic efficiency to enhance the generation of H3K27me3. Consistent with these biochemical data, primary lymphomas and lymphoma cell lines harboring EZH2 mutations have elevated levels of H3K27me3. Mutant EZH2 maintains the proliferation, survival and blocks terminal differentiation of DLBCL cells.

1.2. GSK2816126

GSK2816126 is a potent and highly selective inhibitor of both wild type (WT) and mutant (Y641N/F/C/H/S, A677G and A687V) EZH2 methyltransferase activity. Inhibition of H3K27 methylation by GSK2816126 is competitive with *S*-adenosyl-methionine and non-competitive with peptide substrates [McCabe, 2012]. GSK2816126 is highly selective against other methyltransferases and protein classes. In particular, GSK2816126 is more than 1,000-fold selective for EZH2 versus 20 other human methyltransferases, including both SET-domain-containing and non-SET-domain-containing methyltransferases. EZH1, which is 96% identical to EZH2 within the SET domain, and 76% identical, overall, is inhibited more than 150-fold less potently [McCabe, 2012].

1.2.1. Pharmacokinetics of GSK2816126 in Humans

GSK2816126 pharmacokinetics (PK) have not yet been completely evaluated in humans. Whole blood human clearance for GSK2816126 was predicted from three species (mouse, rat and dog) using maximum life span power-law allometry to be around 8.2 mL/min/kg. Volume of distribution was predicted from simple power-law allometry to be 4.8 L/kg and half-life around 6.5 hours. A 70 kg adult therefore has a predicted total blood clearance of 35 L/hr and a total blood volume of distribution of 336 L.

1.2.2. Pre-Clinical Pharmacology & Safety of GSK2816126

In Vitro Testing

In cell culture, GSK2816126 induces loss of H3K27me3 in both EZH2 WT and mutant cell lines from diverse tumor types with the half maximal inhibitory concentration (IC_{50}) values ranging from 10 - 252 nM independent of EZH2 mutation status [McCabe, 2012]. In proliferation assays using a panel of B-cell lymphoma cell lines, those of DLBCL origin with EZH2 activating mutations are the most sensitive to GSK2816126. The second most sensitive tumor type evaluated was multiple myeloma where a majority of cell lines exhibited growth inhibition when exposed to GSK2816126. However, the growth of a subset of several other tumor types including NHL, SNF5-mutant malignant rhabdoid tumors, AML, neuroblastoma, prostate, breast, skin, and colon cancers is also sensitive to EZH2 inhibition.

Time course studies demonstrate that inhibition of H3K27me3 is maximal after 2 days. Inhibition of cell proliferation begins as early as 2 days of EZH2 exposure but in some cases takes up to 2 weeks to reach maximal growth inhibition. Both cytostatic and cytotoxic responses are observed among sensitive cell lines. Together, these data indicate that global H3K27me3 can be used to assess on-target activity of an EZH2 inhibitor in both responsive and unresponsive tumors, and that EZH2 activating mutations may provide a strong marker for subject selection in clinical studies.

In Vivo Testing

Pharmacokinetics: The nonclinical pharmacokinetics of GSK2816126 were similar across species. GSK2816126 had moderate blood clearance in the mouse and rat and high blood clearance in the dog. Steady state volume of distribution was moderate to high in all species, indicating good distribution into tissues. GSK2816126 half life was 2.8 hours in mice and rats and 7 hours in dogs. Systemic exposure to GSK2816126 generally increased dose-proportionally in rats and increased greater than or dose proportionally in dogs. In vitro, GSK2816126 was highly bound to plasma proteins (³≥95.7%) in mouse, rat, dog and human.

Nonclinical Pharmacology: In severe combined immunodeficiency (SCID) mice bearing subcutaneous xenografts derived from human DLCBL, multiple myeloma, or prostate cancer cell lines, GSK2816126 inhibits H3K27me3 after repeated daily or twice weekly dosing over 10-11 days. The PD response is durable as H3K27me3 levels did not return to pre-dose levels by 7 days after the last dose. In mice bearing subcutaneous xenografts of EZH2 mutant lymphomas, 90-100% tumor growth inhibition is observed

with daily or twice weekly dosing over a five week period with or without a one week drug holiday in the third week. In some models, tumor stasis or complete tumor eradication is observed upon cessation of dosing. Together, these pre-clinical PD and efficacy data indicate a treatment cycle of twice weekly dosing of GSK2816126 for 2 or 3 weeks followed by a 1 week drug holiday should effectively reduce H3K27me3 levels in the tumor.

The dose-limiting toxicity seen in rat and dog IV infusion toxicology studies conducted with GSK2816126 was vascular damage at the local infusion and/or indwelling catheter sites. On the 4-week toxicity studies in rats (≥30 mg/kg) and dogs (≥100 mg/kg) twice weekly intravenous (IV) infusions (rats: 6 hours; dogs 8 to 16 hours) of GSK2816126 in vehicle containing 5% Captisol, there was vascular necrosis, inflammation, and edema. In these animals, there were secondary histopathologic changes in multiple tissues and clinical pathology findings consistent with an inflammatory response to the vascular damage. Infusion site and secondary histopathologic findings were partially reversible and secondary clinical pathology effects were reversible. Morbidity and mortality in rats given ≥300 mg/kg (maximum observed concentration [C_{max}] ≥40.3 μg/mL; area under the concentration-time curve from time zero (pre-dose) up to 24 hours (AUC_{0-24h}) ≥285 μg.h/mL) or dogs given ≥100 mg/kg (C_{max}=10 μg/mL; AUC_{0-24h}=80 μg.h/mL) were attributable to vascular or extravascular irritant effects of GSK2816126 and prolonged intravenous catheterization. Infusion site reactions are likely related to the hemolytic and/or irritant (vesicant) potential of GSK2816126. While some rats given 300 mg/kg on the 4 week twice weekly dose IV infusion study were terminated early (beginning following 4 doses) due to adverse clinical observations at the local infusion site (Day 1 AUC_{0-24h} of 285 μg.h/mL; C_{max} of 40.3 μg/mL), IV infusions at 300 mg/kg on the 2 week, twice weekly IV infusion study (total number of 4 doses; AUC_{0-24h} of 235 μg.h/mL; C_{max} of 33.2 μg/mL) did not result in similar GSK2816126-related infusion site reactions or early termination. Increased concentrations of Captisol in the vehicle reduced the hemolytic potential in a concentration dependent manner. Inclusion of 10% Captisol in GSK2816126 clinical formulation and administration through a central line (e.g. peripherally inserted central catheter [PICC]) should alleviate the infusion site reactions observed on the non-clinical toxicology studies.

Infusion rate and/or concentration-dependent, histamine reactions, which began within minutes of dose initiation, were observed at ≥300 mg/kg in dogs (C_{max} 66.5 to 130 μg/mL) and 300 mg/kg (C_{max} 33.9 to 54.2μg/mL) in rats. In dogs, histamine reactions resulted in discontinuation of dosing. Histamine-related decreased body temperature, along with increased heart rate (HR) and decreased blood pressure (BP) likely led to mortality in restrained, but not in unrestrained, rats given an IV infusion of 300 mg/kg (5 mL/kg/hr for 4 hours). These effects could be ameliorated by discontinuation of dosing, administration of diphenhydramine hydrochloride, degranulation of mast cells prior to GSK2816126 dosing, and/or lengthening of the infusion time to reduce C_{max}. These observations tended to occur only during the first exposure to the drug and not on subsequent administrations. Human subjects will be monitored during the infusion for evidence of histamine release related symptoms/infusion reactions and treated as needed with supportive care per local standard of care. (e.g., corticosteroids, oxygen, epinephrine, diuretics, IV fluid). The infusion duration can be lengthened with restart of the infusion or at the next infusion.

Premedications (antihistamines or similar) may be provided at the next infusion or prior to treatment of new subjects.

In dogs, a mild, reversible dose dependent decrease in minute (up to 128 mL/min/kg; 49%) and tidal volume (8 mL/kg; 56%) at 100 mg/kg and an elevation in Corrected QT interval duration (QTc) interval at 30 (maximum increase of 12 msec or 5%) and 100 (maximum increase of 18 msec or 8%) mg/kg were observed following the end of a single 8 hour infusion. These effects did not directly correlate with peak GSK2816126 blood levels as the onset was 4-7 hours following the end of the infusion. QTc interval elevations were not observed following repeat dosing.

A direct effect on human ether à go-go-related gene (hERG) channel repolarization is unlikely (IC_{25} of 54.2 μM; 28.61 μg/mL), however, GSK2816126 did block hERG current density in vitro consistent with an effect on hERG channel trafficking. The mechanism for this change is unclear. Evaluation of the QTc interval has been incorporated into this clinical study protocol.

GSK2816126 has evidence of absorbance within the 290-700 nm wavelength range of concern for photosafety. While GSK2816126A has no absorbance peaks (λmax) > than 290 nm, there is an absorbance peak at 285 nm with a small tail of absorbance that extends to ~380 nm and therefore, has a potential risk for phototoxicity. To date, no *in vivo* phototoxicity or Bio-distribution studies of the product in the skin or the eyes have been completed. No photosafety concerns have been observed in humans at doses up to 3000 mg/day, however, only a limited number of patients have received GSK2816126. To minimize the risk for potential phototoxicity, human subjects will be instructed to minimize or avoid prolonged exposure to natural or artificial sunlight (e.g., tanning beds, sunlamps, UVA or UVB treatments) and wear loose fitting clothing with long sleeves, sunglasses, and broad rim hat that protect the skin from sun exposure AND use a broad spectrum sunscreen (e.g., UVA and UVB protective with minimum SPF 30) on any uncovered areas of the body if outdoors from the time of first dose of study medication until at least 2 weeks (14 days) following last dose of study medication due to long elimination phase.

Based on the infusion site reactions in dogs following twice weekly dosing for 4 weeks, the no-observed-adverse-effect-level (NOAEL) is 30 mg/kg ($AUC_{0\text{-}24h}$ of 14.9 μg.h/mL; C_{max} of 1.96 μg/mL) and the highest non-severely toxic dose (HNSTD) is 100 mg/kg ($AUC_{0\text{-}24h}$ of 80.1μg.h/mL; C_{max} of 9.88 μg/mL). In rats following twice weekly dosing for 4 weeks, a NOAEL was not established at the lowest dose tested of 30 mg/kg ($AUC_{0\text{-}24h}$ of 23.5 μg.h/mL and C_{max} of 2.97 μg/mL). Due to similar exposure in rats at 300 mg/kg on Day 1 of the 2 and 4 week studies, the severely toxic dose 10% (STD10) in rats is estimated to be between 100 and 300 mg/kg ($AUC_{0\text{-}24h}$ between 54 and 235 μg.h/mL; C_{max} between 8 and 33 μg/mL; exposures based on twice weekly dosing for 2 weeks). For the purpose of the starting dose justification in this protocol, we will use the lower estimate of 100 mg/kg as the STD10. However, because the smaller calibre of rodent vessels used for the drug infusion are more sensitive to injury and irritant effects, the dog findings are more appropriate to use for the local tolerability.

1.3. Benefit/Risk Assessment

Summaries of findings from nonclinical studies conducted with GSK2816126 can be found in Section 1.2.2 of the protocol and the Investigator's Brochure (IB) [GlaxoSmithKline Document Number 2013N169204_04, 2017]. Toxicology studies performed in dogs and rats suggest that the primary toxicities of GSK2816126 are cardiovascular, hemolytic and allergic (see Section 4 of GSK2816126 IB [GlaxoSmithKline Document Number 2013N169204_04, 2017]).

This section outlines the risk assessment and mitigation strategy for this protocol based on nonclinical and clinical findings. Additional information on clinical findings can be found in Section 1.3.1 of the protocol and Section 5 and Section 6 of the Investigator's Brochure [GlaxoSmithKline Document Number 2013N169204_04, 2017].

1.3.1. Risk Assessment

Potential Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy
Cardiovascular – QT prolongation	**QTc prolongation** was observed (up to 8%; 18 msec in dog) following the end of a single 8 hour infusion Effect did not directly correlate with peak GSK2816126 blood levels; onset was 4-7 hours following the end of the infusion; reversed within 3-8 hours following onset Effects not observed following repeat dosing in dogs No arrhythmias were detected in preclinical studies The mechanism for the QTc prolongation is unlikely due to a direct effect on hERG repolarization as GSK2816126 weekly inhibited hERG tail current (IC25 of 54.2 µM; 28.61 µg/mL). However, GSK2816126 was shown to block hERG current density in vitro consistent with an effect on hERG channel traffickin	Protocol includes cardiovascular eligibility criteria, laboratory assessments (potassium and magnesium), cardiac monitoring (electrocardiograms [ECGs], Holter monitoring during the study, and dose stopping/modification criteria for the management of QT prolongation) Co-administration of medications that are known to prolong the QT interval and have a risk of causing Torsades de Pointes (TdP) are prohibited. Drugs that have a possible risk of TdP will be used with caution and additional ECG monitoring required. All subjects will remain in the clinical research unit (CRU) after receiving their first dose of study medication (Week 1, Day 1) with periodic ECGs and Holter monitoring for 24 hours. Subjects will not be discharged from the unit unless their last measured QTc on an ECG performed immediately prior to discharge after the first dose is <500 msec. Timings for in-house on-drug ECGs are pre-infusion, at the end of infusion, before bed, and before discharge the next morning for Day 1 of cycle 1 only. Refer to Section 7.1 (T&E) for other ECG timings
Local Infusion Site Reaction	**Vascular/perivascular inflammation and necrosis** (in rats at all dose levels, including controls, and in dogs given ≥100 mg/kg) Dose-limiting vascular damage (necrosis, inflammation, edema and/or hemorrhage) at the local infusion and/or	Subjects will be dosed via a central venous access device with a formulation including 10% Captisol Subjects will be monitored closely for infusion site reactions (during infusion and for one hour

Potential Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy
	indwelling catheter sites was observed in rats and dogs following twice weekly IV infusions of GSK2816126 (vehicle containing 5% Captisol) (6 to 16 hours) for 2 to 4 weeks Inflammation at the infusion site led to secondary histopathologic changes in multiple peritoneal and retroperitoneal tissues/organs and clinical pathology findings; morbidity/mortality observed in rats (≥30 mg/kg; Cmax ≥2.97 μg/mL; AUC0-24h ≥23.5 μg.h/mL) and dogs (≥100 mg/kg; Cmax=9.88 μg/mL and AUC0-24h=80.1 μg.h/mL) was attributable to vascular or extravascular irritant (vesicant) effects of GSK2816126 and prolonged intravenous catheterization Infusion site and secondary histopathologic findings were partially reversible and secondary clinical pathology effects were reversible	post infusion) and if reaction occurs, infusion will be interrupted and the appropriate clinical intervention commenced. See Management of Infusion Site Reaction (Section 3.8.2) Laboratories will be monitored as well, including liver function tests (LFTs), other chemistries, and hematology
Histamine Reaction/InfusionReaction	**Acute histamine-like reactions seen in rats and dogs** which began within minutes of dosing were observed at ≥300 mg/kg in dogs (C_{max} 66.5 to 130 μg/mL) and 300 mg/kg (C_{max} 33.9 to 54.2 μg/mL) in rats. In dogs, histamine reactions resulted in discontinuation of dosing. In rats, histamine-related decreased body temperature, along with increased HR and decreased BP likely led to mortality in restrained, but not in unrestrained animals	Subjects will be monitored during the infusion for evidence of histamine release related symptoms/infusion reactions and treated as needed with supportive care per local standard of care (e.g., corticosteroids, oxygen, epinephrine, diuretics, IV fluid). The infusion duration can be lengthened with restart of the infusion or at the next infusion. Premedications (antihistamines or similar) may be provided at the next infusion or prior to treatment of new subjects.
Drug Interactions	No in vivo drug-drug interaction (DDI) studies have been performed. GSK2816126 is metabolized by CYP3A enzymes in vitro. GSK2816126 has also been shown to be a substrate of P-gp and BCRP transporters. Therefore,	The potential for drug-drug interactions will be monitored in clinical trials and some concomitant medications are prohibited or to be used with caution (see Section 9).

Potential Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy
	substances that potently inhibit or induce CYP3A, P-gp or BCRP could lead to higher/lower exposure in subjects, potentially leading to alterations of the pharmacologic effects of GSK2816126. On the other hand, GSK2816126 was shown to inhibit CYP2C8, CYP2C9, CYP2C19 and CYP3A4 with IC_{50} values <5 μM. GSK2816126 activate human PXR [(exposure producing 50% of the maximum effect (EC_{50} = 10 μM)] and, therefore, may have the potential to induce CYP enzymes. A further in vitro study in cultured human hepatocytes (n=3 donors) showed induction of CYP3A4 messenger RNA (mRNA) with a calculated EC_{50} of 4.22-5.43 μM and E_{max} of 3.22-16.5-fold. In vitro studies demonstrated that GSK2816126 (up to 100 μM) has the potential to inhibit human transporters BCRP, OATP1B1, OATP1B3, OCT2, MATE1 and MATE2-K (IC_{50} values of 21, 13, 34, 2.88, 0.025 and 0.95 μM, respectively), however, GSK2816126 did not inhibit P-gp (up to 100 μM) or OAT1 and OAT3 (up to 25 μM). Based upon the current average clinical C_{max} of 58 μM (30.6 μg/mL) at 3000 mg dose, mathematical model simulations suggest that GSK2816126 has the potential to perpetrate a clinical DDI when co-administered with sensitive substrates of transporters OATP1B1, BCRP, OCT2, MATE1 and MATE2-K upon inhibition, and CYP2C8, 2C9, 2C19 upon inhibition, and CYP3A4 upon inhibition or induction.	
Phototoxicity	GSK2816126 has recently been demonstrated to be phototoxic in an in vitro assay for phototoxicity (3T3 Neutral Red Uptake Phototoxicity Test). To date, no photosafety concerns have been observed in humans at doses up	Subjects will be instructed to minimize or avoid prolonged exposure to natural or artificial sunlight (e.g., tanning beds, sunlamps, UVA or UVB treatments) and wear loose fitting

Potential Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy
	to 3000 mg/day, however, only a limited number of subjects have received GSK2816126.	clothing with long sleeves, sunglasses, and broad rim hat that protect the skin from sun exposure AND use a broad spectrum sunscreen (e.g., UVA and UVB protective with minimum SPF 30) on any uncovered areas of the body if outdoors from the time of first dose of study medication until at least 2 weeks (14 days) following last dose of study medication due to long elimination phase.
Hepatic Toxicity	In first in human study EZH117208 (present study), an increase in level of ALT has been noted in the group of subjects receiving doses of 1800 mg to 3000 mg (single infusion dose). None of these ALT increases have been associated with increase in total bilirubin or INR and all have shown improvement following either withholding or discontinuing GSK2816126. The 3000 mg dose has been declared to exceed the MTD. The highest dose being explored in this study is 2400 mg . In nonclinical species given GSK2816126, twice weekly for 2 and/or 4 weeks, changes in liver pathology (inflammation, hyperplasia) in dogs and clinical chemistry parameters (i.e. increases in ALT, AST, alkaline phosphatase (ALP), bilirubin and decreases in albumin) in rats and dogs were observed and were consistent with systemic inflammation. These effects were considered secondary to vascular damage at the infusion and/or surgical site and attributable to vascular or extravascular irritant (vesicant) effects of GSK2816126 and prolonged intravenous catheterization. No current evidence suggests the presence of reactive metabolites. No glutathione conjugates were identified in the *in vitro, ex vivo* studies that were	Dosing at 3000 mg has been discontinued, with the highest dose being explored is at 2400 mg. Continued laboratory and clinical monitoring for liver dysfunction (LFT, coagulation parameters INR/PTT, other blood chemistry, clinical observation for jaundice). Dose management and stopping criteria as per guidelines for non-hematologic toxicity (Section 3.8.3 and Table 4) and hepatic safety monitoring (Section 8.3.1)

Potential Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy
	conducted. GSK2816126 is not a CYP metabolism-dependent inhibitor. Based on in vivo dosing to rats twice weekly for 2 weeks at doses up to 300 mg/kg, no evidence of induction of PXR panel genes was noted. This is in agreement with the observation that GSK2816126 is not a rat PXR activator. It is however a human PXR activator, and an in vitro inducer of CYP3A4 in human hepatocytes, suggesting species differences between rat and human. GSK2816126 is an in vitro inhibitor against hepatic transporters OATP1B1, OATP1B3 and BCRP with a moderate in vitro potency (IC_{50}: 13-34 μM). With the high clinic concentration, a potential risk for inhibiting hepatobiliary excretion of substrates of these transporters cannot be excluded.	

1.3.2. Benefit Assessment

Study EZH117208 is an open-label, dose escalation study and the first study of this agent to be conducted in humans. GSK2816126 has promising growth inhibitory activity in cell lines derived from multiple tumor types; however, it is unknown whether GSK2816126 will have efficacy in patients with these tumors. Thus, any potential beneficial effect for an individual subject attributable to GSK2816126 is unknown. Data obtained in Study EZH117208 may assist in progressing the knowledge base on lymphoma and other tumor types and their treatment(s), or help identify individuals more likely to benefit or have side-effects from GSK2816126. Study participants may benefit from the medical tests and screening performed during the study.

1.3.3. Overall Benefit: Risk Conclusion

Current data from GSK2816126 clinical study and nonclinical development indicate a potential for clinical utility in the treatment of subjects with relapsed and/or refractory DLBCL and/or transformed FL, NHL, multiple myeloma, and other solid tumors. Considering the overall poor outlook of these subjects on failing prior therapy and recognizing the measures taken to minimise risk to subjects participating in the Phase I clinical trials, the potential risks identified in association with GSK2816126 are justified by the anticipated benefits that may be afforded to subjects with the previously mentioned tumor types that have been shown in nonclinical models to respond to GSK2816126.

1.4. Communication Plan for Safety Evaluation

This phase I study is intended to enroll subjects at two or more sites. Safety evaluations will be closely monitored by a GlaxoSmithKline (GSK) Safety Review Team that includes the GSK medical monitor and GSK safety physician. There will be a 2 way communication between the local participating sites and the GSK team via email, fax and phone. The GSK team will review all safety data throughout the study, and safety findings with GSK2816126 will be discussed with investigators from all participating sites on a monthly basis and appropriate action will be taken. Urgent safety information will be shared with all the participating sites at the earliest possible time after the data becomes available, or sooner if necessary.

1.4.1. Contraindications, Warnings and Precautions

The following Contraindications, Warnings and Precautions apply:

Contraindications: Animal reproductive studies have not been conducted with GSK2816126. Therefore, the compound must not be administered to pregnant women or nursing mothers.

Safety and efficacy in the paediatric populations has not been investigated, therefore, GSK2816126 should not be administered to children.

Any known hypersensitivity to agents structurally similar to GSK2816126 or the constituents of the vehicle would contraindicate GSK2816126 use.

Warnings: GSK2816126 is intended for investigational use only by selected investigators familiar with the information in this Protocol and experienced in conducting clinical studies.

GSK2816126 may only be administered to human subjects participating in clinical studies sponsored/approved by GSK and who have provided formal written consent.

Precautions: ECG monitoring for evidence of QTc prolongation must be conducted. Co-administration of medications that are known to prolong the QT interval and have a risk of causing TdP are to be avoided beginning **14 days** prior to the first dose of study drug or longer if necessary, as determined by the primary investigator or medical monitor until discontinuation from the study. Co-administration of medications that are known to prolong the QT interval and have a possible risk of causing TdP are to be used with caution. Subjects will be instructed to minimize or avoid prolonged exposure to natural or artificial sunlight (e.g., tanning beds, sunlamps, UVA or UVB treatments) and wear loose fitting clothing with long sleeves, sunglasses, and broad rim hat that protect the skin from sun exposure AND use a broad spectrum sunscreen (e.g., UVA and UVB protective with minimum SPF 30) on any uncovered areas of the body if outdoors from the time of first dose of study medication until at least 2 weeks (14 days) following last dose of study medication due to long elimination phase.

Potential for Abuse and Dependence: Not Known

Overdosage: There is no specific antidote for overdose with GSK2816126. In the event of a suspected overdose, it is recommended that the appropriate supportive clinical care should be instituted, as dictated by the subjects' clinical status.

2. OBJECTIVES, ENDPOINTS AND HYPOTHESES

2.1. Part 1: Phase I Dose Escalation

Part 1 Objectives		Part 1 Endpoints
Primary	• 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)
Secondary	• 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 (t1/2), time

Part 1 Objectives		Part 1 Endpoints
		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. PD response assessed by change from baseline in tri-methylation of Histone H3K27 (H3K27me3)
	• To determine clinical activity of GSK2816126 in GCB DLBCL and solid tumors containing EZH2 inhibitor sensitizing mutations or prostate cancer	• Best Overall Response rate (complete response [CR] + partial response [PR])
Exploratory	• To confirm tumor EZH2 and GCB-DLBCL status	• Immunohistochemistry (IHC) for confirmation of GCB-DLBCL status
		• PCR or NGS to determine EZH2 mutation status
	• To investigate the mechanism of action of GSK2816126	• Evaluate transcriptional and/or protein changes upon GSK2816126 treatment
	• To identify biomarkers predictive of response or resistance to GSK2816126	• Correlate baseline tumor genomic [deoxyribonucleic acid (DNA)], protein and/or transcription [ribonucleic acid (RNA)] profiles with response
Hypothesis	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 utilize descriptive methods only. The cohort expansion of GCB-DLBCL patients in Part 1 will assess the overall response rate (p) of GCB-DLBCL patients. The null and alternative hypotheses for the overall response rate are detailed below: The null hypothesis is: H_0: p≤20%	

Part 1 Objectives	Part 1 Endpoints
	The alternative hypothesis is: H_A: p≥40% For cohort expansion of solid tumor subjects in Part 1, there is no formal statistical hypothesis being tested. Analysis of the data obtained from solid tumor expansion cohort will utilize descriptive methods only.

2.2. Part 2: Expansion

	Part 2 Objectives	Part 2 Endpoints
Primary	• To determine clinical activity of GSK2816126 in cohorts of subjects with EZH2 mutant and wild type GCB-DLBCL and tFL and subjects with MM	• Overall response rate (% of subjects achieving CR and PR per response criteria)
Secondary	• 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 GSK2816126 exposure and PD parameters	• GSK2816126 exposure markers (dose, concentration, Cmax or AUC) and PD responses. PD response assessed by change from baseline in tri-methylation of Histone H3K27 (H3K27me3)
	• 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
	• 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)
		• GSK2816126 exposure markers (e.g. dose, concentration, Cmax, or AUC) and safety/efficacy/ responses

	Part 2 Objectives	Part 2 Endpoints
	• To evaluate the relationship between exposure and safety/efficacy parameters • To begin to characterize the durability of response and progression free survival with GSK2816126	• Duration of response (DoR) • Progression-free survival (PFS)
Exploratory	• To identify biomarkers predictive of response or resistance to GSK2816126 • To investigate the mechanism of action of GSK2816126 • To investigate the relationship between genetic variants in candidate genes and the pharmacokinetics (PK) and safety profile of GSK2816126 based on Part 1 and 2 data combined	• Evaluation of wild-type (WT) subject tumors for the presence of additional, undefined, mutations in the EZH2 gene • Correlate baseline tumor genomic (DNA), protein and/or transcription (RNA) profiles with response • Evaluate transcriptional and/or protein changes upon GSK2816126 treatment • Pharmacogenomic (PGx) analysis of whole blood
Hypothesis	In Part 2, the overall response rate (p) of GCB-DLBCL and tFL patients will be assessed for each EZH2 mutation status cohort (wild type and mutant), and also for MM patients. • For each of the GCB-DLBCL and tFL cohort, the null and alternative hypotheses of the overall response rate are as following: The null hypothesis is: H_0: p≤20% The alternative hypothesis is: H_A: p≥40% • For MM cohort: The null hypothesis is: H_0: p≤10% The alternative hypothesis is: H_A: p≥25%	

3. INVESTIGATIONAL PLAN

3.1. Study Schematic

Part 1
Accelerated Dose Titration followed by 3+3 Dose Escalation
To determine the safety and tolerability of GSK2816126 in subjects with relapsed/refractory DLBCL, transformed FL, other NHLs, solid tumors and MM

Part 1 will include a cohort expansion at MTD or any dose level to enroll subjects with GCB-DLBCL and solid tumors with EZH2 inhibitor sensitizing mutations or prostate cancer

↓

Part 2
Cohort Expansion in both WT and EZH2 mutation-positive subjects
To determine clinical activity of GSK2816126 in relapsed/refractory GCB-DLBCL and tFL subjects with WT and EZH2 mutation-positive tumors and MM subjects

3.2. Discussion of Study Design

Protocol waivers or exemptions are not allowed. Therefore, adherence to the study design requirements, including those specified in the Time and Events Table (Section 7.1), are essential.

Supplementary study conduct information not mandated to be present in this protocol is provided in the accompanying Study Procedures Manual (SPM). The SPM will provide the site personnel with administrative and detailed technical information that does not impact subject safety.

This is a Phase I, open-label, multiple-dose, multicenter, dose-escalation, first-time-in-human study conducted in two parts. In Part 1, an accelerated dose titration will be employed with one subject per dose level until the first instance of a ≥Grade 2 drug related non-hematological toxicity or dose limiting toxicity (DLT) (Section 3.3.3) occurs. Exceptions for pre-specified Grade 3 non-serious non-hematological drug related adverse events that would allow continuation of accelerated dose escalation are listed in Section 3.3.1.

In the accelerated dose escalation cohorts and the 3+3 dose escalation cohorts, the dose will be escalated based on all available data, including PK data, the safety information from prior cohorts, as well as the recommended dose from a Continuous Reassessment Method [Neuenschwander-Continuous Reassessment Method (N-CRM)] analysis [Neuenschwander, 2008]. The N-CRM is a type of Bayesian adaptive dose-escalation scheme. The method is fully adaptive and makes use of all the DLT information available at the time of each dose assignment. The Fixed and Adaptive Clinical Trial Simulator (FACTS) will be used to conduct the N-CRM analysis. The DLT information

on all subjects enrolled in the trial is used to update the estimated dose-toxicity relationship and to provide supportive information in addition to the 3+3 design in the next escalation/de-escalation decision.

After the accelerated dose titration, subjects will be enrolled in a standard 3+3 dose escalation design. Dose escalation will continue until a recommended Phase 2 dose (RP2D) is determined or until a maximum tolerated dose (MTD) or a dose of 3000 mg twice-weekly is reached. Any dose level during Part 1 dose escalation may be expanded up to 12 subjects to explore safety and preliminary efficacy. At MTD/RP2D the cohort may be expanded to enroll approximately 27 GCB-DLBCL subjects and approximately 15 subjects with solid tumors containing EZH2-sensitive mutations or prostate cancer to explore additional safety and preliminary efficacy. Based on results of the Part 1 analysis in totality, Part 2 expansion cohorts may be opened.and subjectswill be assigned to cohorts based on disease and EZH2 mutation status.

Safety assessments will be performed weekly for the first 4 weeks and then at regular intervals as outlined in the Time and Events Table (Section 7.1).

Disease response in lymphoma and solid tumor subjects will be assessed as described in the T&E table (Section 7.1).

Futility and Efficacy analysis will be performed on GCB-DLBCL subjects enrolled at the MTD/RP2D in cohort expansion of Part 1 as listed in Section 12.2.1.2.

3.3. Part 1: Dose-Escalation Phase

3.3.1. Accelerated Dose Escalation

Initially, an accelerated dose titration scheme will be used starting with a dose of 50 mg [Simon, 1997]. Evaluation of at least one subject who has completed one cycle of treatment is required prior to determining the dose for the next cohort, with one cycle being defined as twice weekly dosing for three weeks and one week off. In the absence of Grade 2 or higher non-hematologic toxicity (described in Section 3.3.2.1) or a Dose Limiting Toxicity (DLT) (described in Section 3.3.3), subsequent cohorts will allow up to 100% dose escalations up to 500 mg (approximately 1/6th of the dog HNSTD). Subsequent dose escalation steps would be up to a maximum of 50% at each step (Table 1). Following the initial occurrence of a Grade 2 toxicity or DLT in a subject during the first cycle (within 28 days of dose 1), accelerated titration will transition to a standard 3+3 dose escalation.

Table 1 Dose Titration Procedures

Dose Level	Toxicity in Study	Increase in Dose
Accelerated Dose Titration Phase		
Dose Level -1		Lower doses may be used if Dose Level 1 exposure is significantly higher than predicted or if there is excessive toxicity. This may be achieved by reducing the dose or by alternate dosing schedules
Dose Level 1		Starting Dose: 50 mg
Subsequent Dose Levels	No subjects with a ≥Grade 2 toxicity (exceptions below in Section 3.3.2.1) or DLT (Section 3.3.3)	Increase by ≤100% increase in dose up to 500 mg, ≤50% increase in dose thereafter (No subjects with ≥Grade 2 drug related toxicity AND no subjects with any DLTs in first 28 days of treatment)
End of Accelerated Dose Titration Phase	One subject ≥Grade 2 drug related non-hematological toxicity in the first 28 days of treatment) or ≥Grade 3 drug related specific toxicity (See Section 3.3.2.1)	Begin 3+3 dose escalation phase (note that once 3+3 phase is initiated, the procedure may revert to the accelerated dose titration phase – see criteria below in Reverting to Accelerated Dose Titration)

3.3.2. 3+3 Dose Escalation Phase

Two additional subjects will be enrolled to the dose level at which accelerated dose titration ends, for a total of at least 3 subjects at that dose level. If no DLTs are observed in any of the 3 subjects, then dosing will proceed to the next higher dose level (≤100% increase in dose up to 500 mg, ≤50% increase in dose thereafter). An additional three subjects will be enrolled at this dose level if 1 of 3 subjects experiences a DLT. Subjects will be entered in a staggered approach with at least 7 days between each subject to minimize the risk of inadvertently exceeding the maximum tolerated dose in multiple subjects. Dose escalation decisions will be made as outlined in Table 1. Escalation to the next dose level will not increase greater than 2 fold from the previous dose level up to a dose of 500 mg. Subsequent dose escalation steps would be up to a maximum of 50% at each step. If 2 or more DLTs are observed at any dose level, the MTD will have been exceeded.

An evaluable subject in Table 2 is defined as a subject who has been on study for at least 28 days (one cycle). Evaluation of safety data from at least 1 subject during the accelerated dose titration or at least 3 subjects in the standard dose titration who have completed 28 days of dosing on study (one cycle) is required prior to defining a new dose and starting the next cohort. Once a higher dose has been cleared, subjects at lower dose levels who remain on study drug and have not experienced dose limiting toxicity will be allowed to escalate up to that level.

In the accelerated dose escalation cohorts and the 3+3 dose escalation cohorts, the dose will be escalated based on all available data, including PK data and the safety profile of prior cohorts, as well as the recommended dose from the N-CRM analysis described in Section 12.

Table 2 3 + 3 Dose Escalation Design

Number of Subjects with DLT in a Cohort	Action
0 out of 3 subjects	Escalate to the next dose level with increase ≤100% up to 500 mg, ≤50% thereafter if none of the subjects have Grade 2 toxicity (in the first 4 weeks of treatment) Escalate to next dose level with an increase of ≤50% if (in the first 4 weeks of treatment) there has been: - One or more subjects with Grade 2 toxicity
1 out of 3 subjects	Accrue 3 additional evaluable subjects at current dose level for a total of 6 evaluable subjects
1 out of 6 subjects	Escalate to the next dose level with an increase of ≤50%
2 or more subjects in a dosing cohort (up to 6 subjects)	MTD has been exceeded. Either evaluate an intermediate dose lower than current dose or expand a prior cohort up to 12 subjects

Reverting from 3+3 Dose Escalation to Accelerated Dose Titration: Once Grade 2 toxicity is seen in one subject, there are 2 scenarios where the accelerated dose escalation may be resumed.

1) If two additional subjects are added at the dose where Grade 2 toxicity was seen in the initial subject and if no Grade 2 or higher toxicity is seen in either of the 2 new subjects, the accelerated dose escalation may be resumed, or
2) If the 3+3 method is used and, at the next higher dose, the 3 subjects do not have a grade 2 or higher toxicity, the accelerated dose escalation may be resumed. (Before any decision is made to reinitiate accelerated dose titration a discussion between the investigators and the GSK medical monitor is required)

3.3.2.1. Toxicity Leading to Termination of Accelerated Titration

The following events will result in an end to accelerated dose escalation:

- Any Grade 2 or higher adverse event that is considered related to the study medication except for alopecia, drug-related Grade 3 fatigue, or asthenia; diarrhea, nausea, and/or vomiting that respond to standard medical care within 48hrs; or Grade 3 or higher electrolyte abnormalities unrelated to underlying malignancy and corrected within 48 hrs
- Grade 2 QT interval corrected for heart rate prolongation (confirmed on triplicate ECGs by manual reading)
- Grade 2 alanine aminotransferase (ALT) increase (unless clearly attributed to the underlying disease)
- Any grade adverse events that are considered in the judgment of the investigator and GSK Medical Monitor to be serious and related to the drug and requiring additional subjects to better understand the toxicity

3.3.3. Dose Limiting Toxicity

Dose-limiting toxicity (DLT): An event will be considered a DLT if it occurs within the first 4 weeks (28 days) of treatment and meets one of the following criteria (Table 3 [NCI-CTCAE, 2009]) unless it can be clearly established that the event is unrelated to treatment.

Table 3 Dose-Limiting Toxicity Criteria

Toxicity	DLT Definition
Hematologic	• Grade 4 absolute neutrophil count (ANC) for >7 days • Febrile neutropenia (according to CTCAE v.4.0 criteria) • Grade 4 thrombocytopenia or anemia for >7 days
Non-hematologic	• Grade 3 or greater nausea, vomiting, or diarrhea that does not respond to standard medical care within 48 hours • Grade 3 or greater clinically significant non-hematologic toxicity per national cancer institute - common terminology criteria for adverse events (NCI-CTCAE), v 4.0
Infusion reactions	• Infusion reactions will not be considered a DLT unless a ≥grade 3 reaction recurs after administration of optimal prophylaxis
Other	• Inability to receive >75% of scheduled doses in treatment period due to toxicity • Grade 2 or higher toxicity that does not meet the above definitions but, in the judgment of the investigator and GSK medical monitor, is dose limiting • Grade 2 or higher toxicity which occurs beyond 28 days which in the judgment of the investigator and GSK Medical Monitor is considered to be a DLT

3.3.4. Maximum Tolerated Dose

The MTD will be exceeded if 2 or more subjects in a cohort of up to 6 subjects experience a DLT.

The RP2D will be determined based on the MTD or biologically active dose (example: clinical response), the safety profile, and available PD data generated from all subjects in Part 1. If necessary, alternate schedules can be explored to determine additional biologically active doses even after a RP2D is defined.

3.3.5. Intra-subject Dose Escalation

Intra-subject dose escalations may be considered on a case-by-case basis, provided that the subject has not experienced a ≥Grade 2 drug related non-hematological toxicity or DLT in the accelerated dose escalation phase (Section 3.3.1 and Section 3.3.3), or a DLT in the 3+3 dose escalation, and contingent upon one of the following:

- A higher dose level cohort has been cleared in either the accelerated dose titration phase or the 3+3 phase.

- If a dose level has been cleared and no subjects have been identified for enrollment at the next dose level, and after the subject has completed a minimum of 8 weeks of dosing on that regimen without a DLT, that subject may be escalated to the next higher dose level after review of all safety data, and approval by a GSK Medical Monitor. In this case, the subject must follow the dosing schedule outlined in the Time and Events Table (Section 7.1) (starting at Day 1) as he/she will be the first subject exposed to the higher dose level.

Decision on intra-subject dose escalation will be made after review of all safety data and approval by a GSK Medical Monitor and discussion with the investigator. In this case, the subject may begin dosing at the higher dose level as it will have already been demonstrated to be tolerable and monitoring will be performed as described in the protocol. Subjects approved for intra-subject dose escalation may require additional limited PK and/or PD sampling as determined by GSK Clinical Pharmacology. Additional safety assessments may be specified at the time of the dose escalation or schedule modification based on the safety profile in previous subjects at the higher dose level.

3.3.6. Alternative Dosing Schedules

Alternative schedules may be evaluated based on emerging data. Less frequent dosing schedules (e.g., once weekly) may be implemented without an amendment if emerging data suggest that twice weekly administration will result in excessive toxicity or if PD data suggest less frequent administration may be warranted. In this case, the starting dose would be one dose level above the highest dose which has been determined to be tolerable when administered twice weekly. In addition, alternative dosing schedules which result in increased frequency of administration may be considered if the safety, PK, and PD data suggest that a sufficient therapeutic exposure cannot be achieved using the initial dosing schedule; this would require a protocol amendment. Dose escalation will continue using the guidelines outlined in Table 2.

3.3.7. Part 1: Futility and Efficacy Analysis for GCB-DLBCL Subjects

There will be a GCB-DLBCL expansion cohort enrolled after the completion of dose escalation in Part 1. For the GCB-DLBCL expansion cohort in Part 1, futility and efficacy evaluation of overall response data will be performed in order to support the early decision regarding opening Part 2 dose expansion. The methodology is based on the Bayesian predictive probability of success if enrollment continues until all planned subjects are recruited [Lee, 2008]. Details of the predictive probability methodology, futility and efficacy evaluation are explained in Section 12.2.1.2. In summary, a minimum of 13 and maximum of 27 GCB-DLBCL patients will be enrolled. Once 13 GCB-DLBCL patients at MTD/RP2D have been enrolled (including patients in dose escalation phase) and have completed response assessments of safety and efficacy, response data will be reviewed on an ongoing basis for evidence of futility or efficacy.

For futility/efficacy analysis, subjects evaluable for response assessment will be defined by any or all of the following criteria:

- Subjects who have at least two post-baseline radiological disease assessments and have been on study for at least 28 days (one cycle)

- Subjects who have progressed or have died or have withdrawn from study treatment due to any reason.

Interim analysis (IA) of futility and efficacy can be conducted at any time after 13 GCB-DLBCL subjects have enrolled and are evaluable for response assessment. If the thresholds for futility are met, the Part 1 expansion cohort may be stopped based upon the evaluation of the totality of the data. If the efficacy thresholds are reached, then Part 2 expansion may be opened. If neither futility nor efficacy thresholds are met at any interim analysis, and the totality of the data does not support continuation of the trial, then the trial may be terminated. All available data will be considered in making decision of termination or continuation of the trial.

3.4. Part 2: Expansion Cohorts

Part 2: Expansion Cohorts in both wild type and EZH2 mutation-positive GCB-DLBCL and tFL subjects, and subjects with MM

The primary objective of Part 2 is to investigate whether administration of GSK2816126 at the RP2D has a potentially clinically meaningful activity for more tumor types, if notable response rate is observed in Part 1 expansion cohort of GCB-DLBCL patients. Expansion cohorts will be enrolled in Part 2, including GCB-DLBCL and tFL patients with mutant and wild type EZH2 and patients with MM. Similar to Part 1 expansion design, Part 2 expansion design is planned based on predictive probability methodology. Rather than early stop for either futility or efficacy, Part 2 allows early stop for futility only. For each expansion cohort of GCB-DLBCL and tFL patients, a minimum of 10 and maximum of 32 patients will be enrolled at the RP2D. For MM cohort, a minimum of 14 and maximum of 40 patients will be enrolled at the RP2D. Interim analysis of response data will start from minimum number of patients enrolled and at any time thereafter. Details of Part 2 designs and stopping criteria are elaborated in Section 12.2. All available data will be considered in making decision of termination or continuation of the trial.

It is noted that patients with GCB-DLBCL, tFL and MM enrolled at MTD/RP2D in the previous stages of the trial (dose escalation and cohort expansion in Part 1) will be included for the Part 2 analysis.

3.4.1. Part 2 PK/PD cohort:

In Part 2 a cohort of up to 12 subjects may be enrolled at RP2D to collect adequate data on safety, pharmacokinetics, or pharmacodynamics. Urine, bile, and additional blood samples may be collected following repeated administration for drug metabolite profiling and to obtain information on renal excretion of GSK2816126. Mandatory collection of pre- and post-treatment tumor biopsies will be required for enrollment in a PK/PD cohort

3.5. Rationale

3.5.1. Rationale for Study

Enhancer of zeste homolog 2 (EZH2), a component of the Polycomb Repressor Complex 2 (PRC2), mediates transcriptional repression of target genes through tri-methylation of histone H3 on lysine 27 (H3K27me3). EZH2 and H3K27me3 are dysregulated in many cancers through diverse pathways. While EZH2 mutation plays a significant role in progression of certain lymphomas, data from prostate, breast, and several other solid tumors have demonstrated that increased EZH2 expression correlates with increased aggressiveness of tumors and poor prognosis.

GSK2816126 is a selective and potent inhibitor of wild-type and mutant EZH2 capable of decreasing H3K27me3 levels in all cell types examined. EZH2 inhibition has been shown to decrease the growth of several cell lines derived from EZH2 wild type (WT) and mutant lymphomas, SNF5-mutant malignant rhabdoid tumors, multiple myeloma, AML, neuroblastoma, prostate, breast, skin and colon cancers.

Most of these cancers have an overall poor outlook either because of lack of any effective therapy or standard therapies do not result in a durable remission. This first study of this agent will be conducted in subjects with non-Hodgkin lymphomas, especially germinal center B-cell diffuse large B-cell lymphoma (GCB-DLBCL) and transformed follicular lymphoma (t-FL), and subjects with multiple myeloma or solid tumors who have relapsed or are refractory to prior therapies and have a high degree of unmet medical need in terms of available treatment options.

3.5.2. Rationale for Population

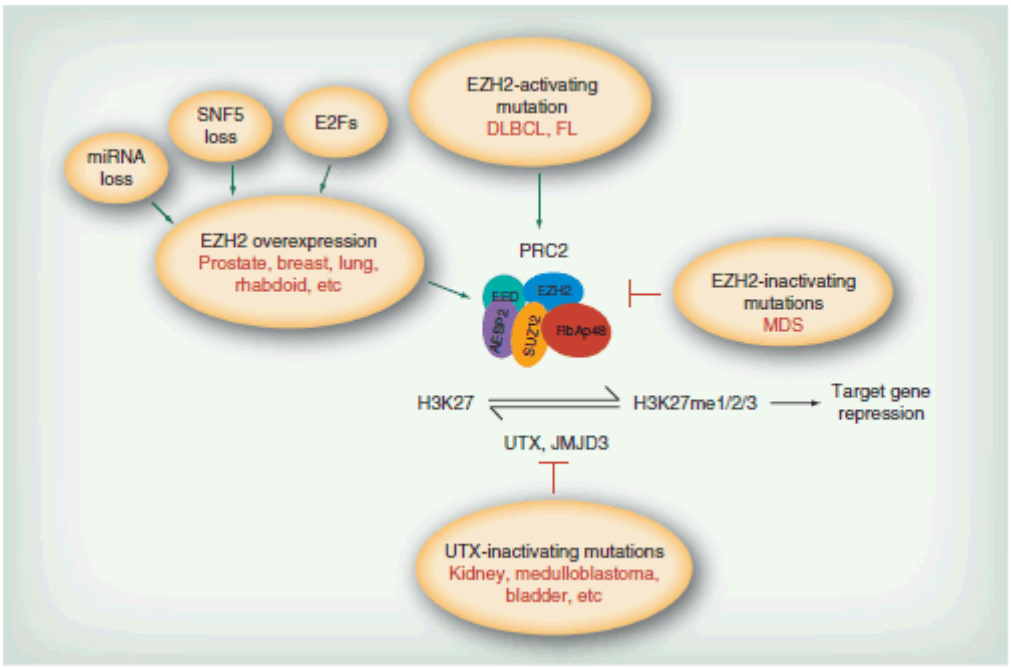
Preclinical studies demonstrate that B-cell lymphomas of DLBCL origin with EZH2 activating mutations are the most sensitive to GSK2816126; however, the growth of a subset of EZH2 wild-type lymphomas, SNF5-mutant malignant rhabdoid tumors, multiple myeloma, AML, neuroblastoma, prostate, breast, skin, and colon cancers are also sensitive to EZH2 inhibition. There is increasing evidence that a large number of solid tumors or subtypes may be driven by EZH2 mutation or over expression. Often, these tumors have poor prognosis. Therefore, the study includes subjects with non-Hodgkin Lymphoma and enriched for subsets (GCB-DLBCL, tFL) as well as multiple myeloma and solid tumors that have relapsed or are refractory to prior treatment with standard of care or do not have standard of care available or refuse standard of care therapy.

Part 1 will be comprised of 2 phases:

- Part 1 dose escalation which will include subjects with MM, relapsed/refractory tFL and DLBCL, other NHLs and solid tumors , and
- Part 1 cohort expansion at the highest tolerated dose/MTD which will include a cohort of subjects with relapsed/refractory GCB-DLBCL and a cohort of subjects with prostate cancer or solid tumors containing EZH2 inhibitior sensitizing mutations.

Part 2 will be comprised of cohort expansions in subjects with GCB-DLBCL, transformed follicular lymphoma and multiple myeloma.

EZH2 and H3K27me3 are dysregulated in nearly all cancers through numerous pathways including 1) recurrent gain-of-function heterozygous mutations in germinal center B-cell (GCB) DLBCL, FL, melanoma, and parathyroid adenoma, 2) EZH2 over-expression in numerous other aggressive tumors including those from prostate, breast, lung, liver, bladder, head and neck, skin, and kidney, and 3) inactivating mutations in UTX. H3K27 demethylase that acts in opposition to EZH2, described in numerous tumor types including transitional cell bladder carcinoma, esophageal squamous cell carcinoma, renal cell carcinoma, multiple myeloma, and subgroup 4 medulloblastoma [McCabe, 2014]. Furthermore, data from prostate, breast, and several other tumor types have demonstrated that increased EZH2 expression correlates with increased aggressiveness of tumors and poor prognosis [GlaxoSmithKline Document Number 2013N169204_04, 2017]



McCabe, 2014

Table 1. Tumor types harboring EZH2-activating mutations.

Tumor type	Tumor subtype	Mutated	Total	Frequency (%)	Mutations observed	Ref.
Lymphoma	NHL	33	127	26.0	*1 A677G* *1 A687V* *31 Y641X*	[28]
	DLBCL	4	25	16.0	*Y641X*	[32]
		5	35	14.3	*Y641X*	[33]
		5	41	12.2	*1 A677G* *4 Y641X*	[12]
		31	320	9.7	*Y641X*	[13]
		1	73	1.4	*Y641X*	[34]
	GCB DLBCL	18	83	21.7	*Y641X*	[13]
	ABC DLBCL	0	42	0.0	*Y641X*	[13]
	FL	101	366	27.6	*7 A677G* *5 A687V* *50 Y641X*	[26]
		12	55	21.8	*Y641X*	[33]
		9	60	15.0	*Y641X*	[32]
		26	221	11.8	*Y641X*	[10]
		18	251	7.2	*Y641X*	[13]
	Burkitt lymphoma	0	23	0.0	*Y641X*	[33]

With regard to haematological indications for GSK2816126, preclinical studies demonstrate that B-cell lymphomas of DLBCL with EZH2 activating mutations are the most sensitive to GSK2816126. Approximately 22% of GCB-DLBCL tumors have an EZH2-activating mutation, whereas ABC DLBCL does not contain EZH2- activating mutations (McCabe, 2014). Early follicular lymphoma lesions have been shown to have EZH2 mutations, as well as mutations in other genes that disrupt chromatin structure [Friedberg, 2015].

Of particular interest is that there is some data to suggest that certain tumor types may respond to EZH2 inhibitors regardless of EZH2 inhibitor sensitizing status. Data presented at ASH Lymphoma Biology 2016 [Morschhauser, 2016] suggests that patients who have DLBCL (both GCB or nonGCB) and EZH2 mutated FL who are treated with the EZH2 targeted agent tazemetostat can achieve responses, providing proof of concept in DLBCL. Patients with GCB-DLBCL were analysed by EZH2-mutation status. Of patients with EZH2 mutation 1/5 had a PR [Overall Response Rate (ORR)=20%]. Of those without a mutation, 3/19 had PR or CR (ORR=15.7%; 2 with CR). Therefore, Part 1 cohort expansion in GCB-DLBCL will enroll patients regardless of EZH2 related mutation status.

Neuroendocrine prostate cancer (NEPC) is a subtype of castration-resistant prostate cancer associated with aggressive clinical features and poor overall survival (Wang, 2014). Mounting evidence suggests that NEPC evolves from prostate adenocarcinoma as one mechanism of resistance to androgen. Data from metastatic biopsies obtained from patients progressing on abiraterone or enzalutamide suggests that at least 10% of patients with late-stage castration-resistant prostate adenocarcinoma (CRPC) eventually develop small-cell NEPC. NEPC cancer is driven by N-Myc. N-Myc in turn drives EZH2, making neuroendocrine prostate cancer sensitive to inhibition [Dardenne, 2016]. Additionally,

EZH2 has been described as an epigenetic driver of aggressive prostate cancer. EZH2 dysregulation may be involved in the progression from early prostate cancer to late [Yang, 2013]. One of the most prevalent genetic modifications observed in prostate cancer is the fusion between the TMPRSS2 and ERG genes, resulted from an abnormal translocation on chromosome 21. Detected in more than half of all prostate tumors, this fusion gene consisting of the androgen-responsive TMPRSS2 promoter and the ERG coding region is able to substantially upregulate ERG expression, which has been proven to induce cell proliferation and invasion [Kumar-Sinha, 2008]. Notably, it has been demonstrated that ERG can directly activate EZH2, which synergistically result in cancer progression through histone methylation linked de-differentiation [Yu, 2010]. Several studies have also confirmed that expression of EZH2 shows a correlated pattern with the stage of prostate cancer development [Berezovska, 2006; Saramaki, 2006; Hoffmann, 2007].Therefore, subjects with prostate cancer will be enrolled regardless of EZH2 related mutation status.

This study of GSK2816126 will focus primarily on the GCB-DLBCL NHL in order to ascertain a clinical benefit in a defined tumor type, for which there is high probability of potential benefit. However, solid tumors with changes to EZH2 inhibitor sensitizing mutations will be evaluated. These will be targeted as it is felt that they are most likely to show benefit. The exception in the solid tumor cohort will be prostate cancer, for which no mutation status will be required.

3.5.3. Rationale for Dose and Schedule

The doses of GSK2816126 for evaluation in this study were selected based on available preclinical biology, toxicology, and pharmacokinetic data as well as predicted pharmacokinetic and response information for humans. Refer to the IB for more information [GlaxoSmithKline Document Number 2013N169204_04, 2017].

Human Pharmacokinetic Extrapolation

Whole blood human clearance was predicted from three species (mouse, rat and dog) using maximum life span power-law allometry to be around 8.2 ml/min/kg. Volume of distribution was predicted from simple power-law allometry to be 4.8 L/kg and half-life around 6.5 hours. A 70 kg adult therefore has a predicted total clearance of 35 L/hr and a total volume of distribution of 336 L.

Starting Dose and Infusion Duration

Three approaches have been considered to establish the starting dose for GSK2816126 in hematological malignancies assuming a 70 kg adult with a surface area of 1.7 m^2.

- <u>One tenth of the rat STD10 as per ICH S9 guidance</u>

  The STD10 in the rat was defined as 100 mg/kg administered over 6-hour infusion twice-weekly for 2 to 4 weeks. One-tenth (1/10) of the rat STD10 is 60 mg/m^2. These doses were well tolerated in dogs. A starting dose based on 1/10 of the rat STD10 would be 110 mg using the human equivalent dose calculation.

- One sixth of the dog HNSTD as per ICH S9 guidance

  Based on tolerability, the HNSTD in the dog was defined as 100 mg/kg administered as an 8–hour infusion twice-weekly for 4 weeks. A starting dose based on 1/6 of the dog HNSTD would be 610 mg using the human equivalent dose calculation.

- The minimum anticipated biologically effective dose

  A daily dose of 15 mg/kg or twice-weekly dose of 50 mg/kg in the Pfeiffer xenograft mouse model resulted in minimum target engagement as measured by a 15% reduction in H3K27 tri-methylation and 35% to 38% tumor growth inhibition. The minimum anticipated biologically effective dose is 287 mg twice-weekly based on providing similar free exposure while the dose would be 800 mg based on providing similar total blood exposure.

An infusion duration of 2-hours is proposed for this clinical study. This infusion duration is shorter than the infusion duration used in animals but can be justified based on the following points:

- With infusion of a volume of 250 mL over 2 hours, GSK2816126 doses up to 1250 mg will provide infusion concentration up to the infusion concentration of 5 mg/mL used in dogs while doses up to 2500 mg will provide infusion concentration up to the concentration of 10 mg/mL used in rats. A 3000 mg dose would provide an infusion concentration of 12 mg/mL.
- The infusion will be performed into a larger (central) vein in humans than in animals. A shorter infusion duration and higher local blood flow would lead to a shorter exposure of the local area of the vein to high concentrations of GSK2816126.
- The main factor for the long infusion duration in animals was the histamine-release like reaction. Subjects will be monitored during the infusion for evidence of histamine release related symptoms/infusion reactions and treated as needed with supportive care per local standard of care (e.g., corticosteroids, oxygen, epinephrine, diuretics, IV fluid). The infusion duration can be lengthened with restart of the infusion or at the next infusion. Premedications (antihistamines or similar) may be provided at the next infusion or prior to treatment of new subjects.

Taking all three approaches into consideration and the shorter infusion duration of 2-hours, a starting dose of 50 mg twice-weekly as a 2-hour infusion is proposed. This dose provides a predicted total blood AUC of 1.43μg.h/mL and a total blood Cmax of 0.428 μg/mL. The AUC is 38-fold lower than the AUC (0-24hr) for the rat STD10 of 100 mg/kg, 18-fold lower than the AUC at the lowest tested dose in rat (30 mg/kg), and 56-fold lower than the AUC for the dog HNSTD of 100 mg/kg. The Cmax is 18-fold lower than the Cmax for the rat STD10 of 100mg/kg, 6.9-fold lower than the Cmax at the lowest tested dose in rat (30 mg/kg), and 23-fold lower than the Cmax for the dog HNSTD of 100 mg/kg. The starting dose of 50 mg will provide a suitable safety margin for the anticipated toxicities, while minimizing the number of subjects with aggressive lymphomas exposed to sub-therapeutic doses.

Predicted Effective Dose and Dosing Frequency

The potential therapeutic dose for GSK2816126 in human was derived using available preclinical, PK and efficacy data from Karpas-422 and Pfeiffer tumor xenograft studies. Based on PK/PD modeling of Karpas-422 and Pfeiffer xenograft data, tumor eradication with GSK2816126 could be achieved in mice with an average total blood concentration target over the dosing interval of 1 ug/mL or an average free concentration of 16ng/mL. This free concentration is similar to the in vitro exposure producing 50% of the maximum effect (EC_{50}) obtained in Karpas-422 or Pfeiffer cell lines and to the average free concentration obtained with 50 mg/kg dosed daily in Karpas-422 xenograft model where more than 90% tumor growth inhibition was observed. This average free concentration could be achieved on average with twice-weekly administration of 950 mg in humans. Due to species differences in protein binding and blood to plasma partitioning, a dose of up to 2700 mg could be needed to achieve the average total blood concentration target of 1 ug/mL.

The rationale for the proposed schedule of twice weekly, 3 weeks on / 1 week off for each 28-day cycle is based on preclinical *in vivo* observations. Briefly, mice with Pfeiffer tumor xenograft were treated daily with 50 mg/kg for 10 days. Tumor H3K27 tri-methylation levels were measured and tri-methylation inhibition was observed up to 5 days after the last administration. Using *in vivo* murine tumor xenograft models, schedules with progressively longer dosing intervals (i.e., from daily to once or twice-weekly to intermittent twice-weekly dosing with 2 weeks on/ 1 week off) were evaluated. Similar tumor growth inhibition were observed for the same total weekly dose, regardless of dosing frequency, except for lower tumor growth inhibition being observed with once weekly dosing.

Taken together, these data support a schedule of twice weekly, 3 weeks on / 1 week off.

3.6. Study Treatment

3.6.1. Treatment Assignment

- This is an open-label study
- Subjects will be identified by a unique subject number that will remain consistent for the duration of the study

3.7. Dosage and Administration of Study Treatment

Due to the risk of infusion site reaction and/or infusion rate/concentration dependent histamine reactions, central venous access such as a port, Hickmann catheter or PICC line will be required.

GSK2816126 will be administered initially twice-weekly 3 weeks on / 1 week off of each 28-day cycle. The dose of the study treatment is discussed in Section 3.3 and Section 3.4.

Investigational product (IP) details are provided in Table 5. It will be diluted in saline or D5W to a fixed 250 mL volume. This volume will be infused over a minimum of 2 hours (up to 4 hours). Additional details are provided in the SPM.

3.8. Safety Management Guidelines

3.8.1. QTcF Stopping Criteria

The QTcF is the QT interval corrected for heart rate according Fridericia's formula (QTcF).

- For eligibility and withdrawal, subjects QTcF value will be used.
- For purposes of data analysis, QTcF values will be used.

If a subject that meets the corrected QTcF[1] interval duration criteria below, study treatment(s) will be withheld.

- QTcF interval ≥500 msec; GSK2816126 will be permanently discontinued.
- QTcF interval increase from baseline ≥60 msec and maximum QTcF <500 msec; GSK2816126 may be restarted one dose level lower once the QTcF returns to baseline. If QTcF prolongation meeting stopping criteria recurs after re-challenge, GSK2816126 must be permanently discontinued.

[1]Based on average QTcF value of triplicate electrocardiograms (ECGs) to include manual over-read. For example, if an ECG demonstrates a prolonged QTcF interval, obtain 2 additional ECGs over a brief period (e.g., within approximately 10 minutes of the abnormal ECG, if possible, and approximately 10 minutes apart from each other), and then use the averaged QTcF values of the 3 ECGs to determine whether the subjects should have study treatment discontinued.

3.8.2. Infusion Reaction Stopping Criteria and Management

A subject may be withdrawn from treatment with GSK2816126 for safety-related reasons if the following criteria are met:

- Occurrence of a ≥Grade 3 infusion-related reaction that does not resolve to ≤Grade 1despite adequate clinical intervention and prevents re-initiation of the infusion on any given treatment day

3.8.2.1. Management of Infusion Reactions

Infusion Related Reaction

Infusion Related Reaction	**Grade 1**: Continue infusion and closely monitor the subject **Grade 2/3**: Temporarily interrupt study medication and: - Administer diphenhydramine or similar anti-histamine - Provide supportive care per local standard of care (e.g., corticosteroids, oxygen, epinephrine, diuretics, IV fluid) - May resume infusion once resolved to ≤grade 1* - For grade 3 reactions, corticosteroids may be considered **Grade 4**: - Discontinue infusion. Administer diphenhydramine, corticosteroids and supportive care per local standard of care - May consider restarting study treatment at a reduced dose or dose level pre-event based on discussion with GSK Medical Monitor

*Recommend following institutional guidelines for re-starting after infusion reactions seen with cytotoxic therapy. A general guideline would be as follows:

- Restart under observation at an infusion rate of 25% of the original rate for the first 30 minutes

- If no reaction, increase infusion rate by 25% of the original rate every half hour until full dose administered

- If Grade 1 reaction, continue at the rate at which the reaction occurs

-If Grade 2 or 3 infusion related reaction consider premedication for all subsequent infusions per local standard of care.

3.8.3. Dose Adjustment for Non-Hematologic Toxicity

See Table 4 Dose Adjustment Guideline for drug related non-hematologic toxicities based on worst grade.

Table 4 Dose Adjustment Guideline for Drug Related Non-Hematologic Toxicity

Worst Grade	Dose Adjustment
G1	No change in dose
G2	Continue dosing with no change OR Consider holding for up to 2 weeks for toxicity to resolve to baseline or ≤ Grade 1, then continue at the same dose OR dose reduce to 1 dose level lower per dose escalation scheme if the toxicity is considered a DLT.
G3 and 4	Hold for up to 2 weeks for toxicity to resolve to baseline or ≤Grade 1, then dose reduce to 1 dose level lower per dose escalation scheme If no recovery to ≤Grade 1* or baseline after 14 days, patient should be withdrawn.

If the non-hematologic toxicity or event resolves to baseline or ≤ Grade 1 within 14 days of stopping therapy, treatment with GSK2816126 may be restarted at 1 dose level lower than the current dose. For a non-DLT, the treatment with GSK2816126 could restart at a full dose, if deemed appropriate.

If the non-hematologic toxicity does not resolve to ≤Grade 1 or baseline within 14 days, the subject should be withdrawn from the treatment permanently (Section 6.3). However, if the investigator and GSK Medical Monitor agree that further treatment will benefit the subject, treatment can restart at 1 dose level lower and under weekly clinical monitoring. If the toxicity resolves to ≤Grade 1 or baseline, the dose may be resumed to the initial dose level.

3.8.4. Dose Adjustment for Hematologic Toxicity

3.8.4.1. For subjects with lymphoma and multiple myeloma:

The treatment may be held for 2 weeks if:

- neutrophil and platelet count did not recover to neutrophils $\geq 0.5 \times 10^9$/L and platelets $\geq 25 \times 10^9$/L

The treatment may resume as soon as count recovery has occurred (i.e., neutrophils ≥0.5 and platelets $\geq 25 \times 10^9$/L).

When the treatment resumes, the dose may be adjusted based on platelet count, i.e., dose can be reduced by 1 or 2 dose levels when the platelet count $\leq 25 \times 10^9$/L (G4 thrombocytopenia) and it is not attributed to the disease. If a subject has persistent G4 thrombocytopenia for 4 weeks not attributed to disease or requires platelet transfusions for bleeding in the absence of the disease, the subject will be withdrawn from the study.

For non drug-related hematologic toxicity institutional guidelines for re-starting may be followed.

3.8.4.2. For subjects with solid tumors:

Thrombocytopenia:

- Grade 1 & 2 (platelet count ≥50,000): Continue dosing at same dose level with weekly or more frequent monitoring as necessary.

- Grade 3 (platelet count between 25,000 to <50,000): After discussion with medical monitor and using sound clinical judgement, continue at same dose or consider dose interruption until count recovery to Grade 2 or less. Monitor platelet count at a minimum of twice weekly.

- Grade 4 (platelet count below 25,000): Interrupt study medication and monitor platelet count every 2-3 days. If platelet counts recover to Grade 2, discuss with medical monitor resuming treatment at the same or adjusted dose based on sound clinical judgement. Platelet transfusion is allowed based on institutional guidelines. In case of platelet transfusion, hold drug for at least 7 days from day of transfusion, and if platelet counts recover to Grade 2 consider initiating treatment at a lower dose using sound clinical judgement and after consulting with the GSK medical monitor. Discontinue treatment if drug has to be held for >14 days or greater than 2 dose reductions required.

3.9. Guidelines for Events of Special Interest and Dose Modifications

3.9.1. Dose Modifications

Dose reductions for GSK2816126 will depend on their starting dose. If a subject has a dose reduction for toxicity the dose will be reduced by one dose level . Approval from the GSK Medical Monitor is required to restart a dose after 14 days of dose interruption. Following a dose reduction subjects may be re-escalated to a higher dose level with the approval of the GSK Medical Monitor if the toxicity has resolved.

4. INVESTIGATIONAL PRODUCT

The term 'study treatment' is used throughout the protocol to describe the investigational product received by the subject as per the protocol design.

4.1. Description of Investigational Product

Table 5 Investigational Product

Product name:	GSK2816126 Injection,15 mg/mL, 30 mL vial with 25 mL fill volume
Formulation description:	Solution containing 15 mg/mL GSK2816126 in water for Injection, methanesulfonic acid, Captisol and acetic acid
Dosage form:	A solution stored at 2-8°C, protected from light
Unit dose strength(s)	15 mg/mL
Route/ Regimen	Delivered as an intravenous solution over 2 - 4 hours Study drug can be diluted into saline or dextrose for a final volume of 250ml at ambient temperature and normal room lighting up to 12 hours prior to infusion. PVH, PE and PA bags and tubing are all acceptable
Physical description:	A clear, pale yellow coloured solution, essentially free from visible particles of foreign matter

GSK2816126 will be provided to sites by GSK. The contents of the label will be in accordance with all applicable regulatory requirements.

4.2. Preparation/Handling/Storage of GSK2816126 GSK Investigational Product

Preparation

Under normal conditions of handling and administration, IP is not expected to pose significant safety risks to site staff. A Material Safety Data Sheet (MSDS) describing the occupational hazards and recommended handling precautions will be provided to site staff if required by local laws or will otherwise be available from GSK upon request.

In the case of unintentional occupational exposure notify the study monitor, the GSK Medical Monitor and/or the study manager.

Take adequate precautions to avoid direct eye or skin contact and the generation of aerosols or mists.

Refer to the Study Procedures Manual (SPM) for detailed procedures for the disposal and/or return of unused study treatment(s).

Storage

GSK2816126 must be stored in a secure area under the appropriate physical conditions for the product. Access to and administration of the GSK2816126 will be limited to the investigator and authorized site staff. GSK2816126 must be dispensed or administered only to subjects enrolled in the study and in accordance with the protocol.

GSK2816126 is to be stored protected from light in 30 mL Type 1glass vials, at a temperature range of [2°C/36°F to 8°C/46°F]. Maintenance of a temperature log (manual or automated) is required.

4.3. Product Accountability

In accordance with local regulatory requirements, the investigator, designated site staff, or head of the medical institution (where applicable) must document the amount of IP dispensed and/or administered to study subjects, the amount returned by study subjects, and the amount received from and returned to GSK, when applicable. Product accountability records must be maintained throughout the course of the study. Refer to the SPM for further detailed instructions on product accountability.

4.4. Treatment Compliance

When subjects are dosed at the study site, they will receive study treatment directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents. The dose of study treatment and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study treatment.

GSK2816126 will be intravenously administered to subjects at the study site. Administration will be documented in the source documents and reported in the electric case report form (eCRF). Treatment start and stop dates, including dates for treatment delays and/or dose reductions will also be recorded in the eCRF.

4.5. Treatment of Investigational Product Overdose

In the event of an overdose (defined as administration of more than the protocol-specified dose) of GSK2816126 the investigator should:

- Contact the GSK Medical Monitor immediately
- Closely monitor the subject for AEs/SAEs and laboratory abnormalities until GSK2816126 can no longer be detected systemically
- Obtain a plasma sample for PK analysis within 24 hours from the date of the last dose of study treatment if requested by the GSK Medical Monitor (determined on a case-by-case basis)
- Document the quantity of the excess dose as well as the duration of the overdosing in the eCRF

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the GSK Medical Monitor based on the clinical evaluation of the subject.

5. STUDY POPULATION

5.1. Number of Subjects

A maximum of approximately 250 subjects will be enrolled. See Section 12.2 for sample size assumptions.

The number of dose levels and the level at which the RP2D [or maximum tolerated dose (MTD) or maximum feasible dose (MFD)] is reached cannot be determined in advance. An adequate number of subjects will be enrolled into the study to establish the recommended dose(s) for further study. It is estimated that approximately 40 subjects will be enrolled into Part 1 dose-escalation of the study. Additionally in Part 1 cohort expansion, approximately 27 GCB-DLBCL subjects and approximately 15 solid tumor subjects containing EZH2 inhibitor sensitizing mutations or subjects with prostate cancer will be enrolled.

Approximately up to 168 subjects will be enrolled in Part 2 in five expansion cohorts: two GCB-DLBCL cohorts with up to 32 subjects from the EZH2 wild-type population, and up to 32 subjects from the EZH2 mutation positive population, and two tFL cohorts with up to 32 subjects from the EZH2 wild-type population and up to 32 subjects from the EZH2 mutation positive population and up to 40 subjects in the MM cohort. Additional subjects/cohorts may be enrolled to allow for evaluation of additional dose levels.

In Part 1 (dose-escalation) of the study, if subjects prematurely discontinue, additional subjects may be enrolled and assigned to the same treatment sequence at the discretion of the Sponsor in consultation with the investigator. Subjects will not be replaced in Part 2 (expansion cohort) of the study.

5.2. Subject Selection Criteria

5.2.1. Part 1 Inclusion Criteria

Deviations from inclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

Subjects eligible for enrollment in the study must meet all of the following criteria:

1. Provided signed written informed consent.

2. Males and females ≥18 years of age (at the time consent is obtained).

3. Tumor type criteria

- Relapsed/refractory non-Hodgkin's lymphoma (NHL) that meets the following criteria:
    - Germinal Center B cell Diffuse large B cell lymphoma (GCB-DLBCL) relapsed or refractory to at least one prior regimen (e.g., rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone [R-CHOP]) AND not a candidate for standard salvage regimens or autologous or allogeneic stem cell transplant. Local confirmation of lymphoma subtype GCB-DLBCL is allowed for enrollment but must be confirmed through central laboratory testing.

- Solid tumors that meet the following criteria:
    - Measurable disease by RECIST 1.1 in at least 1 site
        - For Castrate Resistant Prostate Cancer (CRPC) measurable disease can also include PSA level (see below)
    - Disease progression with the last line of therapy and at least one prior standard of care regimens, or tumor for which there is no approved therapy, or for which standard therapy is unsuitable or refused.
    - Mutation Status:
        - Solid tumor types, other than prostate, must have one of the following EZH2 inhibitor sensitizing mutations as determined via local testing:
            - An activating mutation in EZH2 (Y641F/C/S/H/N, A677V/G, and/or A687V
            - Loss of a component of the SWI/SNF complex, including, but not limited to, ARID1A, SMARCB1 (aka SNF5/INI1/BAF47), SMARCA4 (aka BRG1), or PBRM1 (aka PB1) as determined by molecular testing (bi-allelic loss or mutation) or immunohistochemistry
            - Loss of BAP1 (ubiquitin carboxy-terminal hydrolase) as determined by molecular testing (bi-allelic loss or mutation) or immunohistochemistry
    - CRPC subjects:
        - Must have measurable disease by either:
            - RECIST1.1 (see Appendix 5) or,
            - A minimum PSA of 5 ng/mL
        - Disease progression on last line of therapy and must have progressed on abiraterone, enzalutamide, or taxane chemotherapy
        - Subjects may continue GnRH agonists
        - Small cell prostate cancer is eligible

4. For all subjects: Availability of archival tissue, or willingness to undergo fresh biopsy if archival tissue is not available as described in Section 7.6.1.1,Section 7.6.1.2 and Section 7.6.5.
5. Must have a pre-existing central venous access such as a port, Hickmann catheter, or a peripherally inserted central catheter (PICC line) or be willing and able to have one inserted.
6. ECOG Performance Status of 0 or 1 (see Appendix 2).
7. Men with a female partner of childbearing potential must have either had a prior bilateral vasectomy with resultant azoospermia, bilateral orchiectomy, or must agree to use one of the contraception methods listed in Section 10.1 from the time of the first dose of study medication until at least 2 weeks (14 days) after the last dose of study treatment due to long elimination phase.
8. A female subject is eligible to participate if she is of:
    - Non-childbearing potential as defined in Section 10.1.1
    - Child bearing potential as defined in Section 10.1.1 and agree to use effective contraception, as defined in Section 10.1, for an appropriate period of time (as determined by the product label) prior to the start of dosing to sufficiently minimize the risk of pregnancy and for at least 2 weeks (14 days) following the last dose of study treatment. Women of childbearing potential must have a negative serum pregnancy test within 7 days of first dose of study treatment followed by negative urine or serum pregneancy test once every 4 weeks (prior to next dose cycle) thereafter.
9. Adequate organ system function as defined below:

System	LABORATORY VALUES
Hematologic	
ANC Hemoglobin Platelets PT/INR and PTT	≥1.2 x 10^9/L ≥9 g/dL ≥75x 10^9/L ≤1.5 x ULN
Hepatic	
Albumin Total bilirubin AST and ALT	≥2.5 g/dL ≤1.5 times ULN ≤2.5 times ULN without liver metastases ≤5 times ULN if documented liver metastases
Renal	
Calculate Creatinine Clearance[a, b]	≥50 mL/min
Reproductive/Endocrine for CRPC only	
Testosterone	<50 ng/dL (only for subjects with CRPC)
Cardiac	
Left Ventricular Ejection Fraction (LVEF)	≥LLN (minimum of 50% LVEF) by ECHO or MUGA[c]

Abbreviation(s): ANC, absolute neutrophil count; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ECHO, echocardiogram; INR, international normalization ratio, MUGA, multigated (radionuclide) angiogram; PT, prothrombin time, PTT, partial thromboplastin time, ULN, upper limit of normal , LLN, lower limit of normal.

a. Calculated by Cockcroft-Gault formula
b. For MM subjects, adequate renal function is defined as calculated creatinine clearance ≥30 mL/min.
c. ECHO is the preferred method and should always be used if available

NOTE: Laboratory results obtained during Screening should be used to determine eligibility criteria. In situations where laboratory results are outside the permitted range, the investigator may opt to retest the subject and the subsequent within range screening result may be used to confirm eligibility.

5.2.2. Part 2 Inclusion Criteria

1. In addition to inclusion criteria listed for Part 1, Part 2 will enroll **GCB-DLBCL, tFL and MM subjects only.**
    - Relapsed and/or refractory MM or tFL that have failed prior standard therapy and for which there is no standard salvage regimen
2. Lymphoma subjects will be required to undergo EZH2 mutation testing. This will require availability of archival tissue, or willingness to undergo fresh biopsy, for central testing of EZH2 mutation status.
3. Based on the results of the mutation test, lymphoma subjects may be enrolled in one of four cohorts:
    - GCB-DLBCL EZH2 mutant cohort:
        - Tumors must contain one, or more, of the following EZH2 activating mutations: Y641F; Y641N; Y641S; Y641H; Y641C; A677G; and/or A687V
    - GCB-DLBCL EZH2 wild type cohort:
        - Tumors that do not contain one of the above mutations
        - Subjects with tumors harboring EZH2 mutations other than the seven outlined above will be enrolled in the EZH2 wild type cohort
    - tFL EZH2 mutant cohort:
        - Tumors must contain one, or more, of the following EZH2 activating mutations: Y641F; Y641N; Y641S; Y641H; Y641C; A677G; and/or A687V
    - tFL EZH2 wild type cohort:
        - Tumors that do not contain one of the above mutations
        - Subjects with tumors harboring EZH2 mutations other than the seven outlined above will be enrolled in the EZH2 wild type cohort

5.2.3. Part 1 and 2 Exclusion Criteria

Deviations from exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

Subjects meeting any of the following criteria must not be enrolled in the study:

1. Receiving any cancer therapy within 2 weeks of first dose (including surgery and/or tumor embolization)

   Note: the following are allowed:

   - Corticosteroids to control systemic or local symptoms, up to a dose of 10 mg prednisone or equivalent daily and stable for at least 7 days **pri**or to enrollment.
   - Subjects with prostate cancer may remain on GnRH agonists. Other hormonal therapies (e.g., bicalutamide, abiraterone and enzlutimide) for prostate cancer must be stopped 4 weeks prior to enrolment.

   Note: the following are NOT allowed:

   - Chemotherapy regimens with delayed toxicity within the last 3 weeks.
   - Nitrogen mustards, Melphalan, Monoclonal antibody or Nitrosourea within the last 6 weeks.

2. Any major surgery, radiotherapy or immunotherapy within the 4 weeks prior to first dose of study drug, or palliative radiotherapy to a single symptomatic lesion within the 2 weeks prior to first dose of study drugs.
3. Subjects with prior allogeneic transplant are excluded: however, subjects who have previously received an autologous stem cell transplant are allowed if a minimum of 100 days has elapsed from the time of transplant and the subject has recovered from transplant-associated toxicities prior to the first dose of GSK2816126
4. Received an investigational anti-cancer drug within 6 weeks, or within 5 half-lives (whichever is shorter) of the first dose of study drug. A minimum of14 days must have passed between the last dose of prior investigational agent and the first dose of study drug.
5. Current use of a prohibited medication or expected to require any of these medications during treatment with study drugs (see Section 9).
6. Known human immunodeficiency virus (HIV), or serological evidence for Hepatitis B (positive HBsAg) or chronic Hepatitis C infection.
   - Subjects who are negative for HBsAg, but HBcAb positive, a HBV DNA (viral load) test will be performed and if negative are eligible.

- Subjects with positive Hepatitis C antibody serology with a negative HCV RNA test results are eligible.

7. Concurrent use of therapeutic warfin is allowed. However, anticoagulants that do not have reversal agents available are prohibited (see Section 9.2). .
8. Unresolved toxicity greater than Grade 1 National Cancer Institute – Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4 from previous anti-cancer therapy, with the exception of alopecia and peripheral neuropathy [NCI-CTCAE, 2009].
    - Lymphoma subjects with ≤Grade 3 lymphopenia can be enrolled at the discretion of the investigator
9. Packed red blood cell or platelet transfusion within 7 days of screening laboratory tests.
10. Psychological, familial, sociological or geographical conditions that do not permit compliance with the protocol.
11. Cardiac exclusion criteria:
    - History of acute coronary syndromes (including myocardial infarction and unstable angina), coronary angioplasty, or stenting within the past 6 months prior to first dose of study drug.
    - QTcF interval >450 msec
    - Uncontrolled arrhythmias. Subjects with rate controlled atrial fibrillation for >1 month prior to first dose of study drugs may be eligible.
    - Class II, III or IV heart failure as defined by the New York Heart Association (NYHA) functional classification system.
12. Known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to the study drug or their excipients.
13. Pregnant or lactating female.
14. Unwillingness or inability to follow the procedures outlined in the protocol.
15. Uncontrolled diabetes or other medical condition that may interfere with assessment of toxicity.
16. Central nervous system (CNS) metastases, with the following exception:
    - Subjects who have previously treated CNS metastases, are asymptomatic, and have no requirement for steroids at least 14 days prior to first dose of study drug.
    - Subjects with carcinomatous meningitis are excluded regardless of clinical stability.
17. Invasive malignancy or history of invasive malignancy other than disease under study, except as noted below:
    - Any other invasive malignancy from which the subject has been disease-free for more than 2 years and, in the opinion of the principal investigator and GSK Medical Monitor, will not affect the evaluation of the effects of

this clinical trial treatment on currently targeted malignancy, can be included in this clinical trial.
- Curatively treated non-melanoma skin cancer and any carcinoma-in-situ.

6. COMPLETION OR WITHDRAWAL OF SUBJECTS

6.1. Screen and Baseline Failures

Data for screen and baseline failures will be collected in source documentation at the site but will not be transmitted to GSK.

Retention of screen-failure tumor tissue: all or a portion of archival or fresh biopsy tissue from screen-failure subjects, used for central testing of GCB-DLBCL or EZH2 mutation status, will be retained. This tissue may be used in the validation of potential diagnostic assays to detect EZH2 mutations and/or for GCB-DLBCL subtyping.

6.2. Subject Completion Criteria

For Part 1 (dose-escalation phase), a completed subject is one who has completed the DLT observation period, has discontinued study treatment for reasons listed in Section 6.3 and completed a post-treatment follow-up visit or has died while receiving study treatment or are receiving ongoing study treatment at the time of the Sponsor's decision to close the study.

For Part 2 (expansion cohort), a completed subject is one who has discontinued study treatment for reasons listed in Section 6.3 and completed a post-treatment follow-up visit or has died while receiving study treatment.

6.3. Permanent Discontinuation from Study Treatment

Subjects will receive study treatment until disease progression, death or unacceptable toxicity, including meeting stopping criteria for liver chemistry defined in Section 8.3.1. In addition, study treatment will be permanently discontinued for any of the following reasons:

- Substantial deviation(s) from the protocol
- Request of the subject or proxy (withdrawal of consent by subject or proxy)
- Investigator's discretion
- A dose delay of >21days unless the investigator and GSK Medical Monitor agree that further treatment may benefit the subject
- Intercurrent illness that prevents further administration of study treatment(s)
- Subject is lost to follow-up
- Study is closed or terminated
- Female subject who becomes pregnant while on study treatment

The primary reason study treatment was permanently discontinued must be documented in the subject's medical records and eCRF.

If the subject voluntarily discontinues from treatment due to toxicity, 'adverse event' will be recorded as the primary reason for permanently discontinuation on the eCRF.

Once a subject has permanently discontinued from study treatment, the subject will not be allowed to be retreated.

All subjects who discontinue from study treatment will have safety/disease assessments at the post study treatment Follow Up Visit as specified in the Time and Events Tables.

6.4. Study Completion

A subject will be considered to have completed the study after they have completed their post treatment follow up visit or if the subject dies or is still in follow-up at the time the study is closed or terminated, whichever is sooner. Document the cause of death in the CRF. A subject will be considered to have withdrawn from the study if the subject has not died and is lost to follow-up, has withdrawn consent, or at the investigator's discretion is no longer being followed.

Per the EU Clinical Trial Directive, the end of the study is defined as the last subject's last visit.

6.5. Treatment after the End of the Study

The investigator is responsible for ensuring that consideration has been given for the post-study care of the subject's medical condition whether or not GSK is providing specific post-study treatment.

7. STUDY ASSESSMENTS AND PROCEDURES

A signed, written informed consent form must be obtained from the subject prior to any study-specific procedures or assessments being performed.

The timing of each assessment is listed in the Time and Events Table (Section 7.1). The timing and number of the planned study assessments may be altered during the course of the study based on newly available data (e.g. to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring for the following assessments: safety, PK, PD/biomarker. The change in timing or addition of time points for any of the planned study assessments listed above must be approved and documented by GSK, but this will not constitute a protocol amendment. The institutional review board (IRB) or ethics committee (EC) will be informed of any safety issues that require alteration of the safety monitoring scheme.

Whenever vital signs, 12-lead ECGs and blood draws are scheduled for the same nominal time, the assessments should occur in the following order: 12-lead ECG, vital signs, blood draws. Detailed procedures for obtaining each assessment are provided in the SPM.

7.1. Time and Events Table(s)

This section consists of the Time and Events Table(s) and supplemental footnotes to describe assessment windows and sequencing of study-specific assessments and procedures.

Table 6 Time and Events(See also PK sampling table for PK sampling schedule on Day 1 and Day 15)

	STUDY PHASE	**SCREEN**	**First Treatment Period Cycle 1**				**Continuation Phase Cycle 2 and beyond**	**Follow-Up[j]**
	VISIT	**Screen**	**Day 1 and 4[a]**	**Day 8 and 11 [a]**	**Day 15 and 18 [a]**	**Day 21**		
	VISIT WINDOW (±days)	-14					±7[l]	±7[l]
Assessments (notes)								
Informed consent		X						
Demographic data		X						
Record subject using interactive voice response system (IVRS) system		X	X					
Height/Weight (Refer to Section 7.3.1)	Measurements in metric scale. Height measured only at screening	X	X				Every 4weeks (Cycle Day 1)	X
Pregnancy test	In females of child bearing potential, a serum[i] B-HCG pregnancy test is required within 7 days of first dose of study drug; urine or serum[i] B-HCG test thereafter.	X					Every 4 weeks (Cycle Day 1)	X

	STUDY PHASE	**SCREEN**	**First Treatment Period Cycle 1**				**Continuation Phase Cycle 2 and beyond**	**Follow-Up[j]**
	VISIT	**Screen**	**Day 1 and 4[a]**	**Day 8 and 11[a]**	**Day 15 and 18[a]**	**Day 21**		
	VISIT WINDOW (±days)	-14					±7[l]	±7[l]
Disease characteristics (Refer to Section 7.2)	Record date of diagnosis, primary tumor type, histology, stage, etc.	X						
Prior anti-cancer therapy & radiation	Record date of therapies	X						
Prior surgical procedures		X						
Past and current medical conditions		X						
Alcohol consumption		X						
Past and current tobacco use		X						
Physical examination		X	Day 1	Day 8	Day 15	X	Every 4 weeks Cycle Day 1	
ECOG PS	See Appendix 2	X	X	X	X	X	X	X
Vital signs	BP, body temperature, pulse rate, respirations Cycle 1 Day 1 vitals should be taken at same time points as PK draws on PK Table 7	X	X (Day 1 follow PK Table 7)	X	X	X	Prior to each infusion	X

	STUDY PHASE	**SCREEN**	**First Treatment Period Cycle 1**				**Continuation Phase Cycle 2 and beyond**	**Follow-Up[j]**
	VISIT	**Screen**	**Day 1 and 4[a]**	**Day 8 and 11[a]**	**Day 15 and 18[a]**	**Day 21**		
	VISIT WINDOW (±days)	-14					±7[l]	±7[l]
ECG[b]	Pre-infusion and at the end of infusion except on Day 1 (Section 7.3.4). Two copies of the ECG tracing should be obtained at the time of the ECG, one to be kept in the study file for retrospective collection by the sponsor if necessary. ECG data should be reviewed by qualified personnel with experience in this study population	X	X[b]	X	X		On Day 4 of each cycle	X

	STUDY PHASE	**SCREEN**	**First Treatment Period Cycle 1**				**Continuation Phase Cycle 2 and beyond**	**Follow-Up[j]**
	VISIT	**Screen**	**Day 1 and 4[a]**	**Day 8 and 11 [a]**	**Day 15 and 18 [a]**	**Day 21**		
	VISIT WINDOW (±days)	-14					±7[l]	±7[l]
Holter Monitoring	Continuous 12-lead Holter ECGs (obtained via a Holter monitor) will be acquired for a total of approximately 24 hours beginning an hour before infusion on **Day 1 only**		X (Day 1)					

	STUDY PHASE	**SCREEN**	**First Treatment Period Cycle 1**				**Continuation Phase Cycle 2 and beyond**	**Follow-Up[j]**
	VISIT	**Screen**	**Day 1 and 4[a]**	**Day 8 and 11[a]**	**Day 15 and 18[a]**	**Day 21**		
	VISIT WINDOW (±days)	-14					±7[l]	±7[l]
ECHO /MUGA	At Screening	X						
Concomitant medications	See Section 9.2 for list of prohibited and cautionary medications	X	X	X	X	X	continuous	X
Adverse events (Refer to Section 8)	Adverse event assessment should be continuous	X	X	X	X	X	continuous	X
Blood Sampling: on dosing days, collect blood samples prior to dosing unless otherwise noted								
Chemistry	No need to repeat at pre-dose Day 1 if screening assessments were performed within 72 hours of first dose (- 1 day visit window after screening)	X	X	X	X	X	Prior to every infusion	X

	STUDY PHASE	**SCREEN**	**First Treatment Period Cycle 1**				**Continuation Phase Cycle 2 and beyond**	**Follow-Up[j]**
	VISIT	**Screen**	**Day 1 and 4[a]**	**Day 8 and 11[a]**	**Day 15 and 18[a]**	**Day 21**		
	VISIT WINDOW (±days)	-14					±7[l]	±7[l]
Hematology	No need to repeat at pre-dose Day 1 if screening assessments were performed within 72 hours of first dose (- 1 day visit window after screening)	X	X	X	X	X	Prior to every infusion	X
Coagulation	PT/PTT/INR. No need to repeat at pre-dose Day 1 if screening assessments were performed within 72 hours of first dose (- 1 day visit window after screening)	X						

	STUDY PHASE	**SCREEN**	**First Treatment Period Cycle 1**				**Continuation Phase Cycle 2 and beyond**	**Follow-Up[j]**
	VISIT	**Screen**	**Day 1 and 4[a]**	**Day 8 and 11[a]**	**Day 15 and 18[a]**	**Day 21**		
	VISIT WINDOW (±days)	-14					±7[l]	±7[l]
Blood sample for circulating biomarkers	A blood sample for circulating biomarkers should be obtained on Day 1 (prior to treatment), Day 21and at the time of disease progression		X			X		X (at progression)
Blood sample for Genetic research	A 6mL blood sample should be collected after screening (preferably on day 1) if informed consent has been obtained for Genetic research		X					

	STUDY PHASE	**SCREEN**	**First Treatment Period Cycle 1**				**Continuation Phase Cycle 2 and beyond**	**Follow-Up[j]**
	VISIT	**Screen**	**Day 1 and 4[a]**	**Day 8 and 11[a]**	**Day 15 and 18[a]**	**Day 21**		
	VISIT WINDOW (±days)	-14					±7[l]	±7[l]
Whole Blood for Biomarkers[g]	Whole blood should be obtained prior to dosing on day 1,day 18 and C2D1 (sample taken prior to dosing)		X (Day 1)		X (Day 18)		X (C2W1D1 pre dose only)	
PK sampling for Part 1	For details, see Table 7		Day 1 (Table 7) Day 4pre-dose and end of infusion	Soon after ECG collection	Day 15 (Table 7)	At the time of circulating biomarker collection	Cycle 2, 4, 6 and 12 – pre-dose and within 5 min prior to end of infusion on Day 4	

	STUDY PHASE	**SCREEN**	**First Treatment Period Cycle 1**				**Continuation Phase Cycle 2 and beyond**	**Follow-Up[j]**
	VISIT	**Screen**	**Day 1 and 4[a]**	**Day 8 and 11[a]**	**Day 15 and 18[a]**	**Day 21**		
	VISIT WINDOW (±days)	-14					±7[l]	±7[l]
PK sampling for Part 2	Three samples to be collected on Day 1 and Day 11: Predose within 60 minutes prior to start of infusion, single draw between 0.5 and 1.9 h from start of infusion, single draw between 3-6h following end of infusion.		Day 1 and pre-dose on Day 4	X (after 4th dose, Day 11)	pre-dose on Day 15		Cycle 2, 4, 6 and 12 – pre-dose and within 5 min prior to end of infusion on Day 4	
Translational Research								
Tumor Tissue for EZH2 mutation and GCB confirmation testing (required: for all GCB DLBCL and tFL subjects)[c]	Availability of archival tissue (or fresh biopsy) is required for central testing of GCB-subtype and EZH2 mutation status	X						

	STUDY PHASE	**SCREEN**	**First Treatment Period Cycle 1**				**Continuation Phase Cycle 2 and beyond**	**Follow-Up[j]**
	VISIT	**Screen**	**Day 1 and 4[a]**	**Day 8 and 11[a]**	**Day 15 and 18[a]**	**Day 21**		
	VISIT WINDOW (±days)	-14					±7[l]	±7[l]
Tumor tissue for solid tumors (including prostate subjects)[c]	Availability of archival tissue (or fresh biopsy)	X						
Tumor biopsy for PD optional for Part 1 and Part 2. Required for PK/PD cohort	A tumor biopsy should be obtained at D1 (up to -14 days) and after 6th dose Day 18(+3 day window)		X		X (After 6th dose, Day 18)[h]			
Tumor biopsy for biomarker research	Recommended for all subjects							X (at pro-gression)
Additional Assessments for PD/PK Cohort[m]								
Blood for metabolite evaluation (Part 2 PK/PD expansion cohort only			Day 1 (Table 7)		Day 15 (Table 7)			
Urine for Metabolite (Part 2 PK/PD expansion cohort only)	On Day 15, urine samples should be collected while subject is in the office		Day 1 prior to first dose and from 0 to 24h		Day 15 from 0 to 8 h			

	STUDY PHASE	**SCREEN**	**First Treatment Period Cycle 1**				**Continuation Phase Cycle 2 and beyond**	**Follow-Up[j]**
	VISIT	**Screen**	**Day 1 and 4[a]**	**Day 8 and 11[a]**	**Day 15 and 18[a]**	**Day 21**		
	VISIT WINDOW (±days)	-14					±7[l]	±7[l]
Bile for metabolite (Part 2 PK/PD expansion cohort only) – at least 4 subjects)					Day 15			
Plasma for 4β-hydroxycholesterol and cholesterol assay (Part 2 PK/PD expansion cohort only)			X (Day 1 prior to First Dose)			X		
Disease Assessments for Lymphoma Subjects: *Baseline disease assessments at screening and repeated 8 weeks after dosing is initiated and every 12 weeks thereafter*								
Computed Tomography (CT)[k]	Must be completed within 4 weeks of first dose of GSK2816126 and repeated 8 weeks after dosing is initiated. Every 12 weeks thereafter	X					X	X[d]

	STUDY PHASE	**SCREEN**	**First Treatment Period Cycle 1**				**Continuation Phase Cycle 2 and beyond**	**Follow-Up[j]**
	VISIT	**Screen**	**Day 1 and 4[a]**	**Day 8 and 11[a]**	**Day 15 and 18[a]**	**Day 21**		
	VISIT WINDOW (±days)	-14					±7[l]	±7[l]
Positron emission tomography (PET)	The use of standalone PET or PET in combination with CT scan is optional. Standalone PET does not replace CT	X[e]					X[e]	X[d,e]
Bone Marrow biopsy	See Section 7.7	X					X[f]	X[f]
B symptoms	See Section 7.7	X	X	X	X	X	X	
Disease Assessments for Multiple Myeloma (MM) subjects: Baseline disease assessments at screening, week 4 and then every 6 weeks there after unless otherwise noted								
Disease Characteristics	Every 6 weeks after Wk4, Including cytogenetics as appropriate	X					X	
Total Protein, CRP, β2 microglobulin	Every 6 weeks after Wk4	X					X	
Response Assessment	Every 6 weeks after Wk4; Response criteria in Appendix 6						X	

	STUDY PHASE	**SCREEN**	**First Treatment Period Cycle 1**				**Continuation Phase Cycle 2 and beyond**	**Follow-Up[j]**
	VISIT	**Screen**	**Day 1 and 4[a]**	**Day 8 and 11[a]**	**Day 15 and 18[a]**	**Day 21**		
	VISIT WINDOW (±days)	-14					±7[l]	±7[l]
SPEP, FLC assay, quantitative immunoglobulins (IgG, IgA, IgM)	Not required for subjects with non-secretory MM	X					X	
UPEP	Only required if paraprotein is present in urine	X						
Extramedullary Disease Assessment	Only required for MM with extramedullary disease	X						
BM aspirate and biopsy	Required for non-secretory MM, or as appropriate for other subjects	X			Day 18		Week 10, Day 1	
Disease Assessments for Solid Tumors: Baseline disease assessments at screening and repeated every 8 weeks after dosing is initiated								
CT/ Magnetic Resonance Imaging (MRI)[k]	Must be completed within 4 weeks of first dose of GSK2816126 and repeated every 8 weeks	X					X[d]	X[d]

	STUDY PHASE	**SCREEN**	**First Treatment Period Cycle 1**				**Continuation Phase Cycle 2 and beyond**	**Follow-Up[j]**
	VISIT	**Screen**	**Day 1 and 4[a]**	**Day 8 and 11[a]**	**Day 15 and 18[a]**	**Day 21**		
	VISIT WINDOW (±days)	-14					±7[l]	±7[l]
Positron emission tomography (PET)	The use of standalone PET or PET in combination with CT scan is optional. Standalone PET does not replace CT	X[e]					X[d,e]	X[d,e]
Disease Assessments for Prostate Cancer: (in addition to those assessments for all solid tumor subjects): Baseline disease assessments at screening and repeated as noted below after dosing is initiated								
PSA	Wk 9 and every 4 weeks thereafter	X					X	X
Study Medication								
GSK2816126 Dosing[a]	Dosed 2x weekly with at least 2-3 non-dosing days in between dosing days (3 weeks on/1 week off)							

a. A subject is to receive two doses per week which should be given with at least 2 non-dosing days in between on the same day of the week during Cycle 1.- If there is a need to change scheduling after Cycle 1, the scheduled days of the week can change as long as there are 2-3non-dosing days between dosing days.
b. Timings for triplicate in-house on-drug ECGs are pre-infusion, at the end of infusion, before bed, and before discharge the next morning for Day 1 of cycle 1 only. Other protocol-mandated ECGs should be performed in triplicate pre-infusion and at the end of infusion (Section 7.3.4). Two copies of the ECG tracing should be obtained at the time of the ECG, one to be kept in the study file for retrospective collection by the sponsor if necessary. ECG data should be reviewed by qualified personnel with experience in this study population
c. Retention of screen-failure tumor tissue: all or a portion of archival or fresh biopsy tissue from screen-failure subjects, used for central testing of GCB-DLBCL or EZH2 mutation status, will be retained. This tissue may be used in the validation of potential diagnostic assays to detect EZH2 mutations and/or for GCB-DLBCL subtyping.
d. If the Follow-up visit ≥ 8weeks from the previous response scan time point, scans should be obtained to confirm/ evaluate response.
e. Standalone PET dose not replace CT. Diagnostic CT is the preferred method of disease assessment. PET/CT may be used as an alternative at the investigator's discretion.

f. Only if initially and/or previously positive & required for CR or as clinically indicated.
g. Whole Blood for Biomarker sample at Cycle 2 day 1 must be taken prior to start of dosing.
h. If tissue sample not able to be taken at C1D18, site should discuss with GSK regarding having the sample taken at the next possible Cycle visit
i. Serum beta-human chorionic gonadotropin (B-HCG) pregnancy test
j. Follow up visit should be performed 30 days from last dose of study medication
k. Baseline brain scans are required for all subjects. Thereafter brain scans should be conducted as clinically indicated. Bone scans are to be conducted as clinically indicated at baseline and subsequent follow up timepoints. Subjects undergoing baseline full body CT/PET will not require this additional scans, unless clinically indicated.
l. After Cycle 1, assessments that are conducted at less frequent intervals (i.e., every 8 weeks) will have a visit window of $\pm$ 7 days after Cycle 1
m. Part 2 subjects enrolled into the PK/PD cohort will have these assessments performed in addition to all other study assessments included in the Time and Events table

Table 7 Time and Events, PK Sampling Table for Part 1, Day 1 and Day 15

	Duration of Infusion in hours		
	2	**3**	**4**
From start of infusion - 60 mins	Predose	Predose	Predose
± 5 mins	0.5 hr	0.5 hr	0.5 hr
± 5 mins	1 hr	1 hr	1 hr
- 5 mins	2 hr (prior to end of infusion)	2 hr	2 hr
- 5 mins		3 hr (prior to end of infusion)	4 hr (prior to end of infusion)
From end of infusion ± 5 mins	0.5 h	0.5 h	0.5 h
± 5 mins	1 hr	1 hr	1 hr
± 5 mins	2 hr	2 hr	2 hr
± 15 mins	4 hr	4 hr	4 hr
± 15 mins	6 hr	6 hr	6 hr
From start of infusion ± 1hour	12 hr (Day 1 only)	12 hr (Day 1 only)	12 hr (Day 1 only)
± 1 hour	18 hr (Day 1 only)	18 hr (Day 1 only)	18 hr (Day 1 only)
± 1 hour	24 hr	24 hr	24 hr
± 2 hour	**72 or 96 hr	72 or 96 hr	72 or 96 hr

**72 hour sample corresponds to Cycle 1 Day 4 pre infusion sample. EOI sample should also be taken at C1D4.

7.2. Demographic/Medical History and Baseline Assessments

The following demographic parameters will be captured during Screening: date of birth (in accordance with local data protection legislation), gender, race and ethnicity.

Baseline (Screening) assessments obtained will include:

- Complete physical examination, including height (in cm) and weight (in kg)
- Vital signs (BP, temperature, respiratory rate, pulse rate)
- Past and current medical conditions, alcohol and tobacco use
- ECOG performance status
- Lactate dehydrogenase (LDH) level
- Disease characteristics for all subjects including:
    - Date of initial diagnosis
    - Initial diagnosis tumor histology
    - ECOG performance status at initial diagnosis
    - Tumor location involvement at initial diagnosis
    - Previous cancer treatments (e.g., cytotoxics, radiotherapy, maintenance, surgery)
    - Ongoing toxicities related to previous treatment
    - Best response to previous treatment(s)
    - Date of relapse/refractory diagnosis
    - Tumor histology (if relapse/refractory tumor biopsy completed). For Part 2 subjects, tumor biopsy is mandatory for inclusion. See Section 7.6.5.
    - ECOG performance score at time of first relapse/refractory diagnosis (as applicable)

- Diagnostic quality CT imaging with contrast within 28 days of first dose of study treatment identifying nodes, nodal masses, spleen/liver nodules and, if applicable measurable extra nodal disease. Diagnostic quality CT imaging is the preferred method of disease assessment. If PET/CT has been performed within this window, diagnostic CT will not be required. See Section 7.7 for further information.
- If completed and will be utilized for assessment of disease, PET imaging within 28 days of first dose of study treatment. Images may be obtained from standalone PET scanners or via combination PET/CT scanners. Standalone PET does not replace diagnostic CT. See Section 15.4 for further information.
- For NHL, unilateral or bilateral bone marrow biopsy within 35 days prior to commencing study therapy.
- Clinical laboratory tests: hematology, clinical chemistry, coagulation parameters

- Serum beta-human chorionic gonadotropin (β-HCG) pregnancy test for female subjects of childbearing potential only
- 12-lead ECG
- ECHO or MUGA
- Review of concomitant medications
- Baseline assessments for subjects with GCB-DLBCL
    - Ann Arbor stage of initial diagnosis for NHL
    - Ann Arbor stage of relapse/refractory diagnosis for NHL
    - GCB testing confirming status
    - LDH level at initial diagnosis
    - LDH level at time of first relapse/refractory diagnosis (as applicable)

- Baseline assessment for Subjects with multiple myeloma
        - International staging system (ISS) stage at initial diagnosis and screening
        - Type (active or smoldering)
        - Presence of plasmacytoma
        - Cytogenetics
        - Presence of extramedullary disease
        - Laboratory assessment: Total protein, paraprotein, CRP and β2-microglobulin; for secretory MM: SPEP, UPEP, IgG, IgA, IgM, FLC assay

Procedures conducted as part of the subject's routine clinical management (e.g., blood count, imaging study) and obtained prior to signing of informed consent may be utilized for Screening or baseline purposes provided the procedure meets the protocol-defined criteria and has been performed in the timeframe of the study.

7.2.1. Critical Baseline Assessments

Cardiovascular medical history/risk factors will be assessed at baseline.

7.3. Safety Evaluations

Planned time points for all safety assessments are provided in the Time and Events Table (Section 7.1).

7.3.1. Physical Examinations

A complete physical examination will include assessments of the head, eyes, ears, nose, throat, skin, thyroid, neurological, lungs, cardiovascular, abdomen (liver and spleen), lymph nodes and extremities. Height and weight will also be measured and recorded.

A brief physical examination will include assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).

7.3.2. ECOG Performance Status

The performance status will be assessed using the ECOG scale (Section 15.2) as specified in the Time and Events Table (Section 7.1).

7.3.3. Vital Signs

Vital sign measurements will include systolic and diastolic BP, temperature, respiration rate and pulse rate. Vital signs should be measured after resting for at least 5 minutes in a semi-supine position. Vital signs will be measured more frequently if warranted by clinical condition of the subject. On days where vital signs are measured multiple times (Cycle 1 Day 1), temperature does not need to be repeated unless clinically indicated. Refer to the SPM for details regarding measurement of vital signs.

7.3.4. Safety Electrocardiogram

Safety twelve-lead ECGs will be obtained in triplicate over a brief (e.g., 5-10 minute) recording period at designated time points during the study using an ECG machine that automatically calculates the HR and measures PR, QRS, QT, and QTc intervals. At each assessment, a 12-lead ECG will be performed by qualified personnel at the site after the subject has at least a 5 minute rest and is in a semi-[recumbent or supine] position. Refer to the SPM for details regarding ECG procedures.

Standard 12-lead ECGs (safety ECGs) will be performed as part of the real-time assessment of subjects. ECGs should be reviewed by the investigator on an ongoing basis for safety purposes. The dosing for each new week in the first cycle should not begin until the safety ECG has been reviewed and no significant abnormalities have been detected

The QTc is the QT interval corrected for heart rate according to Fredericia's formula (QTcF).

- For eligibility and withdrawal, QTcF will be used for all subjects
- For purposes of data analysis, QTcF values will be used

Baseline results are defined by the nearest timepoint prior to first dose. For this trial the baseline QTcF value is determined by the mean of the triplicate C1D1 predose QTcF results. If these results are not available, then the mean of QTcF of the screening triplicate ECG results would be used.

Timings for in-house on-drug ECGs on Day 1 only are pre-infusion, post-infusion, before bed (between 9-10 pm) and before discharge the next morning. These ECGs are in addition to the Holter monitoring. Subjects will not be discharged from their overnight stay in the Phase I unit after dose 1 until the QTcF is <500 msec.

For all doses after the first dose, ECGs will be recorded pre-infusion and at the end of infusion. See Time & Events Table (Section 7.1) for exact timings.Refer to Section 3.8.1 for QTc withdrawal/stopping criteria. Additional QTc readings may be necessary.

7.3.5. Holter Monitoring

In addition to the 12-lead safety ECGs performed during the study, continuous 12-lead Holter ECGs (obtained via a Holter monitor) will be acquired for a total of approximately 24 hours beginning an hour before the first infusion. Subjects will be monitored overnight in the CRU. The Holter monitor-derived ECGs will not provide real-time assessment of cardiac rhythm and morphology but will be analyzed retrospectively and included in the DLT and concentration QT analysis.

Refer to Section 3.8.1 for QTc interval withdrawal criteria and additional readings that may be necessary. Refer to the SPM for details regarding Holter monitoring procedures.

7.3.6. Laboratory Assessments

All protocol required laboratory assessmentsshould be performed according to the Time and Events Table (Section 7.1). Details for the preparation and shipment of samples will be provided in the SPM.

Prior to administration of the first dose of study treatment, results of laboratory assessments should be reviewed. Any laboratory test with a value outside the normal range may be repeated (prior to the first dose) at the discretion of the investigator.

If additional non-protocol specified laboratory assessments are performed at the institution's local laboratory and result in a change in patient management or are considered clinically significant by the Investigator (for example SAE or AE or dose modification) the results must be recorded in the subject's CRF. Refer to the SPM for appropriate processing and handling of samples to avoid duplicate and/or additional blood draws.

Abnormal laboratory results that are considered by the investigator to be clinically significant should be recorded on the eCRF as AEs. All laboratory tests with values that are significantly abnormal during participation in the study or within 30 days after the last dose of study treatment should be repeated until the values return to normal or baseline. If such values do not return to normal within a period judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

Hematology, clinical chemistry, urinalysis and additional parameters to be tested are listed below and are to be performed at the institutions local laboratory:

Table 8 List of Clinical Laboratory Tests

Hematology			
Platelet Count		*RBC Indices*:	*Automated WBC Differential:*
RBC Count		MCV	Neutrophils
WBC Count (absolute)		MCH	Lymphocytes
Reticulocyte Count		MCHC	Monocytes
Hemoglobin			Eosinophils
Hematocrit			Basophils
Clinical Chemistry			
BUN	Potassium	AST	Total and direct bilirubin
Creatinine	Chloride	ALT	Uric Acid
Sodium	Calcium	Alkaline phosphatase	Total Protein
Magnesium	Glucose	LDH	
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)			

Abbreviation(s): ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; FSH, follicle stimulating hormone; LDH, lactate dehydrogenase; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; RBC, red blood cell; WBC, white blood cell.

7.3.7. Pregnancy Testing and Reporting

The need for a screening pregnancy test depends on whether a female subject is of childbearing potential or non-childbearing potential.

If a female subject is of childbearing potential, she must have a serum β-HCG pregnancy test performed within 7 days prior to the first dose of study treatment. Subjects with positive pregnancy test result must be excluded from the study. Subjects with negative pregnancy test result must agree to use an effective contraception method as described in Section 10.1 during the study until at least 2 weeks (14 days) after permanent discontinuation of study treatment.

Any pregnancy that occurs during study participation must be reported using a clinical trial pregnancy notification and follow –up form. To ensure subject safety, each pregnancy must be reported to GSK within 2 weeks of learning of its occurrence. The pregnancy must be followed up to determine outcome (including premature termination) and status of mother and child. While pregnancy itself is not considered to be an AE or SAE, pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous abortions must be reported as an SAE.

Any SAE occurring in association with a pregnancy brought to the investigator's attention after the subject has completed the study and considered by the investigator as possibly related to the study treatments, must be promptly reported to GSK.

Any female subject who becomes pregnant while participating in the study will be withdrawn from the study. Study treatment should be immediately withdrawn from a subject who becomes pregnant during the study in order to eliminate further exposure of the embryo to the study treatment.

In addition, the investigator must attempt to collect pregnancy information on any female partners of male study subjects who become pregnant while the subject is enrolled in the study. Pregnancy information must be reported to GSK as described above.

7.4. Pharmacokinetics

7.4.1. Blood Sample Collection for Pharmacokinetics

Blood samples for PK analysis of GSK2816126 will be collected at the time points indicated in the Time and Events Schedule (Section 7.1). Some of the blood drawn may be used to produce dry blood matrix samples at the same time points. Each PK sample should be collected as close as possible to the planned time relative to the dose (i.e., time zero) administered to the subject on PK days. The actual date and time of each blood sample collection will be recorded. The timing of PK samples may be altered and/or PK samples may be obtained at additional time points to ensure thorough PK monitoring. This would not require a protocol amendment.

Subjects participating in the Part 2 PK/PD expansion cohort, additional blood samples will be collected for metabolite profiling.

Details on PK blood sample and dry blood matrix sample collection, processing, storage and shipping procedures are provided in the SPM.

7.4.2. Bile Sample Collection for Pharmacokinetics

Subjects participating in the Part2 PK/PD expansion cohort, bile samples for analysis of GSK2816126 and its metabolites may be collected via the Entero-Test [Guiney, 2011] over the time period specified in the Time and Events Table (see Section 7.1).

Full details of the Entero-Test sample collection, processing, storage and shipping procedures are provided in the SPM.

7.4.3. Urine Sample Collection for Pharmacokinetics

Urine may be collected for metabolic profiling in subjects in the PK/PD expansion cohort of Part 2 at the time points indicated in the Time and Events Schedule (Section 7.1).

7.4.4. Plasma Sample for CYP3A4 Enzyme Activity

Plasma collected in the Part 2 PK/PD expansion cohort may be analyzed for 4β-hydroxycholesterol (as well as cholesterol) as a potential in vivo marker of CYP3A4 enzyme activity and the results will be reported under a separate Mechanistic Safety and Disposition protocol. Samples collected pre-treatment and at steady-state will be compared to evaluate this potential biomarker.
Details on CYP3A4 enzyme activity marker plasma sample collection, processing, storage and shipping procedures are provided in the SPM.

7.4.5. Pharmacokinetic Sample Analysis

Blood sample analysis will be performed under the management of Bioanalysis Immunogenicity and Biomarker, In Vitro In Vivo Translation , Platform Technology and Science, GSK. Concentrations of GSK2816126 will be determined in blood samples using the most current approved and validated analytical methodology. Blood raw data will be stored in the Good Laboratory Practices (GLP) Archives, GSK. Once the blood has been analyzed for GSK2816126, any remaining blood may be analyzed qualitatively for circulating metabolites and the results reported under a separate drug metabolism and pharmacokinetics (DMPK) protocol.

If dry blood matrix samples are collected, they will be analyzed under the management of Bioanalysis Immunogenicity and Biomarker, *In Vitro In Vivo* Translation , Platform Technology and Science, GSK. Concentrations of GSK2816126 will be determined in dry blood matrix samples using a validated analytical methodology. Dried blood matrix raw data will be stored in the Good Laboratory Practices (GLP) Archives, GSK.

Urine sample analysis may be performed under the management of Bioanalysis, Immunogenicity and Biomarker, *In Vitro In Vivo* Translation , Platform Technology and Science, GSK. Concentrations of GSK2816126 may be determined in urine samples using an investigative analytical methodology. Urine raw data will be stored in the GLP Archives, GSK.

The urine and bile samples may be analyzed for compound-related metabolites and the results will be reported under a separate protocol.

Plasma analysis for 4β-hydroxycholesterol and cholesterol may be conducted and the results reported under a separate protocol.

7.5. Pharmacodynamics

Changes from baseline H3K27me3 will be assessed in pre- and post-treatment samples for tumor or surrogate tissue/body fluid [e.g. Peripheral blood mononuclear cell (PBMCs), blood, skin or hair].

7.6. Translational Research

Translational or biomarker research may be performed on archival tissue, tumor biopsies, blood samples or other surrogate tissue (e.g. skin or hair) collected at various times throughtout the study, to better understand the mechanism of action and response to GSK2816126. The successful collection of quality tissue specimens will be critical to furthering our understanding of EZH2 biology and identifying the best way to treat patients with an EZH2 inhibitor.

Comparative examination of pre-dosing profiles of participants may uncover known or novel candidate biomarkers/profiles which could be used to predict response to treatment with GSK2816126 or provide new insights into lymphoma, other cancers, and medically

related conditions. Comparative examination of post-dosing profiles in conjunction with pre-dosing profiles may yield known and novel candidate biomarkers/profiles and new insights which relate to the action of GSK2816126.

Performance of these investigations may be conditional on the results of the clinical trial principally, but not exclusively, on the primary measures of the clinical trial outcome and samples may be selected for analysis on the basis of the clinical outcome.

Unless stated otherwise, these investigations may be performed irrespective of whether a response to GSK2816126 is observed.

All samples may be retained for a maximum of 15 years after the last subject completes the trial.

Novel candidate biomarkers and subsequently discovered biomarkers of the biological response associated with lymphoma, or other cancers,and/or the action of GSK2816126 may be identified by application of. DNA/gene, RNA and protein analysis of blood and tumor tissue including but not limited to the following analyses:

- Confirmation of GCB-subtype DLBCL status by IHC analysis using the standard methods or tumor Gene Expression Profile (GEP) signature
- Confirmation of EZH2 WT status by targeted sequencing of EZH2 gene
    - Subject tumors determined to be wild-type for the seven pre-defined EZH2 mutations assessed in the screening assay may be evaluated for the presence of additional, undefined, mutations in the EZH2 gene
- DNA analyses may be performed for somatic mutations in genes of interest (including, but not limited to, EZH2,UTX, BAP1, ARID1A, SMARCB1, SMARCA4, and PBRM1). Translocations including, but not limited to, BCL-2, BCL-6 and c-MYC, which have been observed in DLBCL, may also be assessed
- Circulating cell free-DNA (cfDNA) analysis of blood/plasma
- Circulating biomarker (DNA, RNA and/or protein) analysis of plasma
- RNA transcriptome analysis of blood and/or tissue samples.
- Measurement of the levels of a subset of RNA species in blood and/or tissue samples
- Analysis of protein expression by IHC or an alternative method may also be performed for proteins of interest.

7.6.1. Tumor Biomarker Analysis

To evaluate candidate biomarkers and identify novel predictors of sensitivity and/or resistance to GSK2816126, DNA, RNA or protein measurements will be assessed in archival tumor tissue or fresh biopsies. Specific tests, exploratory analyses and tissue requirements for each tumor type are indicated below and/or Table 6.

7.6.1.1. GCB-DLBCL Subtyping (DLBCL subjects only)

Central confirmation of GCB DLBCL status will be confirmed by an IHC test utilizing the Choi algorithm [Choi, 2009] in Part 1 and 2.

Local testing, in advance of central confirmation may be performed to determine GCB status for enrollment using the Choi algorithm or a suitable alternative algorithm.

7.6.1.2. EZH2 Mutation Analysis (required for study entry in Part 2 for GCB-DLBCL and tFL subjects only)

Screening for eligibilityfor Part 2 of the study will be conducted using either an NGS-based gene panel or a custom quantitative real time polymerase chain reaction (RT-PCR) test based on TaqMan PCR chemistry. Both tests detect 7 known activating mutations in the EZH2 gene: Y641F (c.1937A>T); Y641N (c.1936T>A); Y641S (c.1937A>C); Y641H (c.1936T>C); Y641C (c.1937A>G); A677G (c.2045C>G); and A687V (c.2075C>T) .

EZH2 mutation analysis on archival tumor samples or fresh biopsies from subjects enrolled in Part 1 may also be performed, though the presence of an EZH2 mutation is not required for study entry in Part 1.

7.6.2. Circulating cell free DNA/RNA Analysis

Plasma samples may be analyzed to investigate mutations, including but not limited to EZH2, in cfDNA.

Tumor-specific circulating cell-free deoxyribonucleic acid (cfDNA) levels detected in plasma or serum have been found to correlate with increasing tumor burden and decline following therapy. Furthermore, cfDNA in cancer participants can harbor many genetic alterations (mutations, microsatellite alterations, aberrant methylation), which are generally consistent with the tumor. Additionally exosomes, released from tumors cells into circulation, which contain both DNA and RNA are increasingly being recognized as important source of cancer biomarkers. Thus, tumor-specific circulating cfDNA and exosomes have the potential to be a useful source of biomarkers of therapeutic response as well as offering a less invasive blood based technique for identifying and selecting participants for certain treatment. Methylation status of cfDNA may also be investigated.

7.6.3. Circulating biomarker analysis

Levels of circulating biomarkers may be assessed to determine relationships between biomarker expression and response to GSK2816126, as well as to better understand the expression of circulating biomarkers in lymphoma and other tumor types.
Biomarkers circulating in the plasma have been found to correlate with tumor pathway activation. Blood-based markers have the important advantage that specimens are readily available, simple to prepare and store, and can be taken prior to and during treatment. This allows for the assessment of predictive markers based on the baseline evaluation as

well as markers of activity and resistance based on changes that occur during treatment. Therefore, a broad panel of biomarkers may be evaluated in plasma and correlated with clinical outcome to treatment with GSK2816126.

7.6.4. RNA Expression Research

Transcriptional (RNA) analyses may be performed to better understand changes in gene expression profile upon treatment with GSK2816126 in tumor tissue and/or blood.
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RNA expression studies may be conducted using RNA-seq, quantitative RT-PCR, and/or alternative equivalent technologies, which can facilitate the simultaneous measurement of the relative abundances of RNA species resulting in a RNA expression profile for each blood and tumor tissue sample. The RNAs assayed may be those involved in tumor pathogenesis, the absorption, distribution, metabolism, or excretion of GSK2816126, or in the subject's response to GSK2816126. In addition, continuing research may identify other proteins or regulatory RNAs that may be involved in response to GSK2816126 or tumor pathogenesis. The RNAs that code for these proteins and/or regulatory RNAs may also be studied. This will enable the evaluation of changes in RNA expression profiles that may correlate with biological response relating to specific cancers, and medically related conditions or the action of GSK2816126.

7.6.5. Tumor Tissue collection

Part 1:

- DLBCL subjects: the availability of archived tissue (or willingness to undergo fresh biopsy) is required for determination of EZH2 mutation status, and/or GCB-subtype.

- All other subjects: an archival tumor specimen (or willingness to undergo fresh biopsy) for retrospective DNA, RNA or protein testing of potential markers of sensitivity and/or resistance. Subjects for whom archived tissue is not available and biopsies are not feasible will be eligible for enrollment and participation in the study at the discretion of the GSK medical monitor. Contact GSK medical monitor for confirmation of enrollement and sudy entry if biopsies are not feasible.

- Pre and post treatment biopsies for PD and translational research activities are optional for all subjects.

Part 2:

- DLBCL cohorts: a fresh tumor biopsy is required for all screened subjects to determine EZH2 mutation status and GCB-subtype.

- tFL cohorts: a fresh tumor biopsy is required for all screened subjects to determine EZH2 mutation status.

- MM cohort: an archival tumor specimen or fresh tumor biopsy is required.
- PK/PD cohorts: Pre treatment and post treatment biopsies are required
- Pre and post treatment biopsies for PD and translational research activities are optional for all other subjects.

Retention of screen-failure tumor tissue: all or a portion of archival or fresh biopsy tissue from screen-failure subjects, used for central testing of GCB-DLBCL or EZH2 mutation status, will be retained. This tissue may be used in the validation of potential diagnostic assays to detect EZH2 mutations and/or for GCB-DLBCL subtyping.

A tumor biopsy at progression for biomarker research is recommended for all subjects.

Further details on sample requirements and collection will be provided in the SPM.

7.6.6. Blood collection

Blood samples will be collected at multiple time points from all subjects on study (Parts 1 and 2) for pharmacodynamic and exploratory biomarker testing (Section 7.1).

A change in frequency of blood biomarker sampling times may be implemented based on emerging data. This would be determined by GSK and documented in formal communication to sites for implementation but would not require a protocol amendment..

Further details on sample requirements and collection will be provided in the SPM.

7.7. Evaluation of Anti-Cancer Activity

Disease assessment may include imaging and physical examination (as indicated for palpable/superficial lesions). Refer to Appendix 4 for more details on response assessment criteria.

- Disease assessment for lymphomas will be completed within 4 weeks of first dose of GSK2816126 and repeated 8 weeks after dosing is initiated, every 12 weeks thereafter, and at the final study visit.
- Disease assessment for solid tumors will be completed within 4 weeks of first dose of GSK2816126 and repeated every 8 weeks after dosing is initiated, and at the final study visit.
- Disease assessment for MM will be completed within 4 weeks of first dose of GSK2816126, week 4 and repeated every 6 weeks thereafter.

See the Time and Events Table (Section 7.1) for the schedule of assessments of anti-cancer activity. Assessments must be performed on a calendar schedule and should not be affected by dose interruptions/delays. For post-baseline assessments, a window of ±7 days is permitted to allow for flexible scheduling. If the last radiographic assessment was more than 8 weeks prior to the subject's withdrawal from study and progressive

disease has not been documented, a disease assessment should be obtained at the time of withdrawal from study.

For subjects with NHL, the following B symptoms should be assessed at the time points in the Time and Events Table (Section 7.1):

- night sweats without signs of infection
- unintentional weight loss of ≥10% within the previous 6 months
- recurrent, unexplained fever of greater than 38°C for 2 weeks without signs of infection

If a lymphoma subject had involvement of bone marrow at baseline, and a CR is suspected, a bone marrow biopsy must be obtained. A repeat bone marrow biopsy will be performed within 8 weeks of the imaging confirmed CR in accordance with the response guidelines. See Appendix 4: Section 15.4 for additional details.

Tumor response will be assessed as outlined above and in the Time and Events Schedule by the investigator using:

- Lymphoma Subjects: Revised Response Criteria for Malignant Lymphoma (RRCLM)(Appendix 4)
- Solid Tumor RECIST 1.1 (Appendix 5)
- Multiple Myeloma: International Myeloma Working Group (IMWG) (Appendix 6)
- Prostate: RECIST 1.1 and PSA (Appendix 7)

7.8. Genetic Research

The information regarding genetic research is included in Appendix 8.

8. ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

The investigator or site staff will be responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE as outlined in Section 8.1 and Section 8.2, respectively.

8.1. Definition of an AE

Any untoward medical occurrence in a subject or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Note: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this

also includes failure to produce expected benefits, abuse, or misuse. Examples of events meeting the definition of an AE include:

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or grade of the condition
- New conditions detected or diagnosed after study treatment administration even though it may have been present prior to the start of the study
- Signs, symptoms, or the clinical sequelae of a suspected interaction
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication (overdose per se will not be reported as an AE/SAE).

"Lack of efficacy" or "failure of expected pharmacological action" *per se* is not to be reported as an AE or SAE. However, any signs and symptoms and/or clinical sequelae resulting from "lack of efficacy" will be reported as an AE or SAE, if they fulfill the definition of an AE or SAE.

Events that **do not** meet the definition of an AE include:

- Medical or surgical procedure (e.g., endoscopy, appendectomy); the condition that leads to the procedure is an AE.
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- The disease/disorder being studied, or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition.

8.2. Definition of a SAE

A SAE is any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

   NOTE: The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires hospitalization or prolongation of existing hospitalization

   NOTE: In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-subject setting. Complications that occur during hospitalization are

AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in disability/incapacity, or

NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect.

f. Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

g. All events of possible study treatment-induced liver injury with hyperbilirubinemia defined as ALT ≥3 times ULN **and** bilirubin ≥2 times ULN (>35% direct) (or ALT ≥3 times ULN and INR >1.5, if INR is measured) or termed 'Hy's Law' events (INR measurement is not required and the threshold value stated will not apply to subjects receiving anticoagulants).

- **NOTE:** Bilirubin fractionation is performed if testing is available. If testing is not available, record presence of detectable urinary bilirubin on dipstick indicating direct bilirubin elevations and suggesting liver injury. If testing is unavailable and a subject meets the criterion of total bilirubin ≥2 times ULN, then the event is still reported as a SAE. If INR is obtained, include values on the SAE form. INR elevations >1.5 suggest severe liver injury.

8.3. Laboratory and Other Safety Assessment Abnormalities Reported as AEs and SAEs

Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis), or other safety assessments (e.g., ECGs, radiological scans, vital signs measurements) including those that worsen from baseline, and events felt to be clinically significant in the medical and scientific judgment of the investigator are to be recorded as an AE or SAE, in accordance with the definitions provided.

In addition, an associated AE or SAE is to be recorded for any laboratory test result or other safety assessment that led to an intervention, including permanent discontinuation of study treatment, dose reduction, and/or dose interruption/delay.

Any new primary cancer must be reported as a SAE.

However, any clinically significant safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition, are not to be reported as AEs or SAEs.

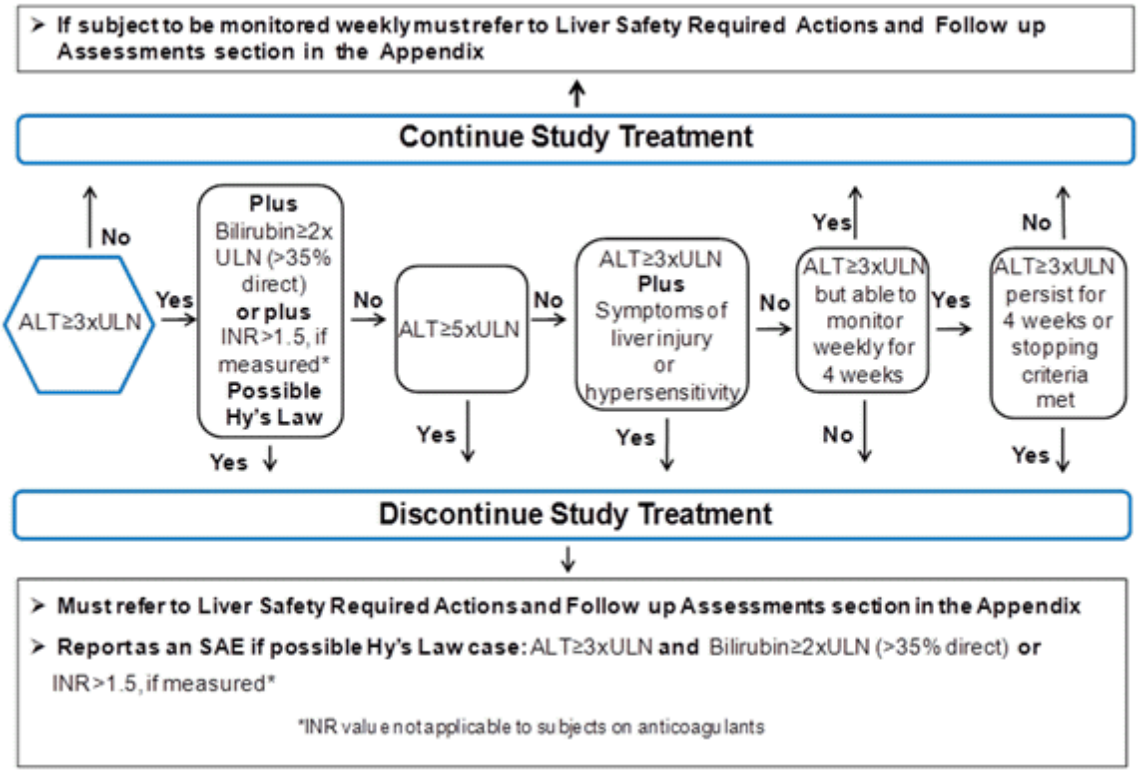
8.3.1. Liver Chemistry Stopping Criteria

Liver chemistry threshold stopping criteria have been designed to assure subject safety and to evaluate liver event etiology during administration of study treatment(s) and the follow-up period (in alignment with the FDA premarketing clinical liver safety guidance).

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

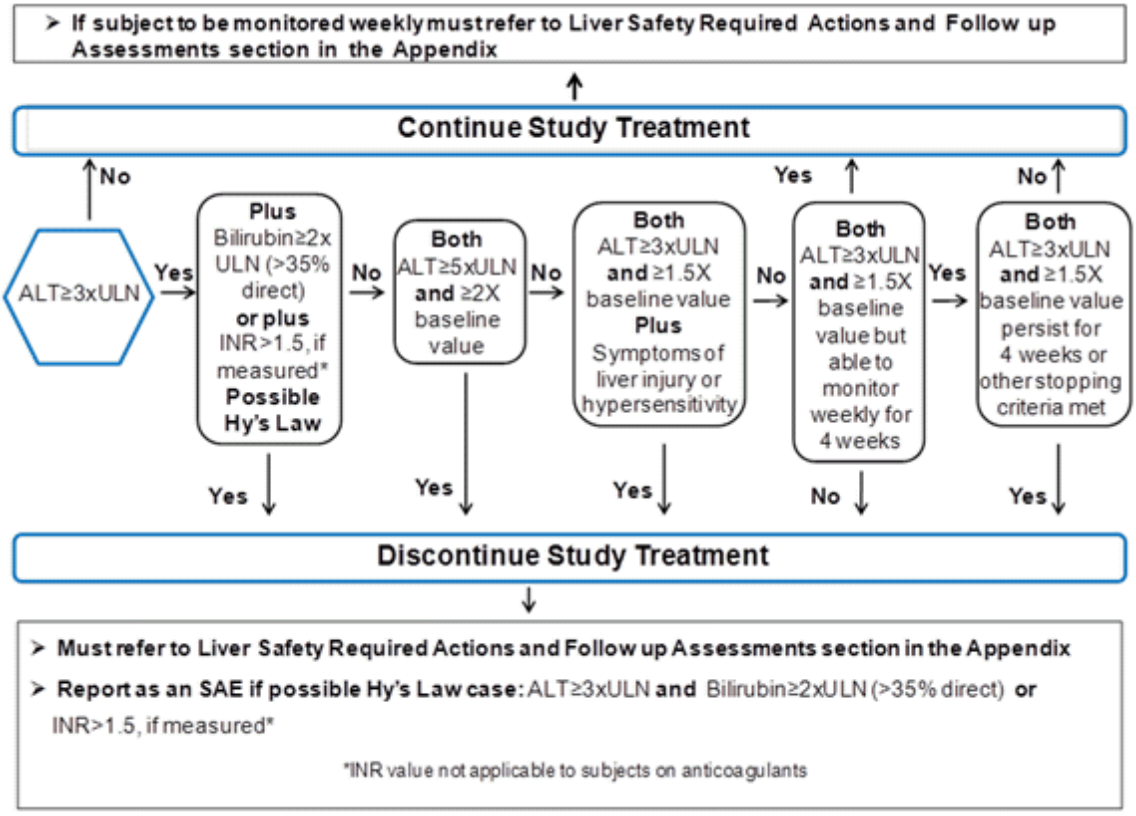
See Figure 1 and Figure 2 for liver stopping criteria for subjects without and with liver metastases, respectively. The algorithms are best read from left to right.

Figure 1 Phase I/II Liver Chemistry Stopping and Increased Monitoring Algorithm for Subjects WITH entry criteria ALT ≤2.5xULN



Liver Safety Required Actions and Follow up Assessments Section can be found in Appendix 3

Figure 2 Phase I/II Liver Chemistry Stopping and Increased Monitoring Algorithm including Subjects WITH documented liver metastases/tumor infiltration at baseline AND entry criteria ALT>2.5xULN but ≤5xULN



Liver Safety Required Actions and Follow up Assessments Section can be found in Appendix 3

8.3.1.1. Study Treatment Restart or Rechallenge

If subject meets liver chemistry stopping criteria do not restart/rechallenge subject with study treatment unless:

- GSK Medical Governance approval **is granted**
- Ethics and/or Institutional Review Board (IRB) approval is obtained, if required, and
- Separate consent for treatment restart/rechallenge is signed by the subject

Refer to Appendix 3 for full guidance

8.3.2. Cardiovascular Events

Investigators will be required to fill out event specific data collection tools for the following AEs and SAEs:

- Myocardial infarction/unstable angina
- Congestive heart failure
- Arrhythmias
- Valvulopathy
- Pulmonary hypertension
- Cerebrovascular events/stroke and transient ischemic attack
- Peripheral arterial thromboembolism
- Deep venous thrombosis/pulmonary embolism
- Revascularisation

This information should be recorded in the specific cardiovascular eCRF within one week of when the AE/SAE(s) are first reported.

8.4. Time Period and Frequency of Detecting AEs and SAEs

The investigator or site staff is responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE.

AEs will be collected from the time the first dose of study treatment is administered until 30 days following discontinuation of study treatment regardless of initiation of a new cancer therapy or transfer to hospice.

SAEs will be collected over the same time period as stated above for AEs. In addition, any SAE assessed **as related** to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy), study treatment or GSK concomitant medication must be recorded from the time a subject consents to participate in the study up to and including any follow-up contact. All SAEs will be reported to GSK within 24 hours, as indicated in Section 8.4.

After discontinuation of study treatment, the investigator will monitor all AEs/SAEs that are ongoing until resolution or stabilization of the event or until the subject is lost to follow-up. At any time after 30 days the investigator may report any AE that they believe possibly related to study treatment.

8.4.1. Method of Detecting AEs and SAEs

Care must be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrence. Appropriate questions include:

"How are you feeling?" or for pediatric studies, "How does your child seem to feel?"

"Have you had any (other) medical problems since your last visit/contact?" or for pediatric studies, "Has your child had any (other) medical problems or seem to act differently in any way since his/her last visit/contact?"

"Have you taken any new medicines, other than those provided in this study, since your last visit/contact?" or for pediatric studies, "Has your child needed to take any medicines, other than those provided in this study, since his/her last visit/contact?"

8.4.2. Prompt Reporting of SAEs and Other Events to GSK

SAEs, pregnancies, and liver function abnormalities and any other events meeting pre-defined criteria will be reported promptly by the investigator to GSK as described in the following table once the investigator determines the event meets the protocol definition for that event.

	Initial Reports		Follow-up Information on a Previous Report	
Type of Event	**Time Frame**	**Documents**	**Time Frame**	**Documents**
All SAEs	24 hours	SAE data collection tool	24 hours	Updated SAE data collection tool
"CV events" and/or "death"	Initial and follow up reports to be completed within one week of when the cardiovascular event or death is reported	"CV events" and/or "death" data collection tool(s) if applicable	Initial and follow up reports to be completed within one week of when the cardiovascular event or death is reported	Updated "CV events" and/or "death" data collection tool(s) if applicable
Pregnancy	2 Weeks	Pregnancy Notification Form	2 Weeks	Pregnancy Follow-up Form
Liver chemistry abnormalities (Section 8.3.1):				
ALT ≥3 times ULN and bilirubin ≥2 times ULN (>35% direct) (or ALT ≥3 times ULN and INR >1.5, if INR is measured)[c]	24 hours[a]	SAE data collection tool; Liver Event eCRF and liver imaging and/or biopsy eCRFs if applicable[b]	24 hours	Updated SAE data collection tool. Updated Liver Event eCRF[b]
ALT ≥5 times ULN; ALT ≥3 times ULN with hepatitis or rash **or** 3 times ULN ≥4 weeks	24 hours[a]	Liver Event eCRF[b]	24 hours	Updated Liver Event eCRF[b]
ALT ≥3 times ULN and <5 times ULN and bilirubin <2 times ULN	24 hours[a]	Liver Event eCRF does not need to be completed unless elevations persist for 4 weeks or subject cannot be monitored weekly for 4 weeks[b]		

a. GSK to be notified at onset of liver chemistry elevations to discuss subject safety.
b. Liver event documents should be completed as soon as possible
c. INR measurement is not required; if measured, the threshold value stated will not apply to subjects receiving anticoagulants.

Methods for detecting, recording, evaluating, and following up on AEs and SAEs are provided in the SPM.

8.4.3. Regulatory reporting requirements for SAEs

Prompt notification of SAEs by the investigator to GSK is essential so that legal obligations and ethical responsibilities towards the safety of subjects are met.

GSK has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. GSK will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/EC and investigators.

Investigator safety reports are prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and GSK policy and are forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a SAE(s) or other specific safety information (e.g., summary or listing of SAEs) from GSK will file it with the IB and will notify the IRB/EC, if appropriate according to local requirements.

9. CONCOMITANT MEDICATIONS AND NON-DRUG THERAPIES

Subjects will be instructed to inform the investigator prior to starting any new medications from the time of first dose of study treatment until the end of the study (Final Study Visit). Any concomitant medication(s), including non-prescription medication(s) and herbal product(s), taken during the study will be recorded in the eCRF. Additionally, a complete list of all prior anti-cancer therapies will be recorded in the eCRF.

If future changes are made to the list of permitted/prohibited medications, formal documentation will be provided by GSK and stored in the study file. Any such changes will be communicated to the investigative sites in the form of a letter.

9.1. Permitted Medications

Subjects should receive full supportive care during the study, including transfusions of blood and blood products, and treatment with antibiotics, antiemetics, antidiarrheals, and analgesics, and other care as deemed appropriate and in accordance with their institutional guidelines and considering the list of contra-indicated medicines included in Section 9 of the protocol.

Palliative radation and/or surgical intervention is permitted after discussion with the GSK medical monitor and documenting the treatment in the eCRF.

Questions regarding concomitant medications should be directed to the GSK Medical Monitor for clarification.

9.2. Prohibited and Cautionary Medications

Subjects should not receive those medications listed as prohibited in Section 9.2

Subjects should not receive other anti-cancer therapy including chemotherapy, radiation therapy, immunotherapy, biologic therapy, investigational therapy, hormone therapy (other than leuprolide or other GnRH angonists for mCRPC), surgery or tumour embolizationwhile on treatment in this study. Other anti-cancer therapy should not be administered unless one of the following occurs: documented disease progression; unacceptable or unmanageable toxicity; subject is withdrawn from the study at the investigator's discretion or consent is withdrawn; or no further clinical benefit is anticipated which requires permanent discontinuation of study drug. .

Concurrent use of therapeutic warfarin may be allowed. However, increased monitoring of INR and bleeding with dose titration for warfarin is recommended due to potential increase in warfarin concentration when administered with study treatment GSK2816126. Anticoagulants that do not have reversal agents available are prohibited from 14 days prior to the first dose of study drug through completion of the Final Study Visit.

9.2.1. Drugs that may alter the Pharmacokinetics of GSK2816126

It has been demonstrated in vitro that GSK2816126 is metabolized by CYP3A enzymes. However, turnover in human liver microsomes and hepatocytes was low and the relative contribution of this pathway to the elimination of GSK2816126 is presently unknown. GSK2816126 has also been shown to be a substrate of P-gp and BCRP transporters. .

Therefore, substances that potently inhibit or induce CYP3A, P-gp or BCRP (Table 9) should be avoided during the course of the study where possible as these drugs could lead to higher/lower exposure in subjects, potentially leading to alterations of the pharmacologic effects of GSK2816126.

The impact of inhibition of P-gp or BCRP on GSK2816126 pharmacokinetics has not been assessed in humans. Drugs that are mild to moderate inhibitors of P-gp and BCRP should be administered with caution because they may alter GSK2816126 levels (Table 10).

Table 9 Prohibited Drugs Potentially Affecting GSK2816126 Pharmacokinetics Resulting in Increased or Decreased GSK2816126 Exposure

PROHIBITED – strong inducers/inhibitors of CYP3A, , Pgp, Bcrp, since levels of GSK2816126 may be decreased/increased	
Strong CYP3A/Pgp/Bcrp Inhibitor/Inducer	**Therapeutic Area**
clarithromycin, telithromycin, rifamycin class agents (e.g. rifampin, rifabutin, rifapentine) troleandomycin	Antibiotics
itraconazole, ketoconazole	Antifungals
Nefazodone	Antidepressants
Amprenavir, atazanivir delaviridine, fosamprenavir indinavir, lopinavir,nelfinavir, ritonavir, saquinavir, tipranivir	Antiretrovirals, Protease Inhibitors
carbamazepine, cyclosporine, phenobarbital, amiodarone	Miscellaneous

Table 10 Use with Caution Drugs Potentially Affecting GSK2816126 Pharmacokinetics Resulting in Increased or Decreased GSK2816126 Exposure

USE WITH CAUTION – Potential for Inducers/inhibitors of CYP3A, Pgp and BCRP since levels of GSK2816126 may be decreased/increased	
Mild/Moderate CYP3A or Pgp Inhibitor/Inducer	**Therapeutic Area**
voriconazole	Antifungal
diltiazem, verapamil	Antiarrhythmics
Cortisone (>50 mg), hydrocortisone (>40 mg), prednisone or prednisolone (>10 mg), methylprednisolone or triamcinolone (>8 mg), betamethasone or dexamethasone (>1.5 mg)	Glucocorticoids (oral)
aprepitant, cimetidine, montelukast,	Miscellaneous
1. NOTE: Topical or inhaled steroids are permitted.	

9.3. Drugs that may have their Pharmacokinetics altered by GSK2816126

The potential for pharmacokinetic interactions with drugs likely to be co-administered with GSK2816126 in vivo has not been assessed. In vitro data suggests that GSK2816126 has the potential to inhibit CYP2C8, CYP2C9, CYP2C19, and CYP3A (IC50's <9 μM). GSK2816126 does not appear to be an inhibitor of CYP1A2 or CYP2D6. GSK2816126 is also an in vitro inhibitor of human transporters BCRP, OATP1B1, OATP1B3, OCT2, MATE1 and MATE2-K (IC_{50} values of 21, 13, 34, 2.88, 0.025 and 0.95 μM, respectively) In addition, GSK2816126 was shown to activate human PXR (EC_{50} = 6.3 μM) and, therefore, may have the potential to induce CYP enzymes. A further in

vitro study showed induction of CYP3A4 mRNA with a calculated EC_{50} of 4.22-5.43 μM and E_{max} of 3.22-16.5-fold.

These results suggest that narrow therapeutic index medications that are substrates of CYP2C8, CYP2C9, CYP2C19 and CYP3A4, and/or transporters BCRP, OATP, OCT2, MATE1 and MATE2-K should be prohibited as their levels may be increased, and could lead to adverse effect (Table 11). Co-administration of sensitive substrates of these CYPs and/or transporters should be **used with caution** as their levels may be increased or decreased (Table 11). Discussion by the PI/staff with the GSK medical monitor(s) must occur before use of these drugs.

Table 11 Prohibited Drugs Potentially Affected by GSK2816126

PROHIBITED – highly sensitive and/or low therapeutic index CYP3A/CYP2C8/CYP2C9/CYP2C19/OCT2/MATE substrates since levels of these drugs may be increased	
CYP3A Substrate	**Therapeutic Area**
alprazolam, diazepam, midazolam, triazolam	Hypnotics and Sedatives
diergotamine, ergotamine, eletriptan	Antimigraine agents
pimozide,	Antidepressant, Antipsychotics, Antianxiety agents
cyclosporine, sirolimus, tacrolimus	Immunosuppressive agents
astemizole	Antihistamine
sildenafil, tadalafil, vardenafil	Erectile Dysfunction agents
eplerenone	Selective Aldosterone Blockers
tizanidine	Muscle Relaxant
quinidine	Antiarrhythmics
CYP2C8, CYP2C9 and CYP2C19 Substrate	
Amiodarone	Antiarrhythmics
Paclitaxel	Anticancer
tolbutamide, nateglinide	Antidiabetic
phenytoin, s-mephenytoin	Anticonvulsants
acenocoumarol	Anticoagulant
Cyclophosphamide	Immunosuppressant
OCT2, MATE1, MATE2-K Substrate	
Cisplatin	Anticancer
Dofetilide, pilsicainide, procainamide	Antiarrhythmics

Table 12 Use with Caution - Drugs Potentially Affected by GSK2816126

USE WITH CAUTION – Monitor for side effects since levels of these drugs may be increased. Consider dose reduction.	
CYP2C8/9/19/3A/OATP1B1/OATP1B3 Substrate	**Therapeutic Area**
felodipine	Calcium Channel Blockers
lovastatin, rosuvastatin, atorvastatin, fluvastatin	HMG-CoA Reductase Inhibitors
oral budesonide	Corticosteroids
fentanyl, alfentanil	Analgesics
Warfarin, cilostazole*	Anticoagulants and Antiplatelets
Rosiglitazone, repaglinide	Antidiabetics
OCT2, MATE1, MATE2-K Substrate	
captopril	Anti-Hypertensive
ganciclovir, tenofovir	Antiviral
gabapentin,	Anticonvulsants
certirizine, ranitidine	H2 Blocker
metformin	Antidiabetics
atecegatran metoxil	Anticoagulants
glycopyrronium	Respiratory, COPD
pindolol, triamterene	Antihypertension
varenicline	Others
USE WITH CAUTION – Monitor for loss of efficacy or substitute another medication	
Substrates of CYP3A4/CYP2B6 that are affected by induction	**Therapeutic Area**
doxycycline, chloramphenicol,	Antibiotics
caspofungin, terbinafine	Antifungals
enalapril, diltiazem, amlodipine, nifedipine, nisoldipine	Antihypertensives
amitriptyline, nortriptyline, desipramine, imipramine, protriptyline, clomipramine, doxepin	Antidepressants
glipizide, glyburide, tolazamide, chlorpropamide	Antidiabetics
zonisamide, valproate, divalproex	Anticonvulsants
buspirone	Antidepressant, Antipsychotics, Antianxiety agents
buprenorphine, naloxone, naltrexone, nalmefene	Opioid agonist/antagonists
aprepitant, clofibrate,, tramadol, methohexital, estazolam, galantamine, leflunomide, solifenacin, sulfasalazine,	Miscellaneous

*Concurrent use of therapeutic warfarin may be allowed. Increased monitoring of INR and bleeding with dose titration of warfarin is recommended due to potential increase in warfarin concentration when co-administered with GSK2816126. However, anticoagulants that do not have reversal agents available are prohibited

9.4. Drugs and QT prolongation

Co-administration of medications that are known to prolong the QT interval and have a risk of causing Torsades de Pointes are **PROHIBITED** for 5 half-lives of the drug **with a minimum of 14 days** prior to the first dose of study drug until discontinuation from the study drug with the exception of **amiodarone** which is prohibited beginning **6 months** prior to Screening through discontinuation from the study. (However, there may be situations when the subject is on study and Advanced Cardiac Life Support requires the use of amiodarone, which should be used as per local clinical guidelines). The medications with a risk of torsade de pointes are provided in Table 13.

Co-administration of medication that are known to prolong the QT interval and have a possible risk of causing Torsades de Pointes "possible-torsadogenic medication"are to be used with Extreme Caution beginning 14 days prior the first dose of study drug until discontinuation from the study. On starting cautionary medications such as in Table 14, additional ECG monitoring should be implemented after cycle 1. Additional ECGs should be taken at the next scheduled study visit following the initiation of the "possible-torsadogenic medication". If there are no abnormalities, regular cardiac safety monitoring can be resumed per Table 6. If there are abnormalities, implement additional cardiotoxcity monitoring as addressed in Section 3.8.1. and contact GSK Medical Monitor.

Neither list is all inclusive and subject to change based on evolving data. Both tables are taken from the www.crediblemeds.org website available as of 09-Jan-2017. Latest list of medications is available on www. crediblemeds.org website.

Questions regarding concomitant medications whould be directed to the GSK Medical Monitor.

Table 13 Drugs Known to prolong the QT interval and have a Risk of Torsades de Pointes that are PROHIBITED for Co-Administration with GSK2816126

Generic Name	Drug Class	Generic Name	Drug Class
Amiodarone	Anti-arrhythmic	Haloperidol	Anti-psychotic
Anagrelide	Phosphodiesterase 3 inhibitor	Ibogaine(only on non US Market)	Psychedelic
Arsenic trioxide	Anti-cancer	Ibutilide	Anti-arrhythmic
Astemizole (Removed from Market)	Antihistamine	Levofloxacin	Antibiotic
Azithromycin	Antibiotic	Levomepromazine(Only on Non US Market)	Antipsychotic
Bepridil (Removed from Market)	Anti-anginal	Levomethadyl acetate (Removed from Market)	Opiate
Chloroquine	Anti-malarial	Levosulpiride (only on non US Market)	Antipsychotic
Chlorpromazine	Anti-psychotic / Anti-	Mesoridazine	Anti-psychotic

Generic Name	Drug Class	Generic Name	Drug Class
	emetic	(Removed from Market)	
Cilostazol	Phosphodiesterase 3 inhibitor	Methadone	Opiate
Ciprofloxacin	Antibiotic	Moxifloxacin	Antibiotic
Cisapride (Removed from Market)	GI stimulant	Ondansetron	Anti-emetic
Citalopram	Anti-depressant, SSRI	Oxaliplatin	Antineoplastic Agent
Clarithromycin	Antibiotic	Papaverine HCL (Intra-coronary)	Vasodilator, Coronary
Cocaine	Local anesthetic	Pentamidine	Antibiotic
Disopyramide	Anti-arrhythmic	Pimozide	Anti-psychotic
Dofetilide	Anti-arrhythmic	Probucol (Removed from Market)	Antilipemic
Domperidone (Only on non US Market)	Anti-nausea	Procainamide	Anti-arrhythmic
Donepezil	Cholinesterase inhibitor	Propofol	Anaesthetic, general
Dronedarone	Anti-arrhythmic	Quinidine	Anti-arrhythmic
Droperidol	Anti-psychotic / Anti-emetic	Roxithromycin (Only on Non US Market)	Antibiotic
Erythromycin	Antibiotic	Sevoflurane	Anesthetic, general
Escitalopram	Anti-depressant, SSRI	Sotalol	Anti-arrhythmic
Flecainide	Anti-arrhythmic	Sparfloxacin (Removed from Market)	Antibiotic
Fluconazole	Antifungal	Sulpiride (Only non US Market)	Anti-psychotic, atypical
Gatifloxacin (Removed from Market)	Antibiotic	Sulyopride (Only on Non US Market)	Anti-psychotic, atypical
Grepafloxacin (Off market worldwide)	Antibiotic	Terlipressin (Only on non US Market)	Vasoconstrictor
Halofantrine	Anti-malarial	Terfenadine (Removed from US Market)	Antihistamine
		Thioridazine	Anti-psychotic
		Vandetanib	Anti-cancer

Data Source: www.crediblemeds.org (9 January 2017)

Table 14 Drugs Known to prolong the QT interval with a Possible Risk of Torsades de Pointes that are Permitted for co-administration with Extreme Caution

Generic Name	Drug Class	Generic Name	Drug Class
Alfuzosin	Alpha1-blocker	Mirabegron	Beta3 adrenergic antagonist
Apomorphine	Dopamine agonist	Mirtazapine	Anti-depressant, Tetracyclic
Aripiprazole	Anti-psychotic, atypical	Moexipril/HCTZ	Anti-hypertensive
		Nicardipine	Anti-hypertensive
Artenimol+piperaquine	Antimalarial	Nilotinib	Kinase inhibitor
Asenapine	Anti-psychotic, atypical	Norfloxacin	Antibiotic
Atomoxetine	Norepinephrine reuptake inhibitor	Nortriptyline	Antibiotic
Bedaquiline	Antibiotic	Ofloxacin	Antibiotic
Bendamustine	Alkylating agent		
Bortezomib	Proteasome inhibitor	Osimertinib	Tyrsine kinase inhibitor
Bosutinib	Tyrosine kinase inhibitor	Oxytocin	Oxytocic
Buprenorphine	Opioid receptor modulator	Paliperidone	Anti-psychotic, atypical
Capecitabine	Anticancer	Panobinostat	Histone deacetylase inhibitor
Ceritinib	Kinase inhibitor	Pasireotide	Somatostatin analog
Clomipreamine	Antidepressant, Tricyclic	Pazopanib	Tyrosine kinase inhibitor
Clozapine	Anti-psychotic, atypical	Perflutren lipid microspheres	Imaging contrast agent
Crizotinib	Kinase inhibitor	Perphenazine	Antipsychotic
Cyamemazine (cyamepromazine)(Only on Non US Market)	Antipsychotic	Pipamperone (On non US Market)	Antipsychotic
Dabrafenib	Anti-cancer	Promethazine	Anti-psychotic / Anti-emetic
Dasatinib	Tyrosine kinase inhibitor		
Degarelix	Gonadotropin Releasing Hormone		
Delamanid (Only on Non US Market)	Antibiotic	Rilpivirine	Anti-viral
Desipramine	Antidepressant, Tricyclic	Risperidone	Anti-psychotic, atypical
Dexmedetomidine	Sedative		
		Romidepsin	Histone deacetylase inhibitor
Dolasetron	Anti-emetic	Saquinavir	Anti-viral
Efavirenz	Antiretroviral	Sertindole (On non US Market)	Anti-psychotic, atypical
Eribulin mesylate	Anti-cancer	Solifenacin	Muscle Relaxant
Ezogabine (Retigabine)	Anticonvulsant	Sorafenib	Tyrosine kinase inhibitor
Famotidine	H2-receptor antagonist	Sunitinib	Anti-cancer
Felbamate	Anti-convulsant		
Fingolimod	Sphingosine phospate receptor modulator	Tamoxifen	Anti-cancer

Generic Name	Drug Class	Generic Name	Drug Class
Flupentixol (Only on Non US Market)	Dopamine 2 and 5HT2a antagonist	Telavancin	Antibiotic
Foscarnet	Anti-viral	Telithromycin	Antibiotic
		Tetrabenazine	Monoamine Transporter Inhibitor
		Tiapride (Only on Non US Market)	Selective D2, D3 dopamine antogonist
Gemifloxacin	Antibiotic	Tizanidine	Muscle relaxant
Granisetron	Anti-emetic	Tolterodine	Muscle relaxant
Hydrocodone-ER	Analgesic	Toremifene	Estrogen agonist/antagonist
Iloperidone	Anti-psychotic, atypical	Trimipramine	Antidepressant, Tricyclic
Imipramine (melipramine)	Antidepressant, Tricyclic	Tropisetron (only on Non US Market)	Antiemetic
Isradipine	Anti-hypertensive	Vardenafil	Phosphodiesterase inhibitor
Lapatinib	Anti-cancer	Vemurafenib	Kinase Inhibitor
Lenvatinib	Anticancer	Venlafaxine	Anti-depressant, SNRI
Leuprolide	Gonadotropin Receptor Anonist	Vorinostat	Histone deacetylase inhibitor
Lithium	Anti-mania		
Melperone (Only on Non US Market)	Antipsychotic, atypical	Zotepine (Only on Non US Market)	Anti-psychotic, atypical
Mifepristone	Progesterone antagonist		

Data Source: www.crediblemeds.org (9 January 2017)

If a subject requires medication for hyperemesis, due to the potential of serotonin 5-HT3 receptor antagonists to increase QTcF, palonosetron and ondansetron at a maximum oral dose of 8 mg TID are the only allowed drugs in this class. Intravenous administration of these drugs are not permitted.

9.5. Non-Drug Therapies

Non-drug anti-cancer therapies (e.g., radiation therapy, surgery, and/or tumor embolization) will not be permitted from the screening visit through the post-study follow-up visit.

NOTE: Subjects may receive palliative radiation treatment during this study.

Subjects will abstain from using herbal preparations/medications within 14 days prior to the first dose of GSK2816126 throughout the study until the final study visit. Herbal products include, but are not limited to:

- St. John's Wort, kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone, yohimbe, saw palmetto, and ginseng

The investigator should contact a GSK Medical Monitor before initiating treatment with any herbal preparation including marijuana.

10. LIFESTYLE AND/OR DIETARY RESTRICTIONS

10.1. Contraception

10.1.1. Female Subjects

A female of non-childbearing potential is defined as:

- Post menopausal women (including all women 60 years of age or older) with 1 year without menses with an appropriate clinical profile (e.g. age appropriate, >45 years) in the absence of hormone replacement therapy (HRT) or medical suppression of the menstral cycle (e.g. leuprolide treatment). In questionable cases for women <60 years of age, a blood sample with simultaneous follicle stimulating hormone (FSH) and estradiol falling into the central laboratory's post-menopausal reference range is confirmatory [Kronenberg, 2008; Strauss and Barbieri, 2004]. Females under 60 years of age, who are on hormone replacement therapy (HRT) and whose menopausal status is in doubt, will be required to use one of the contraceptive methods listed below if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of post menopausal status prior to study enrollment. For most forms of HRT, at least 2-4 weeks will elapse between the cessation of therapy and the blood draw, this interval depends on the type and dosage of HRT. Following confirmation of their post menopausal status, they can resume use of HRT during the study without use of a contraceptive method. If laboratory values for FSH and estradiol are drawn and the results do not confirm menopause on a potential subject that otherwise met the specifications for being post menopausal as defined below without question, the subject may still enroll in the study as a female of non-childbearing potential if approved by the medical monitor and the safety physician.

- Females under 60 year of age with a documented bilateral tubal ligation or salpingectomy, hysteroscopic tubal occlusion procedure with follow up confirmation of bilateral tubal occlusion, hysterectomy or bilateral oophorectomy (surgical menopause) and no plans to utilize assisted reproductive techiniques (e.g., in vitro fertilization or donor embryo transfer).

A female of childbearing potential is defined as any female who does not meet the criteria of non-childbearing potential as described in the previous paragraph and to also include:

- Females with functioning ovaries (i.e. post menarche, premenopausal women with no documented impairment of oviduct or uterine function that would cause sterility).
- Females with oligomenorrhea, females who are peri-menopausal and young females who have begun to menstrusate.

Female subjects of childbearing potential must not become pregnant during the study and so must be sexually inactive by abstinence or use non-hormonal contraceptive methods

with a failure rate of <1% per year when used consistently and correctly and , when applicable, in accordance with the product label. These are defined below.

Abstinence

Sexual inactivity by abstinence must be consistent with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

Complete abstinence from sexual intercourse for 14 days prior to first dose of study treatment, through the dosing period, and for at least two weeks (14 days) after the last dose of study treatment.

Requirements for Female Subjects of Reproductive Potential: Contraceptive Methods with a Failure Rate of <1% per year:

- **GSK2816126 is a potential CYP3A enzyme inducer which may decrease the efficacy of hormonal contraceptives. Therefore the use of hormonalcontraceptives is excluded.**
- Non-hormonal intrauterine device (IUD) or intrauterine system (IUS) that meets the <1% failure rate as stated in the product label.
- Male partner sterilization (vasectomy with documentation of azoospermia) prior to the female subject's entry into the study, and this male is the sole partner for that subject. For this definition, "documented" refers to the outcome of the investigator's/designee's medical examination and/or semen analysis of the subject or review of the subject's medical history or medical history interview provided by the subject or her partner. ,

These allowed methods of contraception are only effective when used consistently, correctly and in accordance with the product label. The investigator is responsible for ensuring subjects understand how to properly use these methods of contraception.

10.1.2. Male Subjects

To prevent pregnancy in a female partner or to prevent exposure of any partner to the study treatment from a male subject's semen, male subjects must use one of the following contraceptive methods from the time of first dose of study medication until at least 2 weeks (14 days) following last dose of study medication:

- Vasecetomy with documentation of azoospermia or bilateral orchiectomy. The documentation on male sterility can come from the site personnel's; review of subjects medical records, medical examination and/or semen analysis, or medical history interview provided by the subject or his partner.
- Abstinence from penile-vaginal intercourse, defined as sexual inactivity consistent with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

- Male condom plus partner use of a highly effective contraceptive (< 1% rate of failure per year as stated in the product label) such as intrauterine device or system or hormonal birth control such as contraceptive subdermal implant, combined estrogen and progestogen oral contraceptive, injectable progestogen, contraceptive vaginal ring, or percutaneous contraceptive patches.

These allowed methods of contraception are only effective when used consistently, correctly and in accordance with the product label. The investigator is responsible for ensuring subjects understand how to properly use these methods of contraception.

10.2. Lactation Restrictions

Female subjects who are lactating must discontinue nursing prior to the first dose of study treatment and must refrain from nursing *throughout the treatment period and for a*t least two weeks (14 days) after last dose of study treatment.

10.3. Caffeine, Alcohol and Tobacco Restrictions

Subjects will abstain from ingesting alcohol, tobacco products, caffeine- or xanthine-containing products (e.g., coffee, tea, cola drinks, chocolate) for 24 hours prior to the start of dosing until collection of the final PK and or PD sample during each session.

10.4. Sun and UV Exposure Restrictions

Prior to starting study drug, subjects should be instructed to follow the below procedures from the time of first dose of study medication until at least 2 weeks (14 days) following last dose of study medication due to long elimination phase of GSK2816126:

- Minimize or avoid prolonged exposure to natural or artificial sunlight (e.g., tanning beds, sunlamps, UVA or UVB treatments)
- Wear loose fitting clothing with long sleeves, sunglasses, and broad rim hat that protect the skin from sun exposure AND use a broad spectrum sunscreen (e.g., UVA and UVB protective with minimum SPF 30) on any uncovered areas of the body if outdoors

11. DATA MANAGEMENT

For this study, data will be collected using defined eCRFs in the validated data system, InForm. Some data (i.e. Biomarker, PK, Holter, ECG) will be transmitted electronically to GSK from an external vendor via a validated data system.

In all cases, subject initials will not be collected or transmitted to GSK according to GSK policy.

GSK requires sites to provide electronic copies (upload digital images or images on CD) of scans for all subjects for central storage which may be transferred to a central independent imaging center. This includes baseline scans and all scans performed during

the course of the study. GSK may request an independent review of scans. See SPM for additional details.

12. DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

12.1. Hypotheses

12.1.1. Part 1: Dose-Escalation Phase

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 utilize descriptive methods only.

The cohort expansion of GCB-DLBCL subjects in Part 1 will assess the overall response rate (p) of GCB-DLBCL patients. The null and alternative hypotheses for the overall response rate are detailed below:

The null hypothesis is:

H_0: $p \leq 20\%$

The alternative hypothesis is:

H_A: $p \geq 40\%$

For cohort expansion of solid tumor subjects in Part 1, there is no formal statistical hypothesis are being tested. Analysis of the data obtained from solid tumor expansion will utilize descriptive methods only.

12.1.2. Part 2: Expansion Cohorts

The null hypothesis and alternative hypothesis for the four expansion cohorts of GCB-DLBCL and tFL patients in Part 2 are same as those in Part 1. That is, for each cohort:

The null hypothesis is:

H_0: $p \leq 20\%$

The alternative hypothesis is:

H_A: $p \geq 40\%$

For MM cohort, the null hypothesis is:

H_0: $p \leq 10\%$

The alternative hypothesis is:

H_A: $p \geq 25\%$

12.2. Sample Size Determination

The sample size planned for Part 1 arises from the predefined criteria for dose selection and is not driven by statistical considerations.

In addition, Part 1 expansion may include up to 27 GCB-DLBCL subjects at MTD/RP2D twice-weekly for 3 out of 4 weeks followed by 1 week off. This will allow futility/success analysis with type I error rate no more than 0.1and at least 80% of power. Additionally, 15 subjects with solid tumors or prostate cancer may be enrolled for the evaluation of safety, futility and efficacy.

The additional 168 subjects in Part 2 of the study (which includes up to 32 subjects each for the EZH2 mutant and EZH2 WT GCB-DLBCL populations, and up to 32 subjects each for EZH2 mutant and EZH2 WT tFL populationsas well as up to 40 MM subjects) will provide additional safety and tolerability information about the treatment and a better precision around the response rate estimate.

Approximately 168 subjects will be enrolled in Part 2 in five expansion cohorts: two GCB-DLBCL cohorts with up to 32 subjects from the EZH2 wild-type population, and up to 32 subjects from the EZH2 mutation positive population, and two tFL cohorts with up to 32 subjects from the EZH2 wild-type population and up to 32 subjects from the EZH2 mutation positive population and up to 40 subjects in the MM cohort. Additional subjects/cohorts may be enrolled to allow for evaluation of additional dose levels.

12.2.1. Part 1: Dose-Escalation Phase

12.2.1.1. Dose Escalation in Part 1

The total number of subjects to be enrolled for dose escalation in Part 1 will depend on the number of subjects needed to characterize individual dose cohorts. The sample size is not driven by statistical considerations. However, it is anticipated that approximately 40 subjects will be enrolled. Given true incidence rates of DLTs, the associated probabilities of escalating to the next dose in a 3+3 scheme are provided for reference below in Table 15.

Table 15 Statistical Basis for Phase I Dose Escalation in a 3+3 Scheme

True incidence of dose-limiting toxicity	10%	20%	30%	40%	50%	60%
Probability of escalating the dose	0.91	0.71	0.49	0.31	0.17	0.08

12.2.1.2. Cohort Expansion in Part 1

For GCB-DLBCL expansion cohort in Part 1, futility and efficacy evaluation of response data will be performed in order to support the early decision of Part 2 expansion. The sample size and stopping rules are based on the predictive probability methodology of Lee & Liu [Lee, 2008]. The predictive probability design is similar to a two-stage design in that it allows for early termination of the trial due to either futility or efficacy. The

differences are that the predictive probability design allows for evaluation of stopping rules on an on-going basis, once a minimum number of subjects are evaluable, rather than at only two stages. While the two designs have comparable type I error rates and power, the probability of early termination is greater with the predictive probability design compared with two-stage design.

The detailed decision rules of the design for Part 1 expansion cohort are listed in Table 16. The decision rules to stop the trial for either futility or efficacy were constructed as follows:

- If Predictive probability of response greater than the null hypothesis$<\theta_L$, then stop the trial and reject the alternative hypothesis (i.e., claim futility); and
- If Predictive probability of response greater than the null hypothesis $>\theta_U$, then stop the trial and reject the null hypothesis (i.e., declare efficacy);
- Otherwise continue enrollment,

Where θ_L and θ_U are prespecified lower and upper limit of probabilities for establishing stopping criteria in terms of futility and efficacy, respectively.

The hypothesis of overall response rate (p) of GCB-DLBCL subjects for the cohort expansion design are detailed below.

The null hypothesis is:

H_0: $p \leq 20\%$

The alternative hypothesis is:

H_A:$p \geq 40\%$

As listed in Table 16, the futility/efficacy evaluation will start with 13 subjects and allow for maximum of 27 subjects (including GCB-DLBCL subjects enrolled at the RP2D in the dose escalation phase.) This design will have a type I error rate (α) of 0.087 and a power of 0.803. In this particular expansion part, the trial is designed to allow stopping for both futility and efficacy. The trial may be stopped early for futility if the predictive probability of the overall response rate greater than the null hypothesis of 20% is very low, i.e.below 5.0% for this design, and may be stopped early for efficacy if the predictive probability of the overall response rate greater than 20% is very high, i.e. 90.0% or above. The type I error rate, power, and predictive probability of success were derived by explicitly stating null and alternative hypothesis of response rate, the minimum and maximum sample size, futility and efficacy stopping boundaries and the selection of the optimizing criterion as the maximization of power under the alternative hypothesis. The Bayesian prior used in determining the design was Beta (0.15, 0.85), a distribution with a mean response rate of 15%. Under the null hypothesis, that is, if the true response rate is 20%, the expected sample size of the design is 16.48 subjects and probability of early termination (PET) is 96.3%. Under the alternative hypothesis, that is,

if the true response rate is at least 40%, the expected sample size of the design is 16.98 subjects and PET is 94.7%.

The input parameters for finding the design shown in Table 16 are:

Nmin	13
Cohort	1
Nmax	27
theta_Lbegin	0.05
theta_Lend	0.05
theta_Lstep	0.001
theta_Upper	0.9
theta_Tbegin	0.9
theta_Tend	0.9
theta_Tstep	0.001
p_0	0.2
p_1	0.4
Prior a0	0.15
Prior b0	0.85
Type I Error	0.1
Power	0.8

Table 16 Stopping Rules for GSK2816126 Part 1 GCB-DLBCL Cohort Expansion

No. of Subjects Evaluated for Response	Stopping Criteria [1]	
	Stop for Futility if No. of Responders (CR+PR) Less Than or Equal To This Number	Declaration of Efficacy if No. of Responders (CR+PR) Greater Than or Equal To This Number
13	2	6
14	2	7
15	2	7
16	3	7
17	3	7
18	3	8
19	4	8
20	4	8
21	5	8
22	5	9
23	5	9
24	6	9

No. of Subjects Evaluated for Response	Stopping Criteria [1]	
	Stop for Futility if No. of Responders (CR+PR) Less Than or Equal To This Number	**Declaration of Efficacy if No. of Responders (CR+PR) Greater Than or Equal To This Number**
25	6	9
26	7	9
27	8	9

[1]: The specific criteria for stopping the GCB-DLBCL expansion cohort for futility or efficacy. For instance, if there are 20 subjects, then the trial may be stopped for futility if No. of Responders ≤4, or Part 2 opened for efficacy if No. of Responders ≥8.

12.2.2. Part 2: Expansion Cohort

Upon completion of cohort expansion in Part 1 and the totality of data supports opening Part 2, GCB-DLBCL and tFL patients in both mutation status, as well as patients with MM will be enrolled at RP2D for Part 2 study. There are 5 cohorts in Part 2, i.e. 2 cohorts for GCB-DLBCL patients (mutant and wild type), 2 cohorts for tFL petients (mutant and wild type), and 1 cohort for MM patients.

For each of GCB-DLBCL and tFL cohorts, at least 10 subjects and up to 32 subjects will be enrolled at the RP2D (including subjects enrolled in the previous stage), using decision rules defined in Table 17. The sample size and stopping rules are based on the methodology of Lee & Liu [Lee, 2008].

The assumptions underlying the design are detailed below for GCB-DLBCL and tFL cohorts. The null hypothesis is:

H_0: $p \leq 20\%$

The alternative hypothesis is:

H_A:$p \geq 40\%$

As listed in Table 17, the futility/efficacy evaluation will start with 10 subjects and until maximum of 32 subjects. This design allows to stop early for futility only. The design will have a type I error rate (α) of 0.066 and a power of 0.801. The trial may be stopped early for futility if the predictive probability of the overall response rate greater than the null hypothesis of 20% is below 10% for this design. The type I error rate, power, and predictive probability of success were derived by explicitly stating null and alternative hypothesis of response rate, the minimum and maximum sample size, futility and efficacy stopping boundaries and the selection of the optimizing criterion as the maximization of power under the alternative hypothesis. The Bayesian prior used in determining the design was Beta (0.15, 0.85), a distribution with a mean response rate of 15%. Under the null hypothesis, that is, if the true response rate is 20%, the expected sample size of the design is 16.06 subjects and probability of early termination (PET) is 90.8%. Under the

alternative hypothesis, that is, if the true response rate is at least 40%, the expected sample size of the design is 29.16 subjects and PET is 18.1%.

The input parameters for the design shown in Table 17 are:

Nmin	10
Cohort	1
Nmax	32
theta_Lbegin	0.1
theta_Lend	0.1
theta_Lstep	0.001
theta_Upper	1
theta_Tbegin	0.9
theta_Tend	0.9
theta_Tstep	0.001
p_0	0.2
p_1	0.4
Prior a0	0.15
Prior b0	0.85
Type I Error	0.1
Power	0.8

Table 17 Stopping Rules for GSK2816126 GCB-DLBCL and tFL Cohort

Expansion in Part 2

Number of evaluable subjects	Stop for Futility if No. of Responders (CR+PR) Less Than or Equal To This Number
10	1
11	1
12	2
13	2
14	2
15	3
16	3
17	3
18	3
19	4
20	4
21	4
22	5

Number of evaluable subjects	Stop for Futility if No. of Responders (CR+PR) Less Than or Equal To This Number
23	5
24	5
25	6
26	6
27	6
28	7
29	7
30	8
31	8
32	9

For MM cohort, at least 14 subjects and up to 40 subjects will be enrolled at the RP2D, using decision rules defined in Table 18. The sample size and stopping rules are based on the methodology of Lee & Liu [Lee, 2008]. The null hypothesis underlying the design is:

H_0: $p \leq 10\%$

The alternative hypothesis is:

H_A; $p \geq 25\%$

The input parameters for the design shown in Table 18 are:

Nmin	14
Cohort	1
Nmax	40
theta_Lbegin	0.1
theta_Lend	0.1
theta_Lstep	0.001
theta_Upper	1
theta_Tbegin	0.9
theta_Tend	0.9
theta_Tstep	0.001
p_0	0.1
p_1	0.25
Prior a0	0.1
Prior b0	0.9
Type I Error	0.1
Power	0.8

Table 18 Stopping Rules for GSK2816126 Cohort Expansion of MM Subjects in Part 2

Number of evaluable subjects	Stop for Futility if No. of Responders (CR+PR) Less Than or Equal To This Number
14	1
15	1
16	1
17	1
18	1
19	1
20	1
21	2
22	2
23	2
24	2
25	2
26	2
27	3
28	3
29	3
30	3
31	3
32	4
33	4
34	4
35	4
36	4
37	5
38	5
39	5
40	6

As listed in Table 18, the futility/efficacy evaluation will start with 14 subjects until maximum of 40 subjects (including MM subjects enrolled at the RP2D in the dose escalation phase, if any). This design allows to stop early for futility only. The design will have a type I error rate (α) of 0.072 and a power of 0.814. The trial may be stopped early for futility if the predictive probability of the overall response rate greater than the null hypothesis of 10% is below 10% for this design. The type I error rate, power, and predictive probability of success were derived by explicitly stating null and alternative hypothesis of response rate, the minimum and maximum sample size, futility and efficacy

stopping boundaries and the selection of the optimizing criterion as the maximization of power under the alternative hypothesis. The Bayesian prior used in determining the design was Beta (0.10, 0.90), a distribution with a mean response rate of 10%. Under the null hypothesis, that is, if the true response rate is 10%, the expected sample size of the design is 20.82 subjects and probability of early termination (PET) is 89.0%. Under the alternative hypothesis, that is, if the true response rate is at least 25%, the expected sample size of the design is 36.56 subjects and PET is 16.7%.

12.3. Data Analysis Considerations

Data will be listed and summarized according to the GSK reporting standards, where applicable. Complete details will be documented in the Reporting and Analysis Plan (RAP). Any deviations from, or additions to, the original analysis plan described in this protocol will be documented in the RAP and final study report.

12.3.1. Analysis Populations

All Subjects Population: This will consist of all subjects who received at least one dose of study treatment. Safety and clinical activity analyses will be evaluated based on this population.

The PK Concentration Population: This will consist of those subjects in All Subjects Population for whom a PK sample is obtained and analyzed.

12.3.2. Analysis Data Sets

The construction of analysis data sets will be performed in accordance with all applicable GSK standards and procedures.

12.3.3. Treatment Comparisons

No formal hypothesis testing will be performed between dose cohorts. Safety, PK, PD marker, and efficacy summaries will be provided by dose cohort and planned time of assessment in Part 1 and by expansion cohort and planned time of assessment in Part 2.

12.3.3.1. Primary Comparisons of Interest

All available data, including adverse events, changes in laboratory values and other safety parameters will be evaluated for each dose cohort in Part 1, in addition to futility and success analyses, and for each expansion cohort in Part 2.

12.3.3.2. Other Comparisons of Interest

- PK: PK parameters will be evaluated and summarized for each dose cohort in Part 1.
- PD marker: Changes from baseline in PD markers will be evaluated and summarized for each dose cohort in Part 1 and for each cohort in Part 2.

- Clinical anti-cancer activity: The number of subjects with complete responses, partial responses, stable disease, and progressive disease for each dose cohort in Part 1 and for each expansion cohort in Part 2 will be listed and summarized if data warrant.

12.3.4. Interim Analysis

12.3.4.1. Part 1

Futility and efficacy interim analysis of overall response rate will be performed continuously for GCB-DLBCL expansion cohort in Part 1 of the study, after 13 subjects have been enrolled. In addition, safety, PK, and PD marker data will be examined during Part 1. Prior to determining the GSK2816126 dose for the next cohort, exploratory analyses will be conducted to assess the relationship of GSK2816126 dose levels with safety, PK and PD parameters using all data from available cohorts. If success criteria are reached at an interim analysis for GCB-DLBCL at MTD/RP2D twice-weekly every 3 out of 4 weeks followed by 1 week off, and the totality of data support opening Part 2, then Part 2 will begin and Part 1 expansion will close.

Full details of procedures and of the analyses planned at the interim analysis will be provided in the Reporting and Analysis Plan (RAP).

12.3.4.2. Part 2

For each expansion cohort, after the initial 10 subjects have enrolled at the RP2D dose, response data will be reviewed on an ongoing basis and the number of responses observed will be compared with the stopping rules provided in Section 12.2.2. In addition, safety, PK, and PD marker data will be analyzed. Full details of procedures and of the analyses planned at the interim analysis will be provided in the Reporting and Analysis Plan (RAP).

12.3.5. Final Analyses

12.3.5.1. Safety Analyses

Safety endpoints are described in Section 2. The All Subjects population will be used for the analysis of safety data. All serially collected safety endpoints (e.g., laboratory tests, vital signs, ECGs) will be summarized according to the scheduled, nominal visit at which they were collected and across all on-treatment time points using a "worst-case" analysis. Complete details of the safety analyses will be provided in the RAP.

A listing by subject including treatment administered and compliance will be generated with dates and times of treatment administered.

All relevant safety data will be listed and summarized according to current standards. The RAP will list the templates for the displays. All AEs will be listed. A summary of the number and percent of subjects reporting each AE at least once will be produced for

all AEs, for drug-related AEs and for SAEs for Part 1 (for each dose cohort) and Part 2. A listing of those AEs identified as dose-limiting toxicities will also be produced for each dose cohort for Part 1. A listing showing the relationship of AE verbatim text to group terms and body systems will also be produced. A listing of withdrawals due to AEs will be provided. Deaths and SAEs will be listed should they occur.

Vital signs and ECG data will be listed and summarized for Part 1(for each dose cohort) and Part 2. Changes from baseline will be included in the listings and summary.

ECOG Performance Status assessments will be listed and summarized for Part 1 (for each dose cohort) and Part 2.

Vital signs and ECG data will be listed and summarized for Part 1(for each dose cohort) and Part 2. Changes from baseline will be included in the listings and summary.

12.3.5.2. Clinical Laboratory Evaluations

Hematology and clinical chemistry data will be summarized using frequencies and proportions according to NCI-CTCAE v4.0 grade [NCI-CTCAE, 2009]. Laboratory test results outside the reference ranges that do not have associated NCI-CTCAE criteria will be summarized using proportions. Summaries will include data from scheduled assessments only, and all data will be reported according to the nominal visit date for which it was recorded (i.e., no visit windows will be applied). Unscheduled data will be included in "overall" and "any post-screening" summaries which will capture a worst case across all scheduled and unscheduled visits post first dose of study treatment. Further details will be provided in the RAP.

12.3.5.3. Pharmacokinetic Analyses

Pharmacokinetic analyses will be the responsibility of the Clinical Pharmacology, Modeling and Simulation Department, GSK.

12.3.5.3.1. Non-compartmental Pharmacokinetic Analyses

Pharmacokinetic analysis of GSK2816126 in Part 1 will be conducted by non-compartmental methods. 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 from time zero (pre-dose) to last time of quantifiable concentration, AUC(0-t) and/or AUC from time zero (pre-dose) extrapolated to infinite time AUC(0-∞)] after single dose and AUC(0-t) and AUC over the dosing interval [AUC(0-tau)] after repeated administration
- apparent terminal phase elimination rate constant (λz)
- apparent terminal phase half-life (t½)
- clearance (CL)
- volume (V)

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.

GSK2816126 concentrations will be determined in urine samples to determine urinary recovery of unchanged drug and renal clearance.

12.3.5.3.2. Metabolic Profiling

In a subset of subjects, blood samples will be pooled and analyzed qualitatively for circulating metabolites; 0-24 hour urine samples will also be analyzed for GSK2816126 and compound related metabolites. These results will be performed under a separate DMPK protocol and reported separately.

12.3.5.3.3. Population Pharmacokinetics

Blood concentration-time data from Part 2 (Expansion Cohorts) will be combined with data from Part 1 and analyzed using a population approach. A nonlinear mixed effects model will be used to determine population pharmacokinetic parameters and identify relevant covariates (e.g., age, weight, or disease related covariates).

12.3.5.3.4. Statistical Analyses of Pharmacokinetic Data

Statistical analyses of the PK parameter data will be the responsibility of Discovery Biometrics, Oncology, GSK.

GSK2816126 concentration-time data will be listed for each subject and summarized by planned time point and dose cohort in Part 1 and by planned time point and expansion cohort in Part 2.

Pharmacokinetic parameters will be listed and summarized descriptively (mean, standard deviation, median, minimum, maximum, geometric mean (excluding tmax), and the standard deviation, CV% and 95% confidence interval (CI) of log-transformed parameters) by dose cohort in Part 1.

Dose Proportionality: If more than 2 dose cohorts are required to reach RP2D, dose proportionality of GSK2816126 AUC(0-∞) and Cmax following single dose administration and AUC(0-tau) and Cmax following repeat dose administration will be evaluated graphically and using the power model as described below:

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

Where a is the intercept and b is the slope.

The power model will be fitted by restricted maximum likelihood using statistical analysis software (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% CI will be estimated from the power model.

12.3.5.4. Efficacy Analyses

Anti-tumor activity for lymphoma subjects will be assessed based on the Response Criteria listed in Section 15.4. Anti-tumor activity for subjects with solid tumors will be assessed based on the Response Criteria listed in 15.5. Anti-tumor activity for subjects with MM will be assessed based on the Response Criteria listed in 15.6. Anti-tumor activity for subjects with prostate cancer will be assessed based on the Response Criteria listed in 15.7. The response data will be summarized by study part, and cohort within Part 2. Full details will be specified in the RAP.

If the data warrant, PFS and DoR will be calculated and listed for each subject in Part 1 and Part 2. PFS is defined as time from the date of first dose to the date of disease progression according to clinical or radiological assessment or death due to any causes, whichever occurs earliest. DoR is defined as the interval of time from first documented evidence of CR or PR until disease progression or death due to any cause.If the subject does not have a documented date of event, PFS will be censored at the date of the last adequate assessment. Further details on rules of censoring will be provided in the RAP. PFS will be summarized using the Kaplan-Meier method if the data warrant.

12.3.6. PK/PD Relationship

Observed or predicted concentrations or exposure measures (Cmax, Cτ, AUC, or averaged observed concentration [Cav]) will be combined with safety, efficacy, exploratory markers and/or PD measures of interest to examine potential exposure response relationships.

The relationships will first be explored graphically. Where evidence of a signal is seen, linear and non-linear models may be fitted to the data to estimate PK/PD parameters of interest; slope, baseline (E0), EC_{50}, and maximum effect (Emax).

12.3.7. Pharmacodynamic Biomarkers and Exploratory Response Prediction Biomarkers

As data warrant, analyses may be performed to explore the relationship between biomarkers (i.e., somatic mutations), subject baseline characteristics, and other clinical outcomes. All endpoints of interest will be descriptively and/or graphically summarized as appropriate to the data.

As data warrant, analyses may be performed to determine relationships between circulating and tumor biomarkers, expression and clinical response, activity, or resistance to GSK2816126.

The results of exploratory biomarker research investigations will be reported separately from the main clinical study report. Full details will be provided in a RAP.

13. STUDY CONDUCT CONSIDERATIONS

13.1. Posting of Information on Clinicaltrials.gov

Study information from this protocol will be posted on clinicaltrials.gov before enrollment of subjects begins.

13.2. Regulatory and Ethical Considerations, Including the Informed Consent Process

Prior to initiation of a study site, GSK will obtain approval from the appropriate regulatory agency to conduct the study in accordance with International Council on Harmonization/Good Clinical Practice (ICH/GCP) and applicable country-specific regulatory requirements.

The study will be conducted in accordance with all applicable regulatory requirements.

The study will be conducted in accordance with ICH GCP, all applicable subject privacy requirements, and the ethical principles that are outlined in the Declaration of Helsinki 2008, including, but not limited to:

- IRB/EC review and approval of study protocol and any subsequent amendments
- Subject informed consent
- Investigator reporting requirements

GSK will provide full details of the above procedures, either verbally, in writing, or both.

Written informed consent must be obtained from each subject prior to participation in the study.

In approving the clinical protocol the IEC/IRB and, where required, the applicable regulatory agency are also approving the optional assessments, e.g. genetic research described in Appendix 5, unless otherwise indicated. Where permitted by regulatory authorities, approval of the optional assessments can occur after approval is obtained for the rest of the study. If so, then the written approval will clearly indicate approval of the optional assessments is being deferred and the study, except for the optional assessments, can be initiated. When the optional assessments are not approved, then the approval for the rest of the study will clearly indicate this and therefore, the optional assessments will not be conducted.

13.3. Urgent Safety Measures

If an event occurs that is related to the conduct of the study or the development of the IP, and this new event is likely to affect the study of subjects, the Sponsor, and the

investigator will take appropriate urgent safety measures to protect subjects against any immediate hazard.

The Sponsor will work with the investigator to ensure the IRB/EC is notified.

13.4. Quality Control (Study Monitoring)

In accordance with applicable regulations, GCP and GSK procedures, the site will be contacted prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and GSK requirements. When reviewing data collection procedures, the discussion will include identification, agreement and documentation of data items for which the eCRF will serve as the source document.

The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents and to allocate their time and the time to their staff to monitor to discuss findings and any issues.

Monitoring visits will be conducted in a manner to ensure that the:

- Data are authentic, accurate, and complete.
- Safety and rights of subjects are being protected.
- Study is conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

13.5. Quality Assurance

To ensure compliance with ICH/GCP and all applicable regulatory requirements, GSK may conduct quality assurance audits of the site. Regulatory agencies may conduct a regulatory inspection at any time during or after completion of the study. In the event of an audit or inspection, the investigator (and institution) must agree to grant the auditor(s) and inspector(s) direct access to all relevant documents and to allocate their time and the time of their staff to discuss any findings/relevant issues.

13.6. Study and Site Closure

The end of the study will be defined as the date of the last visit of the last subject enrolled.

Upon completion or termination of the study, the monitor will conduct site closure activities with the investigator or site staff (as appropriate), in accordance with applicable regulations, ICH/ GCP, and GSK Standard Operating Procedures.

GSK reserves the right to temporarily suspend or terminate the study at any time for reasons including (but not limited to) safety issues, ethical issues, or severe noncompliance. If GSK determines that such action is required, GSK will discuss the reasons for taking such action with the investigator or head of the medical institution (where applicable). When feasible, GSK will provide advance notice to the investigator or head of the medical institution of the impending action.

If a study is suspended or terminated for **safety reasons**, GSK will promptly inform all investigators, heads of the medical institutions (where applicable),and/or institutions conducting the study. GSK will also promptly inform the relevant regulatory authorities of the suspension/termination along with the reasons for such action. Where required by applicable regulations, the investigator or head of the medical institution must inform the IRB/EC promptly and provide the reason(s) for the suspension/termination.

GSK may also close study sites which fail to recruit subjects within a predefined timeframe, as defined within the Study Procedures Manual (SPM).

13.7. Records Retention

Following closure of the study, the investigator or head of the medical institution (where applicable) must maintain all site study records (except for those required by local regulations to be maintained elsewhere) in a safe and secure location. The records must be easily accessible when needed (e.g., for a GSK audit or regulatory inspection) and must be available for review in conjunction with assessment of the facility, supporting systems, and relevant site staff.

Where permitted by local laws/regulations or institutional policy, some or all of the records may be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution must be exercised before such action is taken. The investigator must ensure that all reproductions are legible and are a true and accurate copy of the original. In addition, they must meet accessibility and retrieval standards, including regeneration of a hard copy, if required. The investigator must also ensure that an acceptable back-up of the reproductions exists and that there is an acceptable quality control procedure in place for creating the reproductions.

GSK will inform the investigator of the time period for retaining the site records in order to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to a particular site, as dictated by local laws/regulations, GSK standard operating procedures, and/or institutional requirements.

The investigator must notify GSK of any changes in the archival arrangements, including, but not limited to archival of records at an off-site facility or transfer of ownership of the records in the event that the investigator is no longer associated with the site.

13.8. Provision of Study Results to Investigators, Posting of Information on Publicly Available Clinical Trials Registers and Publication

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.

GSK will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate.

The results summary will be posted to the GSK Clinical Study Register no later than 8 months after the final primary completion date, the date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome. In addition, a manuscript will be submitted to a peer reviewed journal for publication no later than 18 months after the last subject's last visit (LSLV). When manuscript publication in a peer-reviewed journal is not feasible, a statement will be added to the register to explain the reason for not publishing.

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15. APPENDICES

15.1. Appendix 1: COCKCROFT-GAULT FORMULA

ClCr (mL/min) =	$\frac{Q \times (140 - age[yr]) \times ideal\ body\ weight\ [kg]^*}{72 \times serum\ creatinine\ [mg/dL]}$
Q = 0.85 for females Q = 1.0 for males	
OR	
ClCr (mL/min) =	$\frac{K \times (140 - age[yr]) \times ideal\ body\ weight\ [kg]^*}{Serum\ creatinine\ [umol/L]}$
K = 1.0 for females K = 1.23 for males	

*Calculation of Ideal Body Weight Using the Devine Formula [Devine, 1974]
Ideal body weight:
Males = 50.0 kg + (2.3 kg x each inch over 5 feet) or 50.0 kg + (0.906 kg x each cm over 152.4 cm)
Females = 45.5 kg + (2.3 kg x each inch over 5 feet) or 45.5 kg + (0.906 kg x each cm over 152.4 cm)
Example: Male, actual body weight = 90.0 kg, height = 68 inches
Ideal body weight = 50.0 + (2.3) (68-60) = 68.4 kg.
This subject's actual body weight is >30% over ideal body weight. Therefore, in this case, the subject's ideal body weight of 68.4 kg should be used in calculating estimated CrCl.

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15.2. Appendix 2: ECOG Performance Status[1]

CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.

15.3. Appendix 3: Liver Chemistry Monitoring, Interruption Stopping and Follow-up Criteria

15.3.1. Liver Safety Stopping Criteria and Required Action and Follow up Assessments

Phase I/II liver chemistry stopping and increased monitoring criteria have been designed to assure subject safety and evaluate liver event etiology (in alignment with the FDA premarketing clinical liver safety guidance). http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf.

Phase I/II liver chemistry stopping criteria and required follow up assessments

Liver Chemistry Stopping Criteria – Liver Stopping Event **Subject <u>with</u> entry criteria ALT≤ 2.5 x ULN**	
ALT-absolute	ALT ≥5xULN
ALT Increase	ALT ≥3xULN persists for ≥4 weeks
Bilirubin[1, 2]	ALT ≥3xULN **and** bilirubin ≥2xULN (>35% direct bilirubin)
INR[2]	ALT ≥3xULN **and** INR>1.5, if INR measured
Cannot Monitor	ALT ≥3xULN **and** cannot be monitored weekly for 4 weeks
Symptomatic[3]	ALT ≥3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity
Liver Chemistry Stopping Criteria – Liver Stopping Event **Including subjects <u>with documented</u> liver metastases/tumor infiltration at baseline AND entry criteria ALT>2.5 x ULN but ≤5 x ULN**	
ALT-absolute	**Both** ALT ≥5xULN **and** ≥2x baseline value
ALT Increase	**Both** ALT ≥3xULN **and** ≥ 1.5x baseline value that persists for ≥4 weeks
Bilirubin[1, 2]	ALT ≥3xULN **and** bilirubin ≥2xULN (>35% direct bilirubin)
INR[2]	ALT ≥3xULN **and** INR>1.5, if INR measured
Cannot Monitor	**Both** ALT ≥3xULN **and** ≥1.5x baseline value that cannot be monitored for 4 weeks
Symptomatic[3]	**Both** ALT ≥3xULN **and** ≥1.5x baseline value associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity
Required Actions and Follow up Assessments following ANY Liver Stopping Event	

Actions	Follow Up Assessments
• **Immediately** discontinue study treatment • Report the event to GSK **within 24 hours** • Complete the liver event eCRF and complete an SAE data collection tool if the event also meets the criteria for an SAE[2] • Perform liver event follow up assessments • Monitor the subject until liver chemistries resolve, stabilize, or return to within baseline (see **MONITORING** below) • **Do not restart/rechallenge** subject with study treatment unless allowed per protocol and GSK Medical Governance approval **is granted** (refer to *Appendix 3*) • If restart/rechallenge is **not granted**, permanently discontinue study treatment and may continue subject in the study for any protocol specified follow up assessments **MONITORING:** **For bilirubin or INR criteria:** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24 hrs** • Monitor subjects twice weekly until liver chemistries resolve, stabilize or return to within baseline • A specialist or hepatology consultation is recommended **For All other criteria:** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24-72 hrs** • Monitor subjects weekly until liver chemistries resolve, stabilize or return to within baseline	• Viral hepatitis serology[4] • Blood sample for pharmacokinetic (PK) analysis, obtained approximately 48 h after last dose[5] • Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH). • Fractionate bilirubin, if total bilirubin≥2xULN • Obtain complete blood count with differential to assess eosinophilia • Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form • Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications • Record alcohol use on the liver event alcohol intake case report form **For bilirubin or INR criteria:** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG or gamma globulins). • Serum acetaminophen adduct high pressure liquid chromatography (HPLC) assay (quantifies potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week [James, 2009]). • Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy eCRF forms.

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that subject if ALT ≥ 3xULN **and** bilirubin ≥ 2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin) or ALT ≥ 3xULN **and** INR>1.5, if INR measured which may indicate severe liver injury (possible 'Hy's Law'), **must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis)**; INR measurement is not required and the threshold value stated

will not apply to subjects receiving anticoagulants

3. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia)
4. Includes: Hepatitis A IgM antibody; Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM); Hepatitis C RNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody
5. Record the date/time of the PK blood sample draw and the date/time of the last dose of study treatment prior to blood sample draw on the eCRF. If the date or time of the last dose is unclear, provide the subject's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SRM.

Phase I/II Oncology liver chemistry increased monitoring criteria with continued therapy

Liver Chemistry Increased Monitoring Criteria – Liver Monitoring Event	
Criteria	**Actions**
Subject <u>with</u> entry criteria ALT≤2.5x ULN ALT ≥3xULN **but** <5xULN **and** bilirubin <2xULN, **without** symptoms believed to be related to liver injury or hypersensitivity **and** who can be monitored weekly for 4 weeks **Subject <u>with documented</u> liver metastases/tumor infiltration at baseline AND entry criteria ALT>2.5 x ULN but ≤5 x ULN** ALT ≥3x ULN and 1.5x baseline value **but** ALT <5x ULN and 2x baseline value **and** bilirubin <2xULN**, without** symptoms believed to be related to liver injury, or hypersensitivity **and** who can be monitored weekly for 4 weeks	• Notify the GSK medical monitor **within 24 hours** of learning of the abnormality to discuss subject safety. • Subject can continue study treatment • Subject must return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) until they resolve, stabilise or return to within baseline[1] • If at any time subject meets the liver chemistry stopping criteria, proceed as described above **For subjects with entry criteria ALT≤2.5 x ULN** • If, after 4 weeks of monitoring, ALT <3xULN and bilirubin <2xULN, monitor subjects twice monthly until liver chemistries normalize or return to within baseline. **For subjects with documented liver metastases/tumor infiltration at baseline AND entry criteria ALT>2.5 x ULN but ≤5 x ULN** • If, after 4 weeks of monitoring, ALT <3xULN and <1.5x baseline value, and bilirubin <2xULN, monitor subjects twice monthly until liver chemistries normalize or return to within baseline

1. For the purpose of these guidelines "baseline" refers to laboratory assessments performed closest and prior to first dose of study treatment

References

James LP, , Letzig L, Simpson PM, Capparelli E, Roberts DW, Hinson JA, Davern TJ, Lee WM. Pharmacokinetics of Acetaminophen-Adduct in Adults with Acetaminophen Overdose and Acute Liver Failure. *Drug Metab Dispos* 2009; 37:1779-1784.

15.3.2. Liver Safety – Study Treatment Restart or Rechallenge GuidelinesIf subject meets liver chemistry stopping criteria do not restart/rechallenge subject with study treatment unless:

- GSK Medical Governance approval **is granted** (as described below),
- Ethics and/or IRB approval is obtained, if required, and
- Separate consent for treatment restart/rechallenge is signed by the subject

If GSK Medical Governance approval to restart/rechallenge subject with study treatment **is not granted**, then subject must permanently discontinue study treatment and may continue in the study for protocol-specified follow up assessments

1. Rechallenge Following Liver Stopping Events that are Possibly Related to Study Treatment

Following drug-induced liver injury, **drug rechallenge is associated with a 13% mortality across all drugs in prospective studies** [Andrade, 2009]. Clinical outcomes vary by drug, with nearly 50% fatality with halothane readministered within one month of initial injury. However, some drugs seldom result in recurrent liver injury or fatality.

Risk factors for a fatal drug rechallenge outcome include:

- hypersensitivity with initial liver injury (e.g. fever, rash, eosinophilia) [Andrade, 2009]
- jaundice or bilirubin >2xULN with initial liver injury (direct bilirubin >35% of total)
- subject currently exhibits severe liver injury defined by: ALT ≥3xULN, bilirubin ≥2xULN (direct bilirubin >35% of total), or INR≥1.5
- serious adverse event or fatality has earlier been observed with drug rechallenges [Papay, 2009]
- evidence of drug-related preclinical liability (e.g. reactive metabolites; mitochondrial impairment [Hunt, 2010])

Rechallenge refers to resuming study treatment following drug induced liver injury (DILI). Because of the risks associated with rechallenge after DILI this should only be considered for a subject for whom there is compelling evidence of benefit from a critical or life-saving medicine, there is no alternative approved medicine available, and a benefit:risk assessment of rechallenge is considered to be favourable.

Approval by GSK for rechallenge with study treatment can be considered where:

- Investigator requests consideration of rechallenge with study treatment for a subject who is receiving compelling benefit with study treatment that exceeds risk, and no effective alternative therapy is available.
- Ethics Committee or Institutional Review Board approval for rechallenge with study treatment must be obtained, as required.
- If the rechallenge is approved by GSK Medical Governance in writing, the subject must be provided with a clear description of the possible benefits and risks of study treatment administration, including the possibility of recurrent, more severe liver injury or death.
- The subject must also provide signed informed consent specifically for the rechallenge with study treatment. Documentation of informed consent must be recorded in the study chart.
- Study treatment must be administered at the dose specified by GSK.
- Subjects approved by GSK Medical Governance for rechallenge with study treatment must return to the clinic twice a week for liver chemistry tests until stable liver chemistries have been demonstrated and then standard laboratory monitoring may resume as per protocol.
- If after study treatment rechallenge, subject meets protocol-defined liver chemistry stopping criteria, study treatment should be permanently discontinued.
- Medical Monitor, and the Ethics Committee or Institutional Review Board as required, must be informed of the subject's outcome following study treatment rechallenge.
- GSK to be notified of any adverse events, as per Section 8 of the protocol.

2. Restart Following Transient Resolving Liver Stopping Events NOT Related to Study Treatment

Restart refers to resuming study treatment following liver stopping events in which there is a clear underlying cause (other than DILI) of the liver event (e.g. biliary obstruction, pancreatic events, hypotension, acute viral hepatitis). Furthermore, there should be no evidence of alcoholic hepatitis or hypersensitivity, and the study treatment should not be associated with HLA markers of liver injury.

Approval by GSK for study treatment restart can be considered where:

- Investigator requests consideration for study treatment restart if liver chemistries have a clear underlying cause (e.g., biliary obstruction, hypotension and liver chemistries have improved to normal or are within 1.5 x baseline and ALT <3xULN).
- Restart risk factors (e.g. fever, rash, eosinophilia, or hypersensitivity, alcoholic hepatitis, possible study treatment-induced liver injury or study treatment has an

HLA genetic marker associated with liver injury (e.g. lapatinib, abacavir, amoxicillin/clavulanate) are reviewed and excluded

- Ethics Committee or Institutional Review Board approval of study treatment restart must be obtained, as required.
- If restart of study treatment is approved by GSK Medical Governance in writing, the subject must be provided with a clear description of the possible benefits and risks of study treatment administration, including the possibility of recurrent, more severe liver injury or death.
- The subject must also provide signed informed consent specifically for the study treatment restart. Documentation of informed consent must be recorded in the study chart.
- Study treatment must be administered at the dose specified by GSK.
- Subjects approved by GSK Medical Governance for restarting study treatment must return to the clinic once a week for liver chemistry tests until stable liver chemistries have been demonstrated and then laboratory monitoring may resume as per protocol.
- If after study treatment re-start, subject meets protocol-defined liver chemistry stopping criteria, follow usual stopping criteria instructions.
- Medical Monitor, and the Ethics Committee or Institutional Review Board as required, must be informed of the subject's outcome following study treatment restart.
- GSK, or designee, to be notified of any adverse events, as per Section 8.

References:

Andrade RJ, Robles M, Lucena MI. Rechallenge in drug-induced liver injury: the attractive hazard. *Expert Opin Drug Saf.* 2009;8:709-714.

Hunt, CM. Mitochondrial and immunoallergic injury increase risk of positive drug rechallenge after drug-induced liver injury: A systematic review. *Hepatol.* 2010;52:2216-2222.

Papay JI, Clines D, Rafi R, Yuen N, Britt SD, Walsh JS, et al. Drug-induced liver injury following positive drug rechallenge. *Regul Tox Pharm*. 2009;54:84-90.

15.4. Appendix 4: Response Criteria

Non-Hodgkin's Lymphoma Response Criteria

This study employs response criteria from the Revised Response Criteria for Malignant Lymphoma (RRCML), [Cheson, 2007]. These criteria use the following categories of response: CR, PR, Stable Disease (SD), Relapse and Progression. Because the criteria for PR requires a decrease by ≥ 50% in sum of products of the diameters (**SPD**) in the six largest dominant nodes or nodal masses, six dominant nodes and/or nodal masses must be identified if > six involved nodes/nodal masses are present.

Complete Response

To be assigned a status of complete response, all changes must be confirmed by repeat assessments performed no less than four weeks after the criteria for CR were met.

1. Complete disappearance of all detectable clinical evidence of disease and disease related B-symptoms, if present prior to therapy.
2. All lymph nodes and nodal masses must have regressed on CT to normal size. Nodes that were 1.1 to 1.5 cm in their longest diameter and more than 1.0 cm in their shortest diameter prior to treatment must have decreased to ≤ 1.0 cm in their shortest diameter. Nodes that were > 1.5 cm in their longest diameter prior to therapy must have decreased to ≤ 1.5 cm in the longest diameter.
3. The spleen and/or liver, if considered to be enlarged due to lymphoma before therapy on the basis of a CT scan, should be considered normal size by imaging studies, and nodules related to lymphoma should disappear. However, determination of splenic involvement is not always reliable because spleen considered normal in size may still contain lymphoma, whereas an enlarged spleen may reflect variations in anatomy, blood volume, the use of hematopoietic growth factors, or causes other than lymphoma.
4. If the bone marrow was involved by lymphoma prior to treatment, the biopsy must be cleared. The biopsy sample on which this determination is made must be adequate (with a goal of > 20 mm unilateral core). If the sample is indeterminate by morphology, it should be negative by immunohistochemistry. A sample that is negative by immunohistochemistry but that demonstrates a small population of clonal lymphocytes by flow cytometry will be considered a CR until data become available demonstrating a clear difference in subject outcome.

Partial Response

To be assigned a status of partial response, all changes must be confirmed by repeat assessments performed no less than four weeks after the criteria for PR were met.

1. At least a 50% decrease from baseline in the SPD of up six of the largest dominant nodes or nodal masses.

2. No increase in the size of the liver or the spleen. No unequivocal progression in any nonmeasurable or nondominant site.
3. Splenic and hepatic nodules must regress by ≥50% in SPD compared to baseline. If only a single nodule/lesion, it must regress by ≥50% in the greatest transverse diameter compared to baseline.
4. With the exception of splenic and hepatic nodules, involvement of other organs is accessible and no measureable disease should be present.
5. Bone marrow assessment is not relevant for determination of a PR if the sample was positive prior to treatment. However, if positive, the cell type should be specified. Subjects who achieve CR criteria above, except for persistent morphologic bone marrow involvement will be considered partial responders. When the bone marrow was involved before therapy and a clinical CR was achieved, but no bone marrow assessment after therapy, subjects must be considered partial responders.
6. No new sites of disease must be observed.
7. When performed, positron emission tomography (PET) must be positive in at least one previously involved site.

Stable Disease

Neither sufficient shrinkage to qualify for a CR or PR nor sufficient increase to qualify for progressive disease taking as reference the smallest SPD since the treatment started.

When performed, PET should be positive at prior sites of disease with no new areas of involvement on the CT or PET.

Relapsed Disease (after CR)/Progressive Disease (after PR, SD)

Criteria for determining PD for new lesions and target lesions are shown in Table 19:

Table 19 Criteria for determining PD for new lesions and target lesions

	Nodes	**Extranodal ('liver/spleen' & 'other' categories)**
New node/lesion[c]	A node that was normal (≤1.5 x ≤1.0cm, including nodes that were not previously visible) and PET negative at baseline, must increase to >2.0 x ≥ 1.5 cm. The new lesion must not be attributable to non-lymphoma-related causes. **If PET is performed, the lesion must be PET positive.**	An unequivocal new lesion at a site where there was no disease at baseline (including being PET negative), provided the lesion cannot be attributed to non-lymphoma-related causes. **If PET is not performed the new lesion must be >1.5cm in the long axis[a].** **If PET is performed, the lesion must be PET positive.**
Single target node/lesion		
Increase in product of the perpendicular diameters (PPD)	≥50% increase from nadir in the PPD of any baseline dominant node. The long axis must increase by at least 5mm and to >2.0cm.	≥50% increase from nadir in the PPD of any baseline dominant target lesion, and at least a 5mm increase in either of the axes, and the lesion must be

	Nodes	**Extranodal ('liver/spleen' & 'other' categories)**
	If PET is performed, the lesion must be PET positive.	>1.5cm x ≥1.5 cm. **If PET is performed, the lesion must be PET positive**.
Increase in long axis	≥50% increase from nadir in the long axis of any baseline dominant node. The long axis must increase by at least 5mm and to >2.0 cm. **If PET is performed, the lesion must be PET positive**.	≥50% increase from nadir in the long axis of any baseline dominant lesion, and at least a 5mm increase in the long axis, and the lesion must be >1.5cm x ≥1.5cm. **If PET is performed, the lesion must be PET positive**.
Multiple target nodes/lesions		
Increase in SPD	≥50% increase from nadir in the SPD of baseline dominant nodes **and at least one node should have a long axis >1.5cm[b].** **If PET is performed, nodes >1.5cm must be PET positive.**	≥50% increase from nadir in the SPD of baseline dominant lesions **and at least one lesion should have a long axis >1.5cm[b].** **If PET is performed, lesions >1.5cm must be PET positive.**

a. Due to the resolution of PET imaging, requiring a lesion to be PET positive will normally mean it will be at least 1.5cm. To ensure consistency when PET is not performed a minimum lesion size of >1.5cm is required.
b. Requiring that at least one lesion is >1.5cm minimises the risk of declaring PD based on small artefactual changes and allows for the introduction of PET positivity for declaring PD (when PET is performed).
c. Abnormal nodes/extranodal lesions present at baseline that normalise/resolve and then subsequently enlarge/relapse are not to be classified as new lesions.

Response Assessment

CT scans remain the standard for evaluation of nodal disease. Chest, abdominal, and pelvic CT scans should be done even if those areas were not initially involved because of the unpredictable pattern of relapse in NHL. Neck can be evaluated if present at baseline.

References:

Cheson B, Pfister B, Juweid M, Gascoyne RD, Specht L, Horning SJ, et al. Revised response criteria for malignant lymphoma. J Clin Oncol 2007; 25:579-586.

15.5. Appendix 5: RECIST 1.1

I. Efficacy Assessment

Disease progression and response evaluations will be determined according to the definitions established in the Response Evaluation Criteria in Solid Tumors (RECIST 1.1) [Chung, 2010;.Eisenhauer, 2009].

See the Time and Events Table for the schedule of efficacy assessments. Assessments must be performed on a calendar schedule and should not be affected by dose interruptions/delays. For post baseline assessments, a window of ±7 days is permitted to allow for flexible scheduling.

- The following are required at baseline: CT for Chest/Abdomen/Pelvis or MRI for Abdomen/Pelvis and clinical disease assessment for palpable lesions, brain scan and bone scan (bone scan as clinically indicated). At each post baseline assessment, evaluations of the sites of disease identified by these scans are required except for brain scan and bone scans. Brain and Bone scans should be performed as clinically indicated.

Confirmation of CR and PR are required per protocol. Confirmation assessments must be performed no less than 4 weeks after the criteria for response have initially been met and may be performed at the next protocol scheduled assessment. If a confirmation assessment is performed prior to the next protocol schedule assessment, the next protocol scheduled evaluation is still required (e.g. evaluations must occur at each protocol scheduled timepoint regardless of unscheduled assessments).

A baseline bone scan should be performed as clinically indicated. For subjects without bone disease at baseline, subsequent bone scans should only be performed as clinically indicated (e.g. presentation of bone pain). For subjects with bone disease at baseline, a bone scan is required as clinically indicated. In addition, in order to assign a response of CR in a subject with bone disease at baseline, a bone scan must be performed 1 week prior to 4 weeks after.

A baseline brain scan is required for all subjects. For subjects without CNS disease at baseline, subsequent brain scans should only be performed as clinically indicated (e.g. symptoms suggestive of CNS progression). For subjects with CNS disease at baseline, a brain scan is required as clinically indicated. In addition, in order to confirm a CR in a subject with brain disease at baseline, a brain scan must be performed 1 week prior to the 1st set of images showing CR to 4 weeks after the next protocol specified assessment.

Ia. Baseline documentation of target and non-target lesions

- All baseline lesion assessments must be performed within 28 days of randomizations.
- Lymph nodes that have a short axis of <10mm are considered non-pathological and should not be recorded or followed.

- Pathological lymph nodes with <15mm and but ≥10mm short axis are considered non measurable.
- Pathological lymph nodes with ≥15mm short axis are considered measurable and can be selected as target lesions; however, lymph nodes should not be selected as target lesions when other suitable target lesions are available.
- Measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions, and recorded and measured at baseline. These lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically).

Note: Cystic lesions thought to represent cystic metastases should not be selected as target lesions when other suitable target lesions are available.

Note: Measurable lesions that have been previously irradiated and have not been shown to be progressing following irradiation should not be considered as target lesions.

- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by CT or MRI can be considered measurable. Bone scans, [18F]fluorodeoxyglucose (FDG)-PET scans or X-rays are not considered adequate imaging techniques to measure bone lesions.
- All other lesions (or sites of disease) should be identified as non-target and should also be recorded at baseline. Non-target lesions will be group by organ. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

Ib. Assessment Guidelines

Please note the following:

- The same diagnostic method, including use of contrast when applicable, must be used throughout the study to evaluate a lesion.
- All measurements should be taken and recorded in millimeters (mm), using a ruler or calipers.
- Ultrasound is not a suitable modality of disease assessment. If new lesions are identified by ultrasound, confirmation by CT or MRI is required.
- Fluorodeoxyglucose (FDG)-PET is generally not suitable for ongoing assessments of disease. However FDG-PET can be useful in confirming new sites of disease where a positive FDG-PET scans correlates with the new site of disease present on CT/MRI or when a baseline FDG-PET was previously negative for the site of the new lesion. FDG-PET may also be used in lieu of a standard bone scan providing coverage allows interrogation of all likely sites of bone disease and FDG-PET is performed at all assessments.
- If PET/CT is performed then the CT component can only be used for standard response assessments if performed to diagnostic quality, which includes the required

anatomical coverage and prescribed use of contrast. The method of assessment should be noted as CT on the CRF.

Clinical Examination: Clinically detected lesions will only be considered measurable when they are superficial (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler/callipers to measure the size of the lesion, is required. [Chung, 2010;.Eisenhauer, 2009].

CT and MRI: Contrast enhanced CT with 5mm contiguous slices is recommended. Minimum size of a measurable baseline lesion should be twice the slice thickness, with a minimum lesion size of 10 mm when the slice thickness is 5 mm. MRI is acceptable, but when used, the technical specification of the scanning sequences should be optimized for the evaluation of the type and site of disease and lesions must be measured in the same anatomic plane by use of the same imaging examinations. Whenever possible the same scanner should be used. [Chung, 2010;.Eisenhauer, 2009].

X-ray: In general, X-ray should not be used for target lesion measurements owing to poor lesion definition. Lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung; however chest CT is preferred over chest X-ray [Chung, 2010;.Eisenhauer, 2009].

Brain Scan: Baseline brain scans are required, then contrast enhanced MRI is preferable to contrast enhanced CT.

Bone Scan (typically bone scintigraphy): If a bone scan is performed and a new lesion(s) is equivocal, then correlative imaging (i.e.X-ray, CT, or MRI) is required to demonstrate malignant characteristics of the lesion(s).

Note: PET [FDG or fluoride] may be used in lieu of a standard bone scan providing coverage allows interrogation of all likely sites of bone disease and PET is performed at all assessments.

Ic. Follow-up Assessments for Subjects Permanently Discontinued from Study Treatment

Refer to Section 8.3.1.1 and the Time and Events Tables found in the protocol for follow-up assessment of subjects who are to be followed up for disease progression and/or survival after permanently discontinue from study treatment.

Id. Assessment of Subject Completion

If the last radiographic assessment was more than 8 weeks prior to withdrawal from study and progressive disease has not been documented, a disease assessment should be obtained at the time of withdrawal from study.

II. Guidelines for Evaluation of Disease

IIa. Measurable and Non-measurable Definitions

Measurable lesion:

A non nodal lesion that can be accurately measured in at least one dimension (longest dimension) of

- ≥10 mm with MRI or CT when the scan slice thickness is no greater than 5mm. If the slice thickness is greater than 5mm, the minimum size of a measurable lesion must be at least double the slice thickness (e.g., if the slice thickness is 10 mm, a measurable lesion must be ≥ 20 mm).
- ≥10 mm calliper/ruler measurement by clinical exam or medical photography.
- ≥20 mm by chest x-ray.

Additionally lymph nodes can be considered pathologically enlarged and measurable if

- ≥15mm in the short axis when assessed by CT or MRI (slice thickness recommended to be no more than 5mm). At baseline and follow-up, only the short axis will be measured [Chung, 2010; Eisenhauer, 2009].
- **Non-measurable lesion:**

All other lesions including lesions too small to be considered measurable (longest diameter <10 mm or pathological lymph nodes with ≥ 10 mm and <15 mm short axis) as well as truly non-measurable lesions, which include: leptomeningeal disease, ascites, pleural or pericardial effusions, inflammatory breast disease, lymphangitic involvement of the skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques [Eisenhauer, 2009].

Measurable disease: The presence of at least one measurable lesion. Palpable lesions that are not measurable by radiologic or photographic evaluations may not be utilized as the only measurable lesion.

Non-Measurable only disease: The presence of only non-measurable lesions. Note: non-measurable only disease is not allowed per protocol.

III. Response Criteria

IIIa. Evaluation of target lesions

Definitions for assessment of response for target lesion(s) are as follows:

- Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes must be <10mm in the short axis.
- Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as a reference, the baseline sum of the diameters (e.g. percent change from baseline).

- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease.
- Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as a reference, the smallest sum of diameters recorded since the treatment started (e.g. percent change from nadir, where nadir is defined as the smallest sum of diameters recorded since treatment start). In addition, the sum must have an absolute increase from nadir of 5mm.
- Not Applicable (NA): No target lesions at baseline.
- Not Evaluable (NE): Cannot be classified by one of the five preceding definitions.

Note:

- If lymph nodes are documented as target lesions the short axis is added into the sum of the diameters (e.g. sum of diameters is the sum of the longest diameters for non-nodal lesions and the short axis for nodal lesions). When lymph nodes decrease to non-pathological size (short axis <10mm) they should still have a measurement reported in order not to overstate progression.
- If at a given assessment time point all target lesions identified at baseline are not assessed, sum of the diameters cannot be calculated for purposes of assessing CR, PR, or SD, or for use as the nadir for future assessments. However, the sum of the diameters of the assessed lesions and the percent change from nadir should be calculated to ensure that progression has not been documented. If an assessment of PD cannot be made, the response assessment should be NE.
- All lesions (nodal and non-nodal) should have their measurements recorded even when very small (e.g. 2 mm). If lesions are present but too small to measure, 5 mm should be recorded and should contribute to the sum of the diameters, unless it is likely that the lesion has disappeared in which case 0 mm should be reported.
- If a lesion disappears and reappears at a subsequent time point it should continue to be measured. The response at the time when the lesion reappears will depend upon the status of the other lesions. For example, if the disease had reached a CR status then PD would be documented at the time of reappearance. However, if the response status was PR or SD, the diameter of the reappearing lesion should be added to the remaining diameters and response determined based on percent change from baseline and percent change from nadir.

IIIb. Evaluation of non-target lesions

Definitions for assessment of response for non-target lesions are as follows:

- Complete Response (CR): The disappearance of all non-target lesions. All lymph nodes identified as a site of disease at baseline must be non-pathological (e.g. <10 mm short axis).
- Non-CR/Non-PD: The persistence of 1 or more non-target lesion(s) or lymph nodes identified as a site of disease at baseline ≥ 10 mm short axis.
- Progressive Disease (PD): Unequivocal progression of existing non-target lesions.

- Not Applicable (NA): No non-target lesions at baseline.
- Not Evaluable (NE): Cannot be classified by one of the four preceding definitions.

Note:

- In the presence of measurable disease, progression on the basis of solely non-target disease requires substantial worsening such that even in the presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy.
- Sites of non-target lesions, which are not assessed at a particular timepoint based on the assessment schedule, should be excluded from the response determination (e.g. non-target response does not have to be "Not Evaluable").

IIIc. New lesions

New malignancies denoting disease progression must be unequivocal. Lesions identified in follow-up in an anatomical location not scanned at baseline are considered new lesions.

Any equivocal new lesions should continue to be followed. Treatment can continue at the discretion of the investigator until the next scheduled assessment. If at the next assessment the new lesion is considered to be unequivocal, progression should be documented.

IIId. Evaluation of overall response

The table below presents the overall response at an individual time point for all possible combinations of tumor responses in target and non-target lesions with or without the appearance of new lesions for subjects with measurable disease at baseline.

Evaluation of Overall Response for Subjects with Measurable Disease at Baseline

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR or NA	No	CR
CR	Non-CR/Non-PD or NE	No	PR
PR	Non-PD or NA or NE	No	PR
SD	Non-PD or NA or NE	No	SD
NE	Non-PD or NA or NE	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR=complete response, PR = partial response, SD=stable disease, PD=progressive disease, NA= Not applicable, and NE=Not Evaluable

Note:

- Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration." Objective response status is determined by evaluations of disease burden. Every effort should be made to document the objective progression even after discontinuation of treatment.

- In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of CR depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the CR.
- The dosing schedule, dosing interruptions and unique design (see Table 2 of the protocol) should be considered when assessing tumor response. Thus, subjects with PD before Week 8, but without rapid clinical deterioration, may continue planned dosing schedule to allow detection of antitumor response. It is recommended that subjects who experience investigator-determined PD at the week 8, at the discretion of the investigator, may receive additional tumor assessment before the initiation of alternative anticancer therapy.
- During Part 1 or Part 2, is recommended that subjects who experience investigator-determined PD at any time, at the discretion of the investigator, may receive additional tumor assessment before the initiation of alternative anticancer therapy.

IIIe. Evaluation of best overall response

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

- To be assigned a status of SD, follow-up disease assessment must have met the SD criteria at least once after first dose at a minimum interval of 4 weeks.
- If the minimum time for SD is not met, best response will depend on the subsequent assessments. For example if an assessment of PD follows the assessment of SD and SD does not meet the minimum time requirement the best response will be PD. Alternative subjects lost to follow-up after an SD assessment not meeting the minimum time criteria will be considered not evaluable.

IIIf. Confirmation Criteria (recommended):

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

IIIg. Independent Review

Disease progression and response evaluations may be collected centrally during the study and may be reviewed or analyzed by an independent central reviewer. Details will be provided in the SPM.

References:

Chung WH, Hung SL, Chen YT. Genetic predisposition of life-threatening antiepileptic-induced skin reactions. Expert Opin. Drug Saf. 2010; 9: 15-21.

Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D, Verweij J. New response evaluation criteria in solid tumors: Revised RECIST guidelines (version 1.1). European Journal of Cancer. 2009; 45: 228-247.

15.6. Appendix 6: Response Criteria for Multiple Myeloma

Consensus Recommendations [Rajkumar, 2011] **for the Uniform Reporting of Clinical Trials: Report of the International Myeloma Working Group (IMWG) Consensus Panel**

Response Criteria [Durie, 2006]

sCR (stringent complete response):

Complete response as defined below plus:

- normal free light chain (FLC) ratio and
- absence of clonal cells in bone marrow by immunohistochemistry or 2-4 color flow cytometry.

CR (complete response):

- Negative serum and urine immunofixation, and
- Disappearance of any soft tissue plasmacytomas, and
- ≤ 5% plasma cells in bone marrow.

VGPR (very good partial response):

- Serum and urine M-component detectable by immunofixation but not on electrophoresis **OR**
- 90% or greater reduction in serum M-component plus urine M-component < 100mg/24h.

PR (partial response):

- ≥ 50% reduction of serum M-protein and reduction in 24 hour urinary M-protein by ≥ 90% or to < 200mg/24h, and
- If the serum and urine M-protein are not measurable, a ≥ 50% decrease in the difference between involved and uninvolved free light chain levels is required in place of the M-protein criteria. If serum and urine M-protein are not measurable, and serum free light chain assay is also not measurable, ≥ 50% reduction in bone marrow plasma cells is required in place of M-protein, provided baseline bone marrow plasma cell percentage was ≥ 30%, and
- In addition to the above listed criteria, if present at baseline, a ≥ 50% reduction in the size of the soft tissue plasmacytomas is also required.

MR (minimal response):

- ≥25% but ≤49% reduction of serum M-protein and reduction in 24 hour urinary M-protein by 50% to 89%, AND
- If present at baseline, 25% to 49% reduction in the size of soft tissue plasmacytomas is also required.
- No increase in size or number of lytic bone lesions (development of compression fracture does not exclude response).

SD (stable disease):

- Not meeting criteria for CR, VGPR, PR, MR or Progressive Disease.

Progressive Disease:

Requires any one or more of the following:

- Increase of ≥ 25% from lowest response value in any one or more of the following:
  - serum M-component (absolute increase must be ≥ 0.5 g/dl), or
  - urine M-component (absolute increase must be ≥ 200 mg/24h), or
  - the difference between involved and uninvolved free light chain levels (absolute increase must be > 10mg/dl): only for subjects without measurable serum and urine M-protein levels, or
  - bone marrow plasma cell percentage (the absolute % must be ≥10%) – only for subjects without measurable serum and urine M-protein levels and without measurable disease by FLC level.
  - definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas.
  - development of hypercalcemia (corrected calcium > 11.5 mg/dl or 2.65 mmol/l) that can be attributed solely to the plasma cell proliferative disorder.

a. All response categories (CR, sCR, VGPR, PR, MR and Progressive Disease) require two consecutive assessments made at any time before the institution of any new therapy; CR, sCR, VGPR, PR, MR, and SD categories also require no known evidence of progressive or new bone lesions if radiographic studies were performed. VGPR and CR categories require serum and urine studies regardless of whether disease at baseline was measurable on serum, urine, both, or neither. Radiographic studies are not required to satisfy these response requirements. Bone marrow assessments need not be confirmed. For Progressive Disease, serum M-component increases of more than or equal to 1 g/dL are sufficient to define relapse if starting M-component is ≥ 5 g/dL.

b. Clarifications to IMWG criteria for coding CR and VGPR in subjects in whom the only measurable disease is by serum FLC levels: CR in such subjects indicates a normal FLC ratio of 0.26 to 1.65 in addition to CR criteria listed above. VGPR in

such subjects requires a > 90% decrease in the difference between involved and uninvolved FLC levels.

c. Clarifications to IMWG criteria for coding Progressive Disease: Bone marrow criteria for Progressive Disease are to be used only in subjects without measurable disease by M protein and by FLC levels; "25% increase" refers to M protein, FLC, and bone marrow results, and does not refer to bone lesions, soft tissue plasmacytomas, or hypercalcemia and the "lowest response value" does not need to be a confirmed value.

References

Durie BGM, Harousseau J-L, Miguel JS, et. al. International uniform response criteria for multiple myeloma. Leukemia, 2006:20: 1467-73.

Rajkumar SV, Harousseau JL, Durie B, et al. Consensus recommendations for the uniform reporting of clinical trials: Report of the International Myeloma Workshop Consensus Panel 1. Blood. 2011;117:4691-4695.

15.7. Appendix 7: Criteria for Response/Progression: Prostate Cancer

15.7.1. Disease Progression Endpoint

The disease progression endpoint is defined by 1 or more of the following criteria:

- PSA progression according to the PCWG3 criteria
    - Subjects are not required to discontinue treatment on the basis of meeting PSA progression alone.
    - PSA progression [Scher, 2016] is defined as:
        - *If there has been a decline from baseline*: time from start of therapy to first PSA increase that is ≥25% and ≥2 ng/mL in absolute value from the nadir, and which is confirmed by a second value 3 or more weeks later (i.e., a confirmed rising trend) at least 9 weeks after the start of treatment
        - *If there has NOT been a decline from baseline*: time from start of therapy to first PSA increase that is ≥25% and ≥2 ng/mL in absolute value from the baseline value, determined at least 9 weeks after start of treatment
- Radiographic progression by RECIST 1.1 for subjects with measurable disease.(Appendix 5)
- Bone progression on bone scan according to the PCWG3 criteria
    - Bone progression [Scher, 2016] will be determined as the appearance of ≥2 new lesions on bone scan and at least an additional 2 bone lesions at the next scan (every 8 weeks). The date of progression is the date of the first scan that indicates the change. Subjects should not be discontinued from study treatment(s) due to the occurrence of bone scan changes in the first 12 weeks that do not meet PCWG3 guidelines for progression.

15.7.2. DiseaseResponse Endpoints

- PSA response according to the PCWG3 criteria:
    - Only subjects who have a baseline PSA value and at least one post-baseline assessment will be included in the analysis of PSA response.
    - PSA Response Rate is defined as proportion of subjects with a decrease of ≥50% in the PSA concentration from the baseline PSA value determined at least 9 weeks after start of treatment and confirmed after ≥4 weeks by an additional PSA evaluation.
- Radiographic response By Recist 1.1 for subjects with measurable disease (Appendix 5)

References

Scher HI, Morris MJ, Stadler WM, Higano C, Basch E, Fizazi K, et al. Trial design and objectives for castration-resistant prostate cancer: updated recommendations from the Prostate Cancer Clinical Trials Working Group 3. *Journal of Clinical Oncology.* 2016; doi: 10.1200/JCO.2015.64.2702.

15.8. Appendix 8: Genetic Research

Genetic Research Objectives and Analyses

The objectives of the genetic research are to investigate the relationship between genetic variants and:

- Response to medicine, including GSK2816126[redacted] or any concomitant medicines;
- Disease susceptibility, severity, and progression and related conditions

Genetic data may be generated while the clinical study is underway or following completion of the study. Genetic evaluations may include focused candidate gene approaches and/or examination of a large number of genetic variants throughout the genome (whole genome analyses). Genetic analyses will utilize data collected in the clinical study and will be limited to understanding the objectives highlighted above. Analyses may be performed using data from multiple clinical studies to investigate these research objectives.

Appropriate descriptive and/or statistical analysis methods will be used. A detailed description of any planned analyses will be documented in a Reporting and Analysis Plan (RAP) prior to initiation of the analysis. Planned analyses and results of genetic investigations will be reported either as part of the clinical RAP and study report, or in a separate genetics RAP and report, as appropriate.

Study Population

Any subject who is enrolled in the clinical study can participate in genetic research. Any subject who has received an allogeneic bone marrow transplant must be excluded from the genetic research.

Study Assessments and Procedures

A key component of successful genetic research is the collection of samples during clinical studies. Collection of samples, even when no *a priori* hypothesis has been identified, may enable future genetic analyses to be conducted to help understand variability in disease and medicine response.

- A 6 ml blood sample will be taken for Deoxyribonucleic acid (DNA) extraction. Blood sample is collected at the baseline visit, after the subject has been randomized and provided informed consent for genetic research. If a subject initially declines to participate in genetic research and then changes their mind, a sample should be obtained at the earliest opportunity. Instructions for collection and shipping of the genetic sample are described in the laboratory manual. The DNA from the blood sample may undergo quality control analyses to confirm the integrity of the sample. If there are concerns regarding the quality of the sample, then the sample may be destroyed. The blood sample is taken on a single occasion unless a duplicate sample is required due to inability to utilize the original sample.

The genetic sample is labelled (or "coded") with the same study specific number as used to label other samples and data in the study. This number can be traced or linked back to the subject by the investigator or site staff. Coded samples do not carry personal identifiers (such as name or social security number).

Samples will be stored securely and may be kept for up to 15 years after the last subject completes the study or GSK may destroy the samples sooner. GSK or those working with GSK (for example, other researchers) will only use samples collected from the study for the purpose stated in this protocol and in the informed consent form. Samples may be used as part of the development of a companion diagnostic to support the GSK medicinal product.

Subjects can request their sample to be destroyed at any time.

Informed Consent

Subjects who do not wish to participate in the genetic research may still participate in the clinical study. Genetic informed consent must be obtained prior to any blood being taken for genetic analysis.

Subject Withdrawal from Study

If a subject who has consented to participate in genetic research withdraws from the clinical study for any reason other than being lost to follow-up, the subject will be given a choice of one of the following options concerning the genetic sample, if already collected:

- Continue to participate in the genetic research in which case the genetic DNA sample is retained
- Discontinue participation in the genetic research and destroy the genetic DNA sample

If a subject withdraws consent for genetic research or requests sample destruction for any reason, the investigator must complete the appropriate documentation to request sample destruction within the timeframe specified by GSK and maintain the documentation in the site study records.

Genotype data may be generated during the clinical study or after completion of the clinical study and may be analyzed during the clinical study or stored for future analysis.

- If a subject withdraws consent for genetic research and genotype data has not been analyzed, it will not be analyzed or used for future research.
- Genetic data that has been analyzed at the time of withdrawn consent will continue to be stored and used, as appropriate.

Screen and Baseline Failures

If a sample for genetic research has been collected and it is determined that the subject does not meet the entry criteria for participation in the clinical study, then the investigator should instruct the participant that their genetic sample will be destroyed. No forms are required to complete this process as it will be completed as part of the consent and sample reconciliation process. In this instance a sample destruction form will not be available to include in the site files.

Provision of Study Results and Confidentiality of Subject's Data

GSK may summarize the genetic research results in the clinical study report, or separately and may publish the results in scientific journals.

GSK may share genetic research data 'with other scientists to further scientific understanding in alignment with the informed consent. GSK does not inform the subject, family members, insurers, or employers of individual genotyping results that are not known to be relevant to the subject's medical care at the time of the study, unless required by law. This is due to the fact that the information generated from genetic studies is generally preliminary in nature, and therefore the significance and scientific validity of the results are undetermined. Further, data generated in a research laboratory may not meet regulatory requirements for inclusion in clinical care.

15.9. Appendix 9: Protocol Amendment Changes

AMENDMENT 1

Where the Amendment Applies

This amendment applies only to sites in the UK.

Summary of Amendment Changes with Rationale

Following the guidance from the MHRA following the submission of our CTA, GSK agrees to remove wording from the protocol stating that GSK2816126 treatment will continue until commercial availability.

In accord with MHRA's guidance, the stopping criterion based on QTc in Section 3.8.1 of the protocol will be changed to ≥ 500 msec.

In further accordance with the MHRA, a QTc stopping criterion was added where patients will be withdrawn from study if they experience an increase in QTc > 60msec from baseline following dose reduction and re-challenge.

List of Specific Changes

PROTOCOL SYNOPSIS

PREVIOUS TEXT

- **STUDY DESIGN:** This study is divided into 2 parts; Part 1 of the study is a dose escalation phase to select the recommended Part 2 dose (RP2D) based on the safety, PK, and PD profiles observed after IV administration of GSK2816126. Eligible subjects with relapsed/refractory DLBCL and transformed FL malignancies will be enrolled in the dosing cohorts until a RP2D is established. Subjects may continue treatment in the study until disease progression, unacceptable toxicity, withdrawal of consent, or commercial supply of GSK2816126 becomes available to the subject. Expansion cohorts are planned in subjects with both EZH2 mutant positive and EZH2 WT tumors to further explore clinical activity at the RP2D (Part 2).

REVISED TEXT

- **STUDY DESIGN:** This study is divided into 2 parts; Part 1 of the study is a dose escalation phase to select the recommended Part 2 dose (RP2D) based on the safety, PK, and PD profiles observed after IV administration of GSK2816126. Eligible subjects with relapsed/refractory DLBCL and transformed FL malignancies will be enrolled in the dosing cohorts until a RP2D is established. Subjects may continue treatment in the study until disease progression, unacceptable toxicity~~,~~ **or** withdrawal of consent~~, or commercial supply of GSK2816126 becomes available to the subject~~. Expansion cohorts are planned in subjects with both EZH2 mutant positive and EZH2 WT tumors to further explore clinical activity at the RP2D (Part 2).

Section 3.8.1 QTc Stopping Criteria

PREVIOUS TEXT

QTc Stopping Criteria

If a subject that meets the corrected QT (QTc)[1] interval duration criteria below, study treatment(s) will be withheld.

- QT interval (corrected for HR) ≥ 530 msec

REVISED TEXT

QTc Stopping Criteria

If a subject that meets the corrected QT (QTc)[1] interval duration criteria below, study treatment(s) will be withheld.

- QT interval (corrected for HR) ≥~~530~~ **500** msec**; IP will be permanently discontinued.**
- **QTc interval increase from baseline ≥ 60 msec and maximum QTc < 500 msec; IP may be restarted at a 33% reduction in dose once the QTc returns to baseline. If QTc prolongation meeting stopping criteria recurs after re-challenge, IP must be permanently discontinued.**

AMENDMENT [2]

Where the Amendment Applies

This amendment applies to all investigator sites participating in this study and includes changes made in country specific amendment 1.

Summary of Amendment Changes with Rationale

Following the guidance from the FDA after submission of our IND, we have lowered our starting dose of GSK2816126 from 125 mg to 50 mg.

Addressing the FDA's comment "All adverse events, whether believed related or unrelated to study drug, must be included when dose limiting toxicity and stopping rules are invoked," we have updated our Dose Limiting toxicities language.

Based on comments from the FDA, we have revised 100% dose escalation wording

In accordance with FDA comments, we have decreased our baseline QTc Exclusion criterion from >480msec to >450msec and added an increase from baseline QTc stopping criterion of ≥ 60 msec

To better define our ECG testing, we added regular ECG monitoring timings to the Time & Events table

To correct an earlier oversight, blood glucose testing was added to our list of clinical lab tests

In accordance with our laboratory specifications, we have removed any wording pertaining to the use of central labs

Following the guidance from the MHRA following the submission of our CTA, GSK agrees to remove wording from the protocol stating that GSK2816126 treatment will continue until commercial availability.

In accord with MHRA's guidance, the stopping criterion based on QTc in Section 3.8.1 of the protocol will be changed to ≥ 500 msec.

In further accordance with the MHRA, a QTc stopping criterion was added where subjects will be withdrawn from study if they experience an increase in QTc > 60msec from baseline following dose reduction and re-challenge.

At the request of our investigators, to clarify that PET scans are optional in this study, additional wording was added to the T&E Table Section 7.1.

At the request of our investigators, additional wording was added to the T&E Table and Section 7.2 to clarify CT scan timings.

Added explanatory language to T&E Table around coagulation, CT and standalone PET assessments

Changed the corticosteroid exclusion criteria to 7 days in the synopsis and Section 5.2.3

List of Specific Changes

Protocol Synopsis

PREVIOUS TEXT

1. Cardiac exclusion criteria:
   - History of acute coronary syndromes (including myocardial infarction and unstable angina), coronary angioplasty, or stenting within the past 6 months prior to first dose of study drug.
   - QTc interval >480msec
   - Uncontrolled arrhythmias. Subjects with rate controlled atrial fibrillation for > 1 month prior to first dose of study drugs may be eligible.
   - Class II, III or IV heart failure as defined by the New York Heart Association (NYHA) functional classification system.
2. Known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to the study drug or their excipients.
3. Pregnant or lactating female.
4. Unwillingness or inability to follow the procedures outlined in the protocol.
5. Uncontrolled diabetes or other medical condition that may interfere with assessment of toxicity.

- **STUDY TREATMENT DOSAGE/DOSAGE FORM, ROUTE, AND DOSE REGIMEN**: Starting dose will be 125 mg, IV, twice weekly. Dose escalations will be performed in Part 1 and dose adjustments are allowed to address tolerability and safety issues. Alternative schedules may be evaluated if emerging data suggest that twice weekly administration with 2 hour infusions will result in excessive toxicity. In addition, alternative dosing schedules may be considered if the safety, pharmacokinetic (PK), and pharmacodynamic (PD) data suggest that a sufficient therapeutic exposure cannot be achieved using the initial schedule and after a protocol amendment.
- **SAFETY ASSESSMENTS**: Routine physical examinations, vital sign measurements, echocardiograms, and monitoring of adverse events. Cardiac safety monitoring will be required, consisting of triplicate 12-lead electrocardiograms (ECGs) pre-infusion of drug, immediately post-infusion of drug, one at night prior to going to sleep (*e.g.*, 10 pm), and one prior to discharge from the unit. The subject will not be discharged from the unit unless the QTc is <500 msec. In addition, 24 hours of high fidelity 12-lead Holter monitoring will be performed. Tracings from this will be used for

concentration QT analysis as well. Laboratory testing includes at least hematology and clinical chemistry. Additional safety assessments may be necessary based on emerging data.

REVISED TEXT

1. Cardiac exclusion criteria:
   - History of acute coronary syndromes (including myocardial infarction and unstable angina), coronary angioplasty, or stenting within the past 6 months prior to first dose of study drug(s).
   - QTc interval ~~>480msec~~ **>450msec**
   - Uncontrolled arrhythmias. Subjects with rate controlled atrial fibrillation for > 1 month prior to first dose of study drugs may be eligible.
   - Class II, III or IV heart failure as defined by the New York Heart Association (NYHA) functional classification system.
2. Known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to the study drug or their excipients.
3. Pregnant or lactating female.
4. Unwillingness or inability to follow the procedures outlined in the protocol.
5. Uncontrolled diabetes or other medical condition that may interfere with assessment of toxicity.

- **STUDY TREATMENT DOSAGE/DOSAGE FORM, ROUTE, AND DOSE REGIMEN**: Starting dose will be ~~125 mg~~ **50 mg**, IV, twice weekly. Dose escalations will be performed in Part 1 and dose adjustments are allowed to address tolerability and safety issues. Alternative schedules may be evaluated if emerging data suggest that twice weekly administration with 2 hour infusions will result in excessive toxicity. In addition, alternative dosing schedules may be considered if the safety, pharmacokinetic (PK), and pharmacodynamic (PD) data suggest that a sufficient therapeutic exposure cannot be achieved using the initial schedule and after a protocol amendment.

SAFETY ASSESSMENTS:

Routine physical examinations, vital sign measurements, echocardiograms, and monitoring of adverse events. Cardiac safety monitoring will be required, consisting of triplicate 12-lead electrocardiograms (ECGs) pre-infusion of drug, ~~immediately post-~~at the end of infusion of drug, one at night prior to going to sleep (*e.g.*, 10 pm), and one prior to discharge from the unit for Day 1, dose one only. The subject will not be discharged from the unit unless the QTc is <500 msec. In addition, 24 hours of high fidelity 12-lead Holter monitoring will be performed for Dose one. Tracings from this will be used for concentration QT analysis as well. Pre-infusion and end of infusion ECGs will be recorded for all other ECG timepoints. Laboratory testing includes at least

hematology and clinical chemistry. Additional safety assessments may be necessary based on emerging data.

Section 1.2.2 Nonclinical Pharmacology

PREVIOUS TEXT

Based on the infusion site reactions, in dogs following twice weekly dosing for 4 weeks, the no-observed-adverse-effect-level (NOAEL) is 30 mg/kg ($AUC_{0\text{-}24h}$ of 14.9 μg.h/mL; C_{max} of 1.96 μg/mL) and the highest non-severely toxic dose (HNSTD) is 100 mg/kg ($AUC_{0\text{-}24h}$ of 80.1μg.h/mL; C_{max} of 9.88 μg/mL). In rats following twice weekly dosing for 4 weeks, a NOAEL was not established at the lowest dose tested of 30 mg/kg ($AUC_{0\text{-}24h}$ of 23.5 μg.h/mL and C_{max} of 2.97 μg/mL). Due to similar exposure in rats at 300 mg/kg on Day 1 of the 2 and 4 week studies, the severely toxic dose 10% (STD10) in rats is estimated to be between 100 and 300 mg/kg ($AUC_{0\text{-}24h}$ between 54 and 235 μg.h/mL; C_{max} between 8 and 33 μg/mL; exposures based on twice weekly dosing for 2 weeks). However, because the smaller calibre of rodent vessels used for the drug infusion are more sensitive to injury and irritant effects, the dog findings are more appropriate to use for the local tolerability.

REVISED TEXT

Based on the infusion site reactions, in dogs following twice weekly dosing for 4 weeks, the no-observed-adverse-effect-level (NOAEL) is 30 mg/kg ($AUC_{0\text{-}24h}$ of 14.9 μg.h/mL; C_{max} of 1.96 μg/mL) and the highest non-severely toxic dose (HNSTD) is 100 mg/kg ($AUC_{0\text{-}24h}$ of 80.1μg.h/mL; C_{max} of 9.88 μg/mL). In rats following twice weekly dosing for 4 weeks, a NOAEL was not established at the lowest dose tested of 30 mg/kg ($AUC_{0\text{-}24h}$ of 23.5 μg.h/mL and C_{max} of 2.97 μg/mL). Due to similar exposure in rats at 300 mg/kg on Day 1 of the 2 and 4 week studies, the severely toxic dose 10% (STD10) in rats is estimated to be between 100 and 300 mg/kg ($AUC_{0\text{-}24h}$ between 54 and 235 μg.h/mL; C_{max} between 8 and 33 μg/mL; exposures based on twice weekly dosing for 2 weeks). **For the purpose of the starting dose justification in this protocol, we will use the lower estimate of 100 mg/kg as the STD10**. However, because the smaller calibre of rodent vessels used for the drug infusion are more sensitive to injury and irritant effects, the dog findings are more appropriate to use for the local tolerability.

Section 1.3.1 Risk Assessment

PREVIOUS TEXT

Potential Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy
Cardiovascular – QT prolongation	**QTc prolongation** was observed (up to 8%; 18 msec in dog) following the end of a single 8 hour infusion Effect did not directly correlate with peak GSK2816126 blood levels; onset was 4-7 hours following the end of the infusion;	Protocol includes cardiovascular eligibility criteria, laboratory assessments (potassium and magnesium, cardiac monitoring (electrocardiograms [ECGs], Holter monitoring during the study,

Potential Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy
	reversed within 3-8 hours following onset Effects not observed following repeat dosing in dogs No arrhythmias were detected in preclinical studies. The mechanism for the QTc prolongation is unlikely due to a direct effect on hERG repolarization as GSK2816126 weekly inhibited hERG tail current (IC25 of 54.2 µM; 28.61 µg/mL). However, GSK2816126 was shown to block hERG current density in vitro consistent with an effect on hERG channel trafficking.	and dose stopping/modifications criteria for the management of QT prolongation) Co-administration of medications that are known to prolong the QT interval and have a risk of causing Torsades de Pointes and drugs that have a possible risk of Torsades de Pointes are prohibited All subjects will remain in the clinical research unit (CRU) after receiving their first dose of study medication (Week 1, Day 1) with periodic ECGs and Holter monitoring for 24 hours. Subjects will not be discharged from the unit unless their last measured QTc on an ECG performed immediately prior to discharge is <500 msec.

REVISED TEXT

Potential Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy
Cardiovascular – QT prolongation	**QTc prolongation** was observed (up to 8%; 18 msec in dog) following the end of a single 8 hour infusion Effect did not directly correlate with peak GSK2816126 blood levels; onset was 4-7 hours following the end of the infusion; reversed within 3-8 hours following onset Effects not observed following repeat dosing in dogs No arrhythmias were detected in preclinical studies. The mechanism for the QTc prolongation is unlikely due to a direct effect on hERG repolarization as GSK2816126 weekly inhibited hERG tail current (IC25 of 54.2 µM; 28.61 µg/mL). However, GSK2816126 was shown to block hERG current density in vitro consistent with an effect on hERG channel trafficking.	Protocol includes cardiovascular eligibility criteria, laboratory assessments (potassium and magnesium, cardiac monitoring (electrocardiograms [ECGs], Holter monitoring during the study, and dose stopping/modifications criteria for the management of QT prolongation) Co-administration of medications that are known to prolong the QT interval and have a risk of causing Torsades de Pointes and drugs that have a possible risk of Torsades de Pointes are prohibited All subjects will remain in the clinical research unit (CRU) after receiving their first dose of study medication (Week 1, Day 1) with periodic ECGs and Holter

Potential Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy
		monitoring for 24 hours. Subjects will not be discharged from the unit unless their last measured QTc on an ECG performed immediately prior to discharge **after the first dose** is <500 msec. **After Day 1 during the first 3 weeks of treatment and on Day 4 of subsequent cycles, ECGs will be performed pre-infusion and at the end of infusion.**

Section 3.3.1 Accelerated Dose Escalation

PREVIOUS TEXT

Initially, an accelerated dose titration scheme will be used starting with a dose of 125 mg [Simon, 1997]. Evaluation of at least one subject who has completed one cycle of treatment is required prior to determining the dose for the next cohort with one cycle being defined as twice weekly dosing for three weeks and one week off. In the absence of Grade 2 or higher non-hematologic toxicity (described in Section 3.3.2.1) or a Dose Limiting Toxicity (DLT) (described in Section 3.3.3), subsequent cohorts will be dose escalated by up to 100% (Table 1). Following the initial occurrence of a Grade 2 toxicity or DLT in a subject during the first cycle (within 28 days of dose 1), accelerated titration will transition to a standard 3+3 dose escalation.

Table 1 Dose Titration Procedures

Dose Level	Toxicity in Study	Increase in Dose
Accelerated Dose Titration Phase		
Dose Level -1		Lower doses may be used if Dose Level 1 exposure is significantly higher than predicted or if there is excessive toxicity. This may be achieved by reducing the dose or by alternate dosing schedules.
Dose Level 1		Starting Dose: 125 mg
Subsequent Dose Levels	No subjects with a ≥ Grade 2 toxicity (exceptions below in Section 3.3.2.1) or DLT (Section 3.3.3)	Increase by ≤100% increase in dose (No subjects with ≥ Grade 2 drug related toxicity AND no subjects with any DLTs in first 28 days of treatment)
End of Accelerated Dose Titration Phase	One subject ≥ Grade 2 drug related non-hematological toxicity in the first 28 days of treatment) or ≥ Grade 3 drug related specific toxicity (See Section 3.3.2.1)	Begin 3+3 dose escalation phase (note that once 3+3 phase is initiated, the procedure may revert to the accelerated dose titration phase – see criteria below in Reverting to Accelerated Dose Titration)

REVISED TEXT

Initially, an accelerated dose titration scheme will be used starting with a dose of ~~125 mg~~ **50 mg** [Simon, 1997]. Evaluation of at least one subject who has completed one cycle of treatment is required prior to determining the dose for the next cohort with one cycle being defined as twice weekly dosing for three weeks and one week off. In the absence of Grade 2 or higher non-hematologic toxicity (described in Section 3.3.2.1) or a Dose Limiting Toxicity (DLT) (described in Section 3.3.3), subsequent cohorts will ~~be dose escalated by up to 100%~~ allow **up to 100% dose escalations up to 500 mg (approximately 1/6 th of the dog HNSTD). Subsequent dose escalation steps would be up to a maximum of 50% at each step** (Table 1). Following the initial occurrence of a Grade 2 toxicity or DLT in a subject during the first cycle (within 28 days of dose 1), accelerated titration will transition to a standard 3+3 dose escalation.

Table 1 Dose Titration Procedures

Dose Level	Toxicity in Study	Increase in Dose
Accelerated Dose Titration Phase		
Dose Level -1		Lower doses may be used if Dose Level 1 exposure is significantly higher than predicted or if there is excessive toxicity. This may be achieved by reducing the dose or by alternate dosing schedules.
Dose Level 1		Starting Dose: ~~125 mg~~ **50 mg**
Subsequent Dose Levels	No subjects with a ≥ Grade 2 toxicity (exceptions below in Section 3.3.2.1) or DLT (Section 3.3.3)	Increase by ≤100% increase in dose **up to 500 mg, ≤50% increase in dose thereafter.** (No subjects with ≥ Grade 2 drug related toxicity AND no subjects with any DLTs in first 28 days of treatment)
End of Accelerated Dose Titration Phase	One subject ≥ Grade 2 drug related non-hematological toxicity in the first 28 days of treatment) or ≥ Grade 3 drug related specific toxicity (See Section 3.3.2.1)	Begin 3+3 dose escalation phase (note that once 3+3 phase is initiated, the procedure may revert to the accelerated dose titration phase – see criteria below in Reverting to Accelerated Dose Titration)

Section 3.3.2 Dose Escalation Phase

PREVIOUS TEXT

3+3 Dose Escalation Phase

Two additional subjects will be enrolled to the dose level at which accelerated dose titration ends, for a total of at least 3 subjects at that dose level. If no DLTs are observed in any of the 3 subjects, then dosing will proceed to the next higher dose level (≤100% increase in dose). An additional three subjects will be enrolled at this dose level if 1 of 3 subjects experiences a DLT. Subjects will be entered in a staggered approach with at least 7 days between each subject to minimize the risk of inadvertently exceeding the maximum tolerated dose in multiple subjects. Dose escalation decisions will be made as

outlined in Table 1. Escalation to the next dose level will not increase greater than 2 fold from the previous dose level. If 2 or more DLTs are observed at any dose level, the MTD will have been exceeded.

Evaluation of safety data from at least 1 subject during the accelerated dose titration and at least 3 subjects in the standard dose titration who have completed 28 days of dosing on study (one cycle) is required prior to defining a new dose and starting the next cohort. Once a higher dose has been cleared, subjects at lower dose levels who remain on study drug and have not experienced dose limiting toxicity will be allowed to escalate up to that level.

In the accelerated dose escalation cohorts and the 3+3 dose escalation cohorts, the dose will be escalated based on all available data, including PK data and the safety profile of prior cohorts, as well as the predicted dose from N-CRM design [Neuenschwander, 2008] described in Section 12.

Table 2 3 + 3 Dose Escalation Design

Number of Subjects with DLT in a Cohort	Action
0 out of 3 subjects	Escalate to the next dose level with increase ≤100% if none of the subjects have Grade 2 toxicity (in the first 4 weeks of treatment) Escalate to next dose level with an increase of ≤50% if (in the first 4 weeks of treatment) there has been: - One or more subjects with Grade 2 toxicity
1 out of 3 subjects	Accrue 3 additional evaluable subjects at current dose level for a total of 6 evaluable subjects
1 out of 6 subjects	Escalate to the next dose level with an increase of ≤50%
2 or more subjects in a dosing cohort (up to 6 subjects)	MTD has been exceeded. Either evaluate an intermediate dose lower than current dose or expand a prior cohort up to 12 subjects

REVISED TEXT

3+3 Dose Escalation Phase

Two additional subjects will be enrolled to the dose level at which accelerated dose titration ends, for a total of at least 3 subjects at that dose level. If no DLTs are observed in any of the 3 subjects, then dosing will proceed to the next higher dose level (≤100% increase in dose **up to 500 mg, ≤50% increase in dose thereafter**). An additional three subjects will be enrolled at this dose level if 1 of 3 subjects experiences a DLT. Subjects will be entered in a staggered approach with at least 7 days between each subject to minimize the risk of inadvertently exceeding the maximum tolerated dose in multiple subjects. Dose escalation decisions will be made as outlined in Table 1. Escalation to the next dose level will not increase greater than 2 fold from the previous dose level **up to a dose of 500mg. Subsequent dose escalation steps would be up to a maximum of 50% at each step**. If 2 or more DLTs are observed at any dose level, the MTD will have been exceeded.

Evaluation of safety data from at least 1 subject during the accelerated dose titration and at least 3 subjects in the standard dose titration who have completed 28 days of dosing on study (one cycle) is required prior to defining a new dose and starting the next cohort. Once a higher dose has been cleared, subjects at lower dose levels who remain on study drug and have not experienced dose limiting toxicity will be allowed to escalate up to that level.

In the accelerated dose escalation cohorts and the 3+3 dose escalation cohorts, the dose will be escalated based on all available data, including PK data and the safety profile of prior cohorts, as well as the predicted dose from N-CRM design [Neuenschwander, 2008] described in Section 12.

Table 2 3 + 3 Dose Escalation Design

Number of Subjects with DLT in a Cohort	Action
0 out of 3 subjects	Escalate to the next dose level with increase ≤100% **up to 500 mg, ≤50% thereafter** if none of the subjects have Grade 2 toxicity (in the first 4 weeks of treatment) Escalate to next dose level with an increase of ≤50% if (in the first 4 weeks of treatment) there has been: - One or more subjects with Grade 2 toxicity
1 out of 3 subjects	Accrue 3 additional evaluable subjects at current dose level for a total of 6 evaluable subjects
1 out of 6 subjects	Escalate to the next dose level with an increase of ≤50%
2 or more subjects in a dosing cohort (up to 6 subjects)	MTD has been exceeded. Either evaluate an intermediate dose lower than current dose or expand a prior cohort up to 12 subjects

Section 3.3.3 Dose Limiting Toxicity

PREVIOUS TEXT

Dose Limiting Toxicity

Dose-limiting toxicity (DLT) is defined as any adverse event which is related (definitely, probably or possibly) to study drug (using the National Cancer Institute – Common Terminology Criteria for Adverse Events [NCI-CTCAE], v4.0) during the first 28 days of treatment and meets the criteria listed in Table 3 [NCI-CTCAE, 2009].

REVISED TEXT

Dose Limiting Toxicity

Dose-limiting toxicity (DLT): An event will be considered a DLT if it occurs within the first 4 weeks (28 days) of treatment, and meets one of the following criteria (Table 3 [NCI-CTCAE v.4.0, 2009]) unless it can be clearly established that the event is unrelated to treatment. ~~is defined as any adverse event which is related (definitely, probably or possibly) to study drug (using the National Cancer Institute –~~

~~Common Terminology Criteria for Adverse Events [NCI-CTCAE], v4.0) during the first 28 days of treatment and meets the criteria listed in Table 3 [NCI-CTCAE, 2009].~~

Section 3.5.3 Rationale for Dose and Schedule

PREVIOUS TEXT

- One tenth of the rat STD10 as per ICH S9 guidance

  The STD10 in the rat was defined as between100 and 300 mg/kg administered over 6-hour infusion twice-weekly for 2 to 4 weeks. One-tenth (1/10) of the rat STD10 is between 60 and 180 mg/m^2. These doses were well tolerated in dogs. A starting dose based on 1/10 of the rat STD10 would be between 110 and 330 mg using the human equivalent dose calculation.

Taking all three approaches into consideration and the rationale for a 2-hour infusion duration, a starting dose of 125 mg twice-weekly as a 2-hour infusion is proposed. This dose provides a predicted total blood AUC of 3.58 μg.h/mL and a total blood Cmax of 1.07 μg/mL. The AUC is 15 to 66-fold lower than the AUC (0-24hr) for the rat STD10 between 100 and 300 mg/kg, 7-fold lower than the AUC at the lowest tested dose in rat (30 mg/kg), and 22-fold lower than the AUC for the dog HNSTD of 100 mg/kg. The Cmax is 7 to 31-fold lower than the Cmax for the rat STD10 between 100 and 300 mg/kg, 2.8-fold lower than the Cmax at the lowest tested dose in rat (30 mg/kg), and 9.2-fold lower than the Cmax for the dog HNSTD of 100 mg/kg. The starting dose of 125 mg will provide a suitable safety margin for the anticipated toxicities, while minimizing the number of subjects with aggressive lymphomas exposed to sub-therapeutic doses.

REVISED TEXT

- One tenth of the rat STD10 as per ICH S9 guidance

  The STD10 in the rat was defined as ~~between~~100 ~~and 300~~ mg/kg administered over 6-hour infusion twice-weekly for 2 to 4 weeks. One-tenth (1/10) of the rat STD10 is ~~between~~ 60 ~~and 180~~ mg/m^2. These doses were well tolerated in dogs. A starting dose based on 1/10 of the rat STD10 would be ~~between~~ 110 ~~and 330~~ mg using the human equivalent dose calculation.

Taking all three approaches into consideration and the **shorter infusion duration of** ~~rationale for a~~ 2-hour**s** ~~infusion duration~~, a starting dose of ~~125 mg~~ **50 mg** twice-weekly as a 2-hour infusion is proposed. This dose provides a predicted total blood AUC of ~~3.58~~ **43** μg.h/mL and a total blood Cmax of ~~1.07~~ **428** μg/mL. The AUC is ~~15 to 66~~ **38**-fold lower than the AUC (0-24hr) for the rat STD10 ~~between~~ of 100 ~~and 300~~ mg/kg, ~~7~~ **18**-fold lower than the AUC at the lowest tested dose in rat (30 mg/kg), and ~~22~~ **56**-fold lower than the AUC for the dog HNSTD of 100 mg/kg. The Cmax is ~~7 to 31~~ **18**-fold lower than the Cmax for the rat STD10 ~~between~~ **of** 100 ~~and 300~~ mg/kg, ~~2.8~~ **6.9**-fold lower than the Cmax at the lowest tested dose in rat (30 mg/kg), and ~~9.2~~ **23**-fold lower than the Cmax for the dog HNSTD of 100 mg/kg. The starting dose of ~~125 mg~~ **50 mg** will provide a suitable safety margin for the anticipated toxicities, while minimizing the number of subjects with aggressive lymphomas exposed to sub-therapeutic doses.

Section 3.8.1 QTc Stopping Criteria

PREVIOUS TEXT

QTc Stopping Criteria

If a subject that meets the corrected QT (QTc)[1] interval duration criteria below, study treatment(s) will be withheld.

- QT interval (corrected for HR) ≥530 msec

REVISED TEXT

QTc Stopping Criteria

If a subject that meets the corrected QT (QTc)[1] interval duration criteria below, study treatment(s) will be withheld.

- QT interval (corrected for HR) ≥530 msec**; <u>IP will be permanently discontinued.</u>**
- **<u>QTc interval increase from baseline ≥ 60 msec; IP may be restarted at a 33% reduction in dose once the QTc returns to baseline. If QTc prolongation meeting stopping criteria recurs after re-challenge, IP must be permanently discontinued.</u>**

Section 5.2.3 Exclusion Criteria # 10

PREVIOUS TEXT

10. Cardiac exclusion criteria:
    - History of acute coronary syndromes (including myocardial infarction and unstable angina), coronary angioplasty, or stenting within the past 6 months prior to first dose of study drug(s).
    - QTc interval >480msec
    - Uncontrolled arrhythmias. Subjects with rate controlled atrial fibrillation for > 1 month prior to first dose of study drugs may be eligible.
    - Class II, III or IV heart failure as defined by the New York Heart Association (NYHA) functional classification system.

REVISED TEXT

10. Cardiac exclusion criteria:
    - History of acute coronary syndromes (including myocardial infarction and unstable angina), coronary angioplasty, or stenting within the past 6 months prior to first dose of study drug(s).

- QTc interval ~~>480msec~~ **>450msec**
- Uncontrolled arrhythmias. Subjects with rate controlled atrial fibrillation for > 1 month prior to first dose of study drugs may be eligible.
- Class II, III or IV heart failure as defined by the New York Heart Association (NYHA) functional classification system.

Section 7.1 Time & Events Table

PREVIOUS TEXT

ECG	Two copies of the ECG tracing should be obtained at the time of the ECG, one to be kept in the study file for retrospective collection by the sponsor if necessary. ECG data should be reviewed by qualified personnel with experience in this study population	X	X[b]	X	X		Every 4 weeks	X

REVISED TEXT

ECG	**Pre-infusion and at the end of infusion except on Day 1 (Section 7.3.4).** Two copies of the ECG tracing should be obtained at the time of the ECG, one to be kept in the study file for retrospective collection by the sponsor if necessary. ECG data should be reviewed by qualified personnel with experience in this study population	X	X[b]	X	X		~~Every 4 weeks~~ **On Day 4 of each cycle**	X

Section 7.1 Time & Events Table

PREVIOUS TEXT

Chemistry	Evaluations performed by a central laboratory. No need to repeat at pre-dose Day 1 if screening assessments were performed within 14 days of first dose.	X	X	X	X	X	Prior to every infusion
Hematology	Evaluations performed by a central laboratory. No need to repeat at pre-dose Day 1 if screening assessments were performed within 14 days of first dose.	X	X	X	X	X	Every 4 weeks
Coagulation	PT/PTT/INR	X					
Blood sample for circulating biomarkers	A blood sample for circulating biomarkers should be obtained on Day 1 (prior to treatment), Day 21 (and at the time of disease progression.		X			X	
PK sampling for Part 1	For details, see Table 7		Day 1 (Table 7)	Soon after ECG and PD biomarker collection	Day 15 (Table 7)	At time of PD biomarker collection	Cycle 2, 4, 6 and 12 – pre-dose and within 5 min prior to end of infusion on one treatment day between Day 4 and Day 24

PK sampling for Part 2	Three samples to be collected on Day 1 and Day 11: Predose within 60 minutes prior to start of infusion, single draw between 0.5 and 1.9 h from start of infusion, single draw between 3-6h following end of infusion		Day 1 and pre-dose on Day 4	X (after 4th dose, Day 11)	pre-dose on Day 15		Cycle 2, 4, 6 and 12 – pre-dose and within 5 min prior to end of infusion on one treatment day between Day 4 and Day 24

REVISED TEXT

Chemistry	~~Evaluations performed by a central laboratory.~~ No need to repeat at pre-dose Day 1 if screening assessments were performed within 14 days of first dose.	X	X	X	X	X	Prior to every infusion
Hematology	~~Evaluations performed by a central laboratory.~~ No need to repeat at pre-dose Day 1 if screening assessments were performed within 14 days of first dose.	X	X	X	X	X	Every 4 weeks
Coagulation	PT/PTT/INR	X					
Blood sample for circulating biomarkers	A blood sample for circulating biomarkers should be obtained on Day 1 (prior to treatment), Day 21 (and at the time of disease progression.		X			X	

PK sampling for Part 1	For details, see Table 7		Day 1 (Table 7)	Soon after ECG and PD biomarker collection	Day 15 (Table 7)	At time of PD biomarker collection	Cycle 2, 4, 6 and 12 – pre-dose and within 5 min prior to end of infusion on ~~one treatment day between~~ Day 4 ~~and Day 24~~
PK sampling for Part 2	Three samples to be collected on Day 1 and Day 11: Predose within 60 minutes prior to start of infusion, single draw between 0.5 and 1.9 h from start of infusion, single draw between 3-6h following end of infusion		Day 1 and pre-dose on Day 4	X (after 4th dose, Day 11)	pre-dose on Day 15		Cycle 2, 4, 6 and 12 – pre-dose and within 5 min prior to end of infusion on ~~one treatment day between~~ Day 4 ~~and Day 24~~

Section 11.Data Management

PREVIOUS TEXT

DATA MANAGEMENT

For this study, data will be collected using defined eCRFs, transmitted electronically to GSK and combined with data provided from other sources in a validated data system.

When laboratory samples (i.e., hematology and clinical chemistry) are analyzed by a central laboratory the results will be stored in a database maintained by the central laboratory and transferred to GSK at agreed times.

In all cases, subject initials will not be collected or transmitted to GSK according to GSK policy.

REVISED TEXT

DATA MANAGEMENT

~~For this study, data will be collected using defined eCRFs, transmitted electronically to GSK and combined with data provided from other sources in a validated data system.~~

~~When laboratory samples (i.e., hematology and clinical chemistry) are analyzed by a central laboratory the results will be stored in a database maintained by the central laboratory and transferred to GSK at agreed times.~~

For this study, data will be collected using defined eCRFs in the validated data system, InForm. Some data (i.e. Biomarker, PK, Holter ECG) will be transmitted electronically to GSK from an external vendor via a validated data system, the External Alliance Portal.

In all cases, subject initials will not be collected or transmitted to GSK according to GSK policy.

Section 7.1 Time & Events Table reference

PREVIOUS TEXT

a. A subject is to receive two doses per week which should be given 3 days apart. If there is a need to change scheduling, the scheduled days of the week can change as long as there are 3-4 days between doses. Up to 5 days between doses is permitted for exceptional circumstances
b. Timings for in-house on-drug ECGs are pre-infusion, immediately post-infusion, before bed, and before discharge the next morning for Day 1 of cycle 1 only. Other ECGs should be performed as instructed elsewhere within this protocol.
c. Retention of screen-failure tumor tissue: all or a portion of archival or fresh biopsy tissue from screen-failure subjects, used for central testing of GCB-DLBCL or EZH2 mutation status, will be retained. This tissue may be used in the validation of potential diagnostic assays to detect EZH2 mutations and/or for GCB-DLBCL subtyping.
d. If the Follow-up visit ≥ 8weeks from the previous response scan time point, scans should be obtained to confirm/ evaluate response.
e. If utilized for subject evaluation at baseline, PET must continue to be used in subsequent assessment timepoints.
f. Only if initially and/or previously positive & required for CR or as clinically indicated.

REVISED TEXT

a. A subject is to receive two doses per week which should be given 3 days apart. If there is a need to change scheduling, the scheduled days of the week can change as long as there are 3-4 days between doses. Up to 5 days between doses is permitted for exceptional circumstances
b. Timings for in-house on-drug ECGs are pre-infusion, ~~immediately post-infusion~~ **at the end of infusion**, before bed, and before discharge the next morning for Day 1 of cycle 1 only. Other **protocol-mandated** ECGs should be performed ~~as instructed elsewhere within this protocol~~ **pre-infusion and at the end of infusion (Section 7.3.4).**
c. Retention of screen-failure tumor tissue: all or a portion of archival or fresh biopsy tissue from screen-failure subjects, used for central testing of GCB-DLBCL or EZH2 mutation status, will be retained. This tissue may

be used in the validation of potential diagnostic assays to detect EZH2 mutations and/or for GCB-DLBCL subtyping.

d. If the Follow-up visit ≥ 8weeks from the previous response scan time point, scans should be obtained to confirm/ evaluate response.
e. If utilized for subject evaluation at baseline, PET must continue to be used in subsequent assessment timepoints.
f. Only if initially and/or previously positive & required for CR or as clinically indicated.

Section 7.3.4 Electrocardiogram

PREVIOUS TEXT

Electrocardiogram

Twelve -lead ECGs will be obtained in triplicate at designated time points during the study using an ECG machine that automatically calculates the HR and measures PR, QRS, QT, and QTc intervals. At each assessment a 12-lead ECG will be performed by qualified personnel at the site after the subject has at least a 5 minute rest and is in a semi-[recumbent or supine] position.

Timings for in-house on-drug ECGs on Day 1 are pre-infusion, post-infusion, before bed (between 9-10pm) and before discharge the next morning. Subjects will not be discharged until ECG has normalized (QTc < 500 msec).

Refer to Section 3.8.1 for QTc withdrawal criteria. Additional QTc readings may be necessary.

Refer to the SPM for details regarding ECG procedures.

REVISED TEXT

Electrocardiogram

Twelve -lead ECGs will be obtained in triplicate at designated time points during the study using an ECG machine that automatically calculates the HR and measures PR, QRS, QT, and QTc intervals. At each assessment, a 12-lead ECG will be performed by qualified personnel at the site after the subject has at least a 5 minute rest and is in a semi-[recumbent or supine] position. **Refer to the SPM for details regarding ECG procedures.**

Timings for in-house on-drug ECGs on Day 1 **only** are pre-infusion, post-infusion, before bed (between 9-10pm) and before discharge the next morning. **These ECGs are in addition to the Holter monitoring.** Subjects will not be discharged **from their overnight stay in the Phase I unit after dose 1** until ~~ECG has normalized~~ ~~(~~**the** QTc **is** < 500 msec.~~)~~

For all doses after the first dose, ECGs will be recorded pre-infusion and at the end of infusion. See Time & Events Table (Section 7.1) for exact timings.

Refer to Section 3.8.1 for QTc withdrawal/**stopping** criteria. Additional QTc readings may be necessary.

Table 7 List of Clinical Laboratory Tests

REVISED TEXT

List of Clinical Laboratory Tests

Hematology			
Platelet Count	*RBC Indices*:	*Automated WBC Differential:*	
RBC Count	MCV	Neutrophils	
WBC Count (absolute)	MCH	Lymphocytes	
Reticulocyte Count	MCHC	Monocytes	
Hemoglobin		Eosinophils	
Hematocrit		Basophils	
Clinical Chemistry			
BUN	Potassium	AST	Total and direct bilirubin
Creatinine	Chloride	ALT	Uric Acid
Sodium	Calcium	Alkaline phosphatase	Total Protein
Magnesium	**Glucose**	LDH	PO4
FSH and estradiol (as needed in women of non-child bearing potential only)			

Abbreviation(s): ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; FSH, follicle stimulating hormone; LDH, lactate dehydrogenase; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; PO_4, phosphate; RBC, red blood cell; WBC, white blood cell.

PROTOCOL SYNOPSIS

PREVIOUS TEXT

- **STUDY DESIGN:** This study is divided into 2 parts; Part 1 of the study is a dose escalation phase to select the recommended Part 2 dose (RP2D) based on the safety, PK, and PD profiles observed after IV administration of GSK2816126. Eligible subjects with relapsed/refractory DLBCL and transformed FL malignancies will be enrolled in the dosing cohorts until a RP2D is established. Subjects may continue treatment in the study until disease progression, unacceptable toxicity, withdrawal of consent, or commercial supply of GSK2816126 becomes available to the subject. Expansion cohorts are planned in subjects with both EZH2 mutant positive and EZH2 WT tumors to further explore clinical activity at the RP2D (Part 2).

REVISED TEXT

- **STUDY DESIGN:** This study is divided into 2 parts; Part 1 of the study is a dose escalation phase to select the recommended Part 2 dose (RP2D) based on the safety, PK, and PD profiles observed after IV administration of GSK2816126. Eligible subjects with relapsed/refractory DLBCL and transformed FL malignancies will be enrolled in the dosing cohorts until a RP2D is established. Subjects may continue treatment in the study until disease progression, unacceptable toxicity~~,~~ **or** withdrawal of consent~~, or commercial supply of GSK2816126 becomes available to the subject~~.

Expansion cohorts are planned in subjects with both EZH2 mutant positive and EZH2 WT tumors to further explore clinical activity at the RP2D (Part 2).

Section 3.8.1 QTc Stopping Criteria

PREVIOUS TEXT

QTc Stopping Criteria

If a subject that meets the corrected QT (QTc)[1] interval duration criteria below, study treatment(s) will be withheld.

- QT interval (corrected for HR) ≥530 msec

REVISED TEXT

QTc Stopping Criteria

If a subject that meets the corrected QT (QTc)[1] interval duration criteria below, study treatment(s) will be withheld.

- QT interval (corrected for HR) ≥~~530~~ **500** msec**; IP will be permanently discontinued.**
- **QTc interval increase from baseline ≥ 60 msec and maximum QTc < 500 msec; IP may be restarted at a 33% reduction in dose once the QTc returns to baseline. If QTc prolongation meeting stopping criteria recurs after re-challenge, IP must be permanently discontinued.**

Section 7.1 Time & Events Table

PREVIOUS TEXT

CT	Must be completed within 4 weeks of first dose of GSK2816126 and repeated every 8 weeks.	X					X	X[d]

a. A subject is to receive two doses per week which should be given 3 days apart. If there is a need to change scheduling, the scheduled days of the week can change as long as there are 3-4 days between doses. Up to 5 days between doses is permitted for exceptional circumstances.
b. Timings for in-house on-drug ECGs are pre-infusion, at the end of infusion, before bed, and before discharge the next morning for Day 1 of cycle 1 only. Other protocol-mandated ECGs should be performed pre-infusion and at the end of infusion (Section 7.3.4).
c. Retention of screen-failure tumor tissue: all or a portion of archival or fresh biopsy tissue from screen-failure subjects, used for central testing of GCB-DLBCL or EZH2 mutation status, will be retained. This tissue may be used in the validation of potential diagnostic assays to detect EZH2 mutations and/or for GCB-DLBCL subtyping.
d. If the Follow-up visit ≥ 12weeks from the previous response scan time point, scans should be obtained to confirm/ evaluate response.
e. If utilized for subject evaluation at baseline, PET must continue to be used in subsequent assessment timepoints.
f. Only if initially and/or previously positive & required for CR or as clinically indicated.

REVISED TEXT

CT	Must be completed within 4 weeks of first dose of GSK2816126 and repeated ~~every~~**in** 8 weeks. **Every 12 weeks thereafter.**	X					X	X[d]

a. A subject is to receive two doses per week which should be given 3 days apart. If there is a need to change scheduling, the scheduled days of the week can change as long as there are 3-4 days between doses. Up to 5 days between doses is permitted for exceptional circumstances.
b. Timings for in-house on-drug ECGs are pre-infusion, at the end of infusion, before bed, and before discharge the next morning for Day 1 of cycle 1 only. Other protocol-,mandated ECGs should be performed pre-infusion and at the end of infusion (Section 7.3.4).
c. Retention of screen-failure tumor tissue: all or a portion of archival or fresh biopsy tissue from screen-failure subjects, used for central testing of GCB-DLBCL or EZH2 mutation status, will be retained. This tissue may be used in the validation of potential diagnostic assays to detect EZH2 mutations and/or for GCB-DLBCL subtyping.
d. If the Follow-up visit ≥ 12weeks from the previous response scan time point, scans should be obtained to confirm/ evaluate response.
e. ~~If utilized for subject evaluation at baseline, PET must continue to be used in subsequent assessment timepoints.~~ **Diagnostic CT is the preferred method of disease assessment. PET/CT may be used as an alternative at the investigator's discretion.**
f. Only if initially and/or previously positive & required for CR or as clinically indicated.

Section 7.1 Time & Events Table

PREVIOUS TEXT

Positron emission tomography (PET)	The use of standalone PET or PET in combination with CT scan is optional at the discretion of the investigator.	X[e]					X[e]	X[d,e]

REVISED TEXT

Positron emission tomography (PET)	The use of standalone PET or PET in combination with CT scan is **optional** ~~at the descreation of the investigator.~~	X[e]					X[e]	X[d,e]

Section 7.2 Demographic/Medical History and Baseline Assessments

PREVIOUS TEXT

- Diagnostic quality CT imaging with contrast within 28 days of first dose of study treatment identifying nodes, nodal masses, splenic/liver nodules and, if applicable measurable extranodal disease. See Section 7.7 for further information.

REVISED TEXT

- Diagnostic quality CT imaging with contrast within 28 days of first dose of study treatment identifying nodes, nodal masses, splenic/liver nodules and, if applicable measurable extranodal **disease is the preferred method of disease assessment. If PET/CT has been performed within this window, diagnostic CT will not be required**. See Section 7.7 for further information.

Section 7.1 Time & Events Table

REVISED TEXT

Coagulation	PT/PTT/INR. **No need to repeat at pre-dose Day 1 if screening assessments were performed within 14 days of first dose.**	X						
CT	Must be completed within 4 weeks of first dose of GSK2816126 and repeated 8 weeks **after dosing is initiated**. Every 12 weeks thereafter.	X					X	Xd
Positron emission tomography (PET)	The use of standalone PET or PET in combination with CT scan is optional. **Standalone PET dose not replace CT.**	X[e]					X[e]	X[d,e]
Bone Marrow biopsy	See Section 7.7	X					X[f]	X[f]
B symptoms	See Section 7.7	X	X	X	X	X	X	
Disease assessment	Baseline disease identified at screening and repeated every 8 weeks	X					X	X[d]
ECOG Performance status	See Appendix 2	X	X	X	X	X		
Study Medication								
GSK2816126 Dosing			Dosed 2x weekly at least 3 days apart (3 weeks on/1 week off)					

a. A subject is to receive two doses per week which should be given 3 days apart. If there is a need to change scheduling, the scheduled days of the week can change as long as there are 3-4 days between doses. Up to 5 days between doses is permitted for exceptional circumstances.
b. Timings for in-house on-drug ECGs are pre-infusion, at the end of infusion, before bed, and before discharge the next morning for Day 1 of cycle 1 only. Other protocol-mandated ECGs should be performed pre-infusion and at the end of infusion (Section 7.3.4).
c. Retention of screen-failure tumor tissue: all or a portion of archival or fresh biopsy tissue from screen-failure subjects, used for central testing of GCB-DLBCL or EZH2 mutation status, will be retained. This tissue may be used in the validation of potential diagnostic assays to detect EZH2 mutations and/or for GCB-DLBCL subtyping.
d. If the Follow-up visit ≥ 12weeks from the previous response scan time point, scans should be obtained to confirm/ evaluate response.
e. **Standalone PET dose not replace CT**. Diagnostic CT is the preferred method of disease assessment. PET/CT may be used as an alternative at the investigator's discretion.
f. Only if initially and/or previously positive & required for CR or as clinically indicated.

Synopsis and Section 5.2.3

PREVIOUS TEXT

Exclusion Criteria

Deviations from exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

Subjects meeting any of the following criteria must not be enrolled in the study:

1 Currently receiving cancer therapy (chemotherapy, radiation therapy, immunotherapy or biologic therapy) (permitting corticosteroids to control systemic or local symptoms, up to a dose of 10 mg prednisolone or equivalent daily and stable for at least 2 weeks prior to enrollment).

REVISED TEXT

Exclusion Criteria

Deviations from exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

Subjects meeting any of the following criteria must not be enrolled in the study:

1 Currently receiving cancer therapy (chemotherapy, radiation therapy, immunotherapy or biologic therapy) (permitting corticosteroids to control systemic or local symptoms, up to a dose of 10 mg prednisolone or equivalent daily and stable for at least ~~2 weeks~~ **7 days** prior to enrollment).

AMENDMENT [3]

Where the Amendment Applies

This amendment applies to all investigator sites participating in this study.

Summary of Amendment Changes with Rationale

Based on emerging data, addition of solid tumor malignancies and other NHLs to Part 1 of the study and transformed follicular lymphoma subjects to Part 2. Multiple myeloma subjects have been added to both Part 1 and Part 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 8. To accommodate these changes we have also augmented the number of subjects, evaluation of futility, 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. We also updated the Prohibited Meds table 13 and table 14 and removed the PD analysis from Part 2 of the study.

List of Specific Changes

Title page

REVISED TEXT

Title:	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 <u>lymphoma, transformed follicular lymphoma, other Non-Hodgkin's lymphomas, solid tumors and multiple myeloma</u>

REVISED TEXT

Description: <u>This is an open-label, multicenter, 2-part study to determine the recommended Phase 2 dose (RP2D) for GSK2816126 given twice weekly by IV infusion. Part 1 will be conducted in adult subjects with relapsed/refractory diffuse large B cell lymphoma (DLBCL), transformed follicular lymphoma (tFL), other Non-Hodgkin's lymphomas (NHL), solid tumors and multiple myeloma (MM). Expansion cohorts (Part 2) are planned to further explore clinical activity of GSK2816126 in subjects with</u>

EZH2 wild type and EZH2 mutant positive germinal centre B-cell like diffuse large B cell lymphoma (GCB-DLBCL), tFL and MM.

Subject: Relapsed, refractory, Phase I study, dose escalation study, GSK2816126, diffuse large B cell lymphoma, transformed follicular lymphoma, NonHodgkin's lymphoma, solid tumors, multiple myeloma.

Author (s):

PPD	~~Statistics, Oncology TA Group, USA~~ ~~Cancer Research Epigenetics Management, USA~~ Clinical Statistics, USA Molecular Medicine Management, USA Pre-Clinical Safety Assessment, USA Cancer Research Epigenetics Management, USA Clinical Pharmacology Modeling & Simulation, USA Non-Clinical Safety Assessment, USA Global Clinical Operational Sciences, USA Global Clinical Operational Sciences, USA ~~Precision Medicine and Diagnostics, USA~~ Cancer Research Epigenetics Management, USAWhite, Global Regulatory Affairs, USA

Sponsor Signatory:

REVISED TEXT

~~Vicki Goodman, MD~~ Chris Carpenter, MD, PhD ~~Director, Clinical Development~~ VP, DPU Head Cancer Epigenetics	**Date**

Sponsor/Medical Monitor Information Page

REVISED TEXT

Medical Monitor and Sponsor Contact Information:

Role	Name	Day Time Phone Number	After-hours Phone/Cell/ Pager Number	Fax Number	GSK Address
Primary Medical Monitor	PPD ~~MD~~ PPD MD, PhD	PPD	PPD		1250 South Collegeville Rd Mailstop UP 4410 Collegeville, PA 19426, USA PPD PPD
Secondary Medical Monitor	PPD ~~MD~~ PPD MD, PhD	PPD	PPD		1250 South Collegeville Road, Mailstop ~~UP4400~~UP4410 Collegeville, PA 19426, USA PPD PPD

Investigator PROTOCOL Agreement Page

REVISED TEXT

For protocol number EZH117208

I confirm agreement to conduct the study in compliance with the protocol, as amended by this protocol amendment.

I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described study.

I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure that site staff receives the appropriate information throughout the study.

LIST OF ABBREVIATIONS

Added the abbreviations tFL (Transformed Follicular Lymphoma), CRPC (Castrate resistant prostate cancer) and MM (Multiple Myeloma).

PROTOCOL SYNOPSIS

REVISED TEXT

PROTOCOL TITLE: 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 ~~and~~, transformed follicular lymphoma, other Non-Hodgkin's l~~L~~ymphomas, ~~other~~ solid tumors and multiple myeloma. ~~types~~

~~**STUDY RATIONALE:** Current data from GSK2816126 preclinical development indicate a potential to inhibit the Enhancer of Zeste 2 (EZH2) enzyme component ofthe Polycomb Repressive Complex 2 and that this inhibition may have clinical utility in the treatment of certain lymphomas, including DLBCL and transformed FL. Relapsed and/or refractory DLBCL and transformed FL have an overall poor outlook. This is the first study of this agent to be conducted in subjects with these relapsed and/or refractory lymphoma malignancies for which no standard therapies are anticipated to result in a durable remission.~~

STUDY RATIONALE: Enhancer of zeste homolog 2 (EZH2), a component of the Polycomb Repressive Complex 2 (PRC2), mediates transcriptional repression of target genes through tri-methylation of histone H3 on lysine 27 (H3K27me3). EZH2 and H3K27me3 are dysregulated in many cancers through diverse pathways. While EZH2 mutation plays a significant role in progression of certain lymphomas, data from prostate, breast, and several other tumors have demonstrated that increased EZH2 expression correlates with increased aggressiveness of tumors and poor prognosis.

GSK2816126 is a selective and potent inhibitor of wild-type and mutant EZH2 capable of decreasing H3K27me3 levels in all cell types examined. EZH2 inhibition has been shown to decrease the growth of several cell lines derived from EZH2 wild type (WT) and mutant lymphomas, SNF5-mutant malignant rhabdoid tumors, multiple myeloma, AML, neuroblastoma, prostate, breast, skin and colon cancers.

Most of these cancers have an overall poor outlook either because of lack of any effective therapy or standard therapies do not result in a durable remission. This first study of this agent will be conducted in subjects with non-Hodgkin lymphomas, especially germinal center B-cell diffuse large B-cell lymphoma (GCB-DLBCL) and transformed follicular lymphoma (t-FL), and subjects with solid tumors and multiple myeloma (MM) who have relapsed or are refractory to prior therapies and have a high degree of unmet medical need in terms of available treatment options.

- **STUDY OBJECTIVES, ENDPOINTS AND HYPOTHESES:**

Part 1 Objectives	**Part 1 Endpoint**
• To confirm tumor EZH2 and GCB-DLBCL status • To investigate the mechanism of action and additional indicators of sensitivity and resistance to GSK2816126 • To generate samples (data reported separately) with which to investigate the potential for GSK2816126 to affect cytochrome P450 (CYP) 3A4 enzyme activity	• Tumor gene expression profile (GEP) for confirmation of GCB-DLBCL status • Tumor baseline genetic profiles, response • Samples to assess a potential change in 4b-OH cholesterol to cholesterol ratio in plasma following repeat dosing of GSK2816126 (data reported separately)
No formal statistical hypotheses are being tested in Part 1: Phase I dose escalation. Analysis of the data obtained from Part 1 will only utilize descriptive methods	

- **STUDY OBJECTIVES, ENDPOINTS AND HYPOTHESES:**

	Part 2 Objectives	Part 2 Endpoints
Primary	• To determine clinical activity of GSK2816126 in~~a~~ cohort<u>s</u> of subjects with EZH2 <u>mutant and</u> wild type ~~germinal center B-cell-like diffuse large B-cell lymphoma (~~GCB-DLBCL and ~~in a cohort of subjects with GCB-DLBCL harboring mutations in the EZH2 genet~~<u>FL and subjects with MM</u>	• Objective response rate (% of subjects achieving CR and PR per response criteria)
Secondary	• To determine the safety, tolerability of the selected IV dose of GSK2816126 • To characterize the population PK of GSK2816126 • To evaluate the relationship between exposure and safety/efficacy/~~PD~~ parameters • To begin to characterize the durability of response and progression free survival with 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) • 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). • GSK2816126 exposure markers (e.g. dose, concentration, Cmax, or AUC) and safety/efficacy/~~PD~~ responses. ~~Pharmacodynamic response assessed by change from baseline in tri-methylation of H3K27me3~~ • Duration of response (DoR) • Progression-free survival (PFS)
Exploratory	• ~~To confirm tumor EZH2 and GCB-DLBCL status~~ • To identify biomarkers predictive of response or resistance to GSK2816126. • To investigate the mechanism of action of GSK2816126 by evaluating changes in gene expression profiles	• ~~Tumor gene expression profile (GEP) for confirmation of GCB-DLBCL status~~ • Evaluation of wild-type (WT) subject tumors for the presence of additional, undefined, mutations in the EZH2 gene • Deoxyribonucleic acid (DNA), ribonucleic acid (RNA) and protein markers in tumor and blood
Hypothesis	~~The primary goal of Part 2 is to detect whether administration of GSK2816126 could lead to a clinically meaningful response rate of at least 30% in subjects with GCB-DLBCL compared to a 10% or less response rate suggesting inadequate clinical activity in subjects with GCB-DLBCL. This will be conducted by testing the null hypothesis that P0≤10% versus the alternative that P1≥30%, assuming the maximum response rate for an ineffective drug is~~	

	Part 2 Objectives	Part 2 Endpoints
	~~10% and the minimum response rate for an effective drug is 30%.~~ The primary objective of Part 2 is to determine whether administration of GSK2816126 has a potentially clinically meaningful response rate. • In subjects with GCB-DLBCL, this will be determined in each EZH2 mutation status cohort (wild type and mutant) by testing the null hypothesis that the response rate is ≤10%, with about 90% power when the true response rate is 30%. • In subjects with tFL, this will be determined in each EZH2 mutation status cohort by testing the null hypothesis that the response rate is ≤5%, with about 80% power when the true response rate is 25%. In subjects with MM, this will be determined by testing the null hypothesis that the response rate is ≤5%, with about 85% power when the true response rate is 20%.	

- **STUDY DESIGN:** This study is divided into 2 parts; Part 1 of the study is a dose escalation phase to select the recommended Part 2 dose (RP2D) based on the safety, PK, and PD profiles observed after IV administration of GSK2816126. Eligible subjects with relapsed/refractory DLBCL ~~and~~, transformed FL malignancies, other Non Hodgkin's lymphomas (NHL) and solid tumor types will be enrolled in the dosing cohorts until a RP2D is established. Subjects may continue treatment in the study until disease progression, unacceptable toxicity, or withdrawal of consent. Expansion cohorts (Part 2) are planned in subjects with MM, and in subjects with both EZH2 mutant positive and EZH2 WT GCB-DLBCL and tFL to further explore clinical activity at the RP2D.

- **NUMBER OF SUBJECTS:** Approximately ~~100~~ 169 subjects worldwide (inclusive both Parts 1 and 2).

- **INCLUSION/EXCLUSION CRITERIA:**

Part I: Inclusion Criteria

3. Tumor type criteria:

    - Relapsed/refractory NHL that meets one of the following criteria:
        - Diffuse large B cell lymphoma or transformed follicular lymphoma relapsed after, or refractory to at least one prior chemotherapy regimen (e.g., rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone [R-CHOP]) AND not a candidate for standard salvage regimens or autologous stem cell transplant (e.g., due to age, comorbid conditions or failure to respond to salvage chemotherapy). Local confirmation of lymphoma subtype (e.g. GCB-DLBCL) is allowed for enrollment but must be confirmed through central laboratory testing.
        - DLBCL or transformed FL relapsed after or refractory to at least two prior chemotherapy regimens.

- Other NHLs that have failed at least one prior line of therapy and for which there is no standard salvage regimen.

- Relapsed and/or refractory MM that have failed prior standard therapy and for which there is no standard salvage regimen.
- Solid tumors (RECIST evaluable, with the exception of castrate resistant prostate cancer (CRPC)) at least one and not more than three standard of care chemotherapeutic regimens, or tumor for which there is no approved therapy, or for which standard therapy is refused.

4. DLBCL and tFL: Availability of archival tissue, or willingness to undergo fresh biopsy for: confirmation of GCB-DLBCL status (DLBCL subjects); retrospective central testing of EZH2 mutation status (DLBCL ,and tFL subjects).For all other tumor types: availability of either archival tissue or fresh biopsies.
5. Must have a pre-existing central venous access such as a port, Hickmann catheter, or a peripherally inserted central catheter (PICC line) or be willing and able to have one inserted.

Inclusion criteria no. 9:

The laboratory value for Adequate organ system function of prothrombin time/international normalization ratio (PT/INR) and partial thromboplastin time (PTT), under hematology section was changed from ≥1.5 x upper limit of normal (ULN) to ≤1.5 x ULN

System	LABORATORY VALUES
Hematologic	
ANC	≥1.2 x 109/L
Hemoglobin	≥9 g//dL
Platelets	≥75x 109/L
Platelets for Subjects with MM	≥ 50,000 (transfusion independent)
PT/INR and PTT	≤1.5 x ULN
Hepatic	
Albumin	≥2.5 g/dL
Total bilirubin	≤1.5 times ULN
AST and ALT	≤2.5 times ULN without liver metastases ≤5 times ULN if documented liver metastases
Renal	
Serum Creatinine Calculate Creatinine Clearance[a, b] OR 24 hr urine Creatinine Clearance	≤1.5 mg/dL or ≥50 mL/min ≥50mL/min
Reproductive/Endocrine	
Testosterone	<50ng/dL (only for subjects with CRPC)
Cardiac	
Left Ventricular Ejection Fraction (LVEF)	≥LLN (minimum of 50% LVEF) by ECHO or MUGA[c]

Abbreviation(s): ANC, absolute neutrophil count; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ECHO, echocardiogram; INR, international normalization ratio, MUGA, multigated (radionuclide) angiogram; PT, prothrombin time, PTT, partial thromboplastin time, ULN, upper limit of normal , LLN, lower limit of normal.

4. Calculated by Cockcroft-Gault formula
5. For MM subjects, adequate renal function is defined as serum creatinine ≤ 2.5 mg/dL OR creatinine clearance (either calculated or obtained via 24 hr urine collection) ≥ 30 mL/minECHO is the preferred method

Part 2: Inclusion Criteria

1. In addition to inclusion criteria listed for Part 1, Part 2 will enroll **GCB-DLBCL, tFL and MM subjects only.**
2. Lymphoma subjects will be required to undergo EZH2 mutation testing. This will require availability of archival tissue, or willingness to undergo fresh biopsy, for central testing of EZH2 mutation status.
3. Based on the results of the mutation test, lymphoma subjects may be enrolled in one of four cohorts:
    - GCB-DLBCL EZH2 mutant cohort:
        - Tumors must contain one, or more, of the following EZH2 activating mutations: Y641F; Y641N; Y641S; Y641H; Y641C; A677G; and/or A687V
    - GCB-DLBCL EZH2 wild type cohort:
        - Tumors that do not contain one of the above mutations
        - Subjects with tumors harboring EZH2 mutations other than the seven outlined above will be enrolled in the EZH2 wild type cohort
    - tFL EZH2 mutant cohort:
        - Tumors must contain one, or more, of the following EZH2 activating mutations: Y641F; Y641N; Y641S; Y641H; Y641C; A677G; and/or A687V
    - tFL EZH2 wild type cohort:
        - Tumors that do not contain one of the above mutations
        - Subjects with tumors harboring EZH2 mutations other than the seven outlined above will be enrolled in the EZH2 wild type cohort

~~4. Subjects should have accessible tumor and willingness to undergo two biopsies. Subjects for whom biopsies are not feasible will be eligible for enrollment at the discretion of the GSK medical monitor. Contact GSK medical monitor for confirmation of enrollment and study entry if biopsies are not feasible.~~

Exclusion Criteria

Exclusion criteria no.1

Currently receiving cancer therapy (chemotherapy, radiation therapy, immunotherapy or biologic therapy) (permitting corticosteroids to control systemic or local symptoms, up to a dose of 10 mg prednisolone or equivalent daily and stable for at least 7 days prior to enrollment).

- Hormonal (e.g., anti-androgen) therapies for prostate cancer must be stopped 4 to 6 weeks prior to enrolment. Subjects with prostate cancer may remain on luteinizing hormone releasing hormone (LHRH) agonists. Subjects with prostate cancer may also remain on low-dose prednisone or prednisolone (up to 10 mg/day) and still be eligible for this study.

Exclusion criteria no. 8:

Unresolved toxicity greater than Grade 1 National Cancer Institute – Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4 from previous anti-cancer therapy, with the exception of alopecia and peripheral neuropathy [NCI-CTCAE, 2009].

- Lymphoma subjects with ≤ Grade 3 lymphopenia can be enrolled at the discretion of the investigator

- **STATISTICAL METHODS**: Subject demographic and safety data will be collected on electronic case report forms (eCRFs). All data will be pooled and descriptive safety analyses summarized and listed by cohort at study conclusion. Part 2 of the study is designed to evaluate preliminary efficacy. A futility assessment will be conducted after data are available from the first 12 subjects in Part 2 and after that until up to 30 GCB-DLBCL subjects and 16 tFL subjects have been enrolled in each of the EZH2 WT and EZH2 mutant cohorts. Also, in the MM cohort a futility assessment will be conducted after data are available from the first 13 subjects in Part 2 and after that until up to 37 subjects.

- **PHARMACOKINETIC/PHARMACODYNAMIC MEASUREMENTS**: There will be extensive serial blood sampling for PK and PD measurements in Part 1 of this study with limited blood sampling performed on all subjects in Part 2. Urine and bile may be collected in some subjects in the Part 1 PK/PD expansion cohort. Single safety PK blood draws may be collected for subjects with severe adverse events or adverse events of concern. ~~In addition, pre-treatment and post-treatment tumor tissue samples will be optional for Part 1, but required for all subjects in Part 2 (unless discussed with medical monitor) to evaluate target engagement and~~

~~effects of GSK2816126 on tumor biology.~~ Mandatory collection of pre-treatment and post-treatment biopsies will be implemented in Part 1 PK/PD cohorts based on outcome of preliminary PD data in surrogate tissue (e.g. PBMCs from blood).

Section 1:INTRODUCTION

REVISED TEXT

1.1. Background

~~Enhancer of Zeste 2 (EZH2) is the enzyme component of the Polycomb Repressive Complex 2 (PRC2) that methylates histone H3 on lysine 27 (H3K27), resulting in epigenetic silencing of target gene expression. PRC2 activity is essential for maintaining the self-renewal capacity of embryonic and adult stem cells and the dynamic regulation of this activity is critical for proper development and differentiation.~~

Enhancer of zeste homolog 2 (EZH2) is the catalytic subunit of the Polycomb Repressive Complex 2 (PRC2) responsible for maintaining transcriptional repression of target genes through tri-methylation of histone H3 on lysine 27 (H3K27me3). PRC2 activity is essential for maintaining the self-renewal capacity of embryonic and adult stem cells, and the dynamic regulation of this activity is critical for proper development and differentiation.

EZH2 and H3K27me3 are dysregulated in nearly all cancers through numerous pathways including 1) recurrent gain-of-function heterozygous mutations in germinal center B-cell (GCB) diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), melanoma, and parathyroid adenoma, 2) EZH2 over-expression in numerous other aggressive tumors including those from prostate, breast, lung, liver, bladder, head and neck, skin, and kidney, and 3) inactivating mutations in UTX, an H3K27 demethylase that acts in opposition to EZH2, described in numerous tumor types including transitional cell bladder carcinoma, esophageal squamous cell carcinoma, renal cell carcinoma, multiple myeloma, and subgroup 4 medulloblastoma (McCabe & Creasy 2014). Furthermore, data from prostate, breast, and several other tumor types have demonstrated that increased EZH2 expression correlates with increased aggressiveness of tumors and poor prognosis.

In the B-cell lineage, EZH2 is required by germinal center B-cells, which are the cells of origin of the most common forms of Non-Hodgkin's Lymphomas (NHL). GC derived DLBCLs are mostly addicted to EZH2 and require its histone methyltransferase activity for their survival. Recently, somatic activating mutations in EZH2 have been identified in follicular lymphoma (FL) and GCB-DLBCL [Morin, 2010; Morin, 2011; Pasqualucci, 2011; Ernst, 2010]. The frequency of the most prevalent mutation, Y641, is 7-27% in FL and 22% in DLBCL [Bodor, 2013]. Biochemical studies have demonstrated that Y641, A677 and A687 mutants exhibit an altered substrate preference and catalytic efficiency to enhance the generation of H3K27me3. Consistent with these biochemical data, primary lymphomas and lymphoma cell lines harboring EZH2 mutations have elevated levels of H3K27me3. Mutant EZH2 maintains the proliferation, survival and blocks terminal differentiation of DLBCL cells.

1.2.1. Pharmacokinetics of GSK2816126 in Humans

GSK2816126 pharmacokinetics (PK) ~~have~~has not yet been completely evaluated in humans. Whole blood human clearance for GSK2816126 was predicted from three species (mouse, rat and dog) using maximum life span power-law allometry to be around 8.2 mL/min/kg. Volume of distribution was predicted from simple power-law allometry to be 4.8 L/kg and half-life around 6.5 hours. A 70 kg adult therefore has a predicted total blood clearance of 35 L/hr and a total blood volume of distribution of 336 L.

1.2.2. Pre-Clinical Pharmacology & Safety of GSK2816126

In Vitro Testing

In cell culture, GSK2816126 induces loss of H3K27me3 in both EZH2 WT and mutant cell lines from diverse tumor types with the half maximal inhibitory concentration (IC_{50}) values ranging from 10 - 252 nM independent of EZH2 mutation status [McCabe, 2012]. In proliferation assays using a panel of B-cell lymphoma cell lines, those of DLBCL origin with EZH2 activating mutations are the most sensitive to GSK2816126. The second most sensitive tumor type evaluated was multiple myeloma where a majority of cell lines exhibited growth inhibition when exposed to GSK2816126. However, the growth of a subset of several other tumor types including NHL, SNF5-mutant malignant rhabdoid tumors, AML, neuroblastoma, prostate, breast, skin, and colon cancers is also sensitive to EZH2 inhibition.

Time course studies demonstrate that inhibition of H3K27me3 is maximal after 2 days. Inhibition of cell proliferation begins as early as 2 days of EZH2 exposure but in some cases takes up to 2 weeks to reach maximal growth inhibition. Both cytostatic and cytotoxic responses are observed among sensitive cell lines. Together, these data indicate that global H3K27me3 can be used to assess on-target activity of an EZH2 inhibitor in both responsive and unresponsive tumors, and that EZH2 activating mutations may provide a strong marker for subject selection in clinical studies.

Nonclinical Pharmacology

Paragraph 1

In severe combined immunodeficiency (SCID) mice bearing subcutaneous xenografts derived from human DLCBL, multiple myeloma, or prostate cancer cell lines, GSK2816126 inhibits H3K27me3 after repeated daily or twice weekly dosing over 10-11 days. The PD response is durable as H3K27me3 levels did not return to pre-dose levels by 7 days after the last dose. In mice bearing subcutaneous xenografts of EZH2 mutant lymphomas, 90-100% tumor growth inhibition is observed with daily or twice weekly dosing over a five week period with or without a one week drug holiday in the third week. In some models, tumor stasis or complete tumor eradication is observed upon cessation of dosing. Together, these pre-clinical PD and efficacy data indicate a treatment cycle of twice weekly dosing of GSK2816126 for 2 or 3 weeks followed by a 1 week drug holiday should effectively reduce H3K27me3 levels in the tumor ~~be efficacious~~.

Paragraph 3

Infusion rate and/or concentration-dependent, histamine reactions, which began within minutes of dose initiation, were observed at ≥300 mg/kg in dogs (C_{max} 66.5 to 130 µg/mL) and 300 mg/kg (C_{max} 33.9 to 54.2 µg/mL) in rats. In dogs, histamine reactions resulted in discontinuation of dosing. ~~In rats,~~ Histamine-related decreased body temperature, along with increased heart rate (HR) and decreased blood pressure (BP) likely led to mortality in restrained, but not in unrestrained, rats given an IV infusion of 300 mg/kg (5 mL/kg/hr for 4 hours). These effects could be ameliorated by discontinuation of dosing, administration of diphenhydramine hydrochloride, degranulation of mast cells prior to GSK2816126 dosing, and/or lengthening of the infusion time to reduce C_{max}. These observations tended to occur only during the first exposure to the drug and not on subsequent administrations. Human subjects will be monitored during the infusion for evidence of histamine release related symptoms and treated as needed (e.g., with anti-histamines). Subsequent subjects ~~treated at that dose or treated as needed (e.g., with anti-histamines)~~ may be treated prophylactically with antihistamine and/or by lengthening the infusion duration.

Paragraph 4

In dogs, a mild, reversible dose dependent decrease in minute (up to 128 mL/min/kg; 49%) and tidal volume (8 mL/kg; 56%) at 100 mg/kg and an elevation in QTc~~R~~ interval at 30 (maximum increase of 12 msec or 5%) and 100 (maximum increase of 18 msec or 8%) mg/kg were observed following the end of a single 8 hour infusion. These effects did not directly correlate with peak GSK2816126 blood levels as the onset was 4-7 hours following the end of the infusion. QTc~~R~~ interval elevations were not observed following repeat dosing.

Paragraph 5

A direct effect on human ether à go-go-related gene (hERG) channel repolarization is unlikely (IC_{25} of 54.2 µM; 28.61 µg/mL), however, GSK2816126 did block hERG current density in vitro consistent with an effect on hERG channel trafficking. The mechanism for this change is unclear. Evaluation of the QTc interval has been incorporated into ~~the initial~~ this clinical study protocol.~~s~~ ~~including this one.~~

Section 1.3: Benefit:Risk Assessment

REVISED TEXT

1.3.1. Risk Assessment

Potential Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy
Cardiovascular – QT prolongation	**QTc prolongation** was observed (up to 8%; 18 msec in dog) following the end of a single 8 hour infusion Effect did not directly correlate with peak GSK2816126 blood levels; onset was 4-7 hours following the end of the infusion; reversed within 3-8 hours following onset Effects not observed following repeat dosing in dogs No arrhythmias were detected in preclinical studies. The mechanism for the QTc prolongation is unlikely due to a direct effect on hERG repolarization as GSK2816126 weekly inhibited hERG tail current (IC25 of 54.2 µM; 28.61 µg/mL). However, GSK2816126 was shown to block hERG current density in vitro consistent with an effect on hERG channel trafficking.	Protocol includes cardiovascular eligibility criteria, laboratory assessments (potassium and magnesium, cardiac monitoring (electrocardiograms [ECGs], Holter monitoring during the study, and dose stopping/modification~~s~~ criteria for the management of QT prolongation) Co-administration of medications that are known to prolong the QT interval and have a risk of causing Torsades de Pointes and drugs that have a possible risk of Torsades de Pointes are prohibited All subjects will remain in the clinical research unit (CRU) after receiving their first dose of study medication (Week 1, Day 1) with periodic ECGs and Holter monitoring for 24 hours. Subjects will not be discharged from the unit unless their last measured QTc on an ECG performed immediately prior to discharge after the first dose is <500 msec. Timings for in-house on-drug ECGs are pre-infusion, at the end of infusion, before bed, and before discharge the next morning for Day 1 of cycle 1 only. Refer to Section 7.1 (T&E) for other ECG timings ~~After Day 1 during the first 3 weeks of treatment and on Day 4 of subsequent cycles, ECGs will be performed pre-infusion and at the end of infusion.~~

1.3.2. Benefit Assessment

Study EZH117208 is an open-label, dose escalation study and the first study of this agent to be conducted ~~in subjects with relapsed and/or refractory DLBCL or transformed FL~~ in humans. GSK2816126 has promising ~~preclinical~~growth inhibitory activity in ~~DLBCL~~cell lines derived from multiple tumor types, however it is unknown whether GSK2816126 will have efficacy in patients with these tumors ~~DLBCL~~ ~~t~~Thus,, ~~thus~~ any potential beneficial effect for an individual subject attributable to GSK2816126 is unknown. Data obtained in Study EZH117208 may assist in progressing the knowledge base on lymphoma and other tumor types ~~DLBCL~~and their treatment(s), or help identify individuals more likely to benefit or have side-effects from GSK2816126. Study participants may benefit from the medical tests and screening performed during the study.

1.3.3. Overall Benefit: Risk Conclusion

Current data from GSK2816126 preclinical development indicate a potential for clinical utility in the treatment of subjects with relapsed and/or refractory DLBCL and/or transformed FL, NHL, MM and other solid tumor types. Considering the overall poor outlook of these subjects and recognizing the measures taken to minimise risk to subjects participating in the Phase I clinical trials, the potential risks identified in association with GSK2816126 are justified by the anticipated benefits that may be afforded to subjects with the previously mentioned tumor types that have been shown in preclinical models to respond to GSK2816126.

Section 2:OBJECTIVES, ENDPOINTS AND HYPOTHESES

REVISED TEXT 2.1

Part 1 Objectives	**Part 1 Endpoint**
• To confirm tumor EZH2 and GCB-DLBCL status • To investigate the mechanism of action and additional indicators of sensitivity and resistance to GSK2816126 • To generate samples (data reported separately) with which to investigate the potential for GSK2816126 to affect cytochrome P450 (CYP) 3A4 enzyme activity	• Tumor gene expression profile (GEP) for confirmation of GCB-DLBCL status • Tumor baseline genetic profiles, response • Samples to assess a potential change in 4b-OH cholesterol to cholesterol ratio in plasma following repeat dosing of GSK2816126 (data reported separately)
No formal statistical hypotheses are being tested in Part 1: Phase I dose escalation. Analysis of the data obtained from Part 1 will only utilize descriptive methods	

REVISED TEXT

2.2 Part 2: Expansion

	Part 2 Objectives	Part 2 Endpoints
Primary	• To determine clinical activity of GSK2816126 in cohorts of subjects with EZH2 mutant and wild type GCB-DLBCL and tFL and subjects with MM ~~To determine clinical activity of GSK2816126 in a cohort of subjects with EZH2 wild type germinal center B-cell-like diffuse large B-cell lymphoma (GCB-DLBCL) and in a cohort of subjects with GCB-DLBCL harboring mutations in the EZH2 gene~~	• Objective response rate (% of subjects achieving CR and PR per response criteria)
Secondary	• To determine the safety, tolerability of the selected IV dose of GSK2816126 • To characterize the population PK of GSK2816126 • To evaluate the relationship between exposure and safety/efficacy~~/PD~~ parameters • To begin to characterize the durability of response and progression free survival with 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) • 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). • GSK2816126 exposure markers (e.g. dose, concentration, Cmax, or AUC) and safety/efficacy~~/PD~~ responses. ~~Pharmacodynamic response assessed by change from baseline in tri-methylation of H3K27me3~~ • Duration of response (DoR) • Progression-free survival (PFS)
Exploratory	~~• To confirm tumor EZH2 and GCB-DLBCL status~~ • To identify biomarkers predictive of response or resistance to GSK2816126. • To investigate the mechanism of action of GSK2816126 by evaluating changes in gene expression profiles	~~• Tumor gene expression profile (GEP) for confirmation of GCB-DLBCL status~~ • Evaluation of wild-type (WT) subject tumors for the presence of additional, undefined, mutations in the EZH2 gene • Deoxyribonucleic acid (DNA), ribonucleic acid (RNA) and protein markers in tumor and blood
Hypothesis	~~The primary goal of Part 2 is to detect whether administration of GSK2816126 could lead to a clinically meaningful response rate of at least 30% in subjects with GCB-DLBCL compared to a 10% or less response rate suggesting inadequate clinical activity in subjects with GCB-~~	

	Part 2 Objectives	Part 2 Endpoints
	~~DLBCL. This will be conducted by testing the null hypothesis that $P_0 \leq 10\%$ versus the alternative that $P_1 \geq 30\%$, assuming the maximum response rate for an ineffective drug is 10% and the minimum response rate for an effective drug is 30%.~~ The primary objective of Part 2 is to determine whether administration of GSK2816126 has a potentially clinically meaningful response rate. • In subjects with GCB-DLBCL, this will be determined in each EZH2 mutation status cohort (wild type and mutant) by testing the null hypothesis that the response rate is ≤10%, with about 90% power when the true response rate is 30%. • In subjects with tFL, this will be determined in each EZH2 mutation status cohort by testing the null hypothesis that the response rate is ≤5%, with about 80% power when the true response rate is 25%. In subjects with MM, this will be determined by testing the null hypothesis that the response rate is ≤5%, with about 85% power when the true response rate is 20%.	

Section 3: INVESTIGATIONAL PLAN

REVISED TEXT

3.1. Study Schematic

Part 1 **Accelerated Dose Titration followed by 3+3 Dose Escalation** To determine the safety and tolerability of GSK2816126 in subjects with relapsed/refractory DLBCL ~~and~~, transformed FL, other NHLs ~~subjects,~~ solid tumors and MM ↓
Part 2 **Cohort Expansion in both WT and EZH2 mutation-positive subjects** To determine clinical activity of GSK2816126 in relapsed/refractory GCB-DLBCL and ~~transformed~~tFL subjects with WT and EZH2 mutation-positive tumors and MM subjects

3.2. Discussion of Study Design

Paragraph 3

This is a Phase I, open-label, multiple-dose, multicenter, dose-escalation, first-time-in-human study conducted in two parts. In Part 1, an accelerated dose titration will be employed with one subject per dose level until the first instance of a ≥ Grade 2 drug related non-hematological toxicity or dose limiting toxicity (DLT) (Section 3.3.3) occurs. Exceptions for ~~except for a~~pre-specified Grade 3 non-serious non-hematological drug related adverse events that would allow continuation of accelerated dose escalation are listed in Section 3.3.2.1. ~~or dose limiting toxicity (DLT) (Section 3.3.3).~~

In the accelerated dose escalation cohorts and the 3+3 dose escalation cohorts, the dose will be escalated based on all available data, including PK data, ~~and~~ the safety ~~profile~~ information from~~of~~ prior cohorts, as well as the recommended ~~predicted~~ dose from ~~Neuenschwander B~~ a Continuous Reassessment Method (N-CRM) ~~design~~ analysis [Neuenschwander, 2008]. The N-CRM is a type of Bayesian adaptive dose-escalation scheme. The method is fully adaptive and makes use of all the DLT information available at the time of each dose assignment. The Fixed and Adaptive Clinical Trial Simulator (FACTS) will be used to conduct the N-CRM analysis. The DLT information on all subjects enrolled in the trial ~~are~~ is used to update the estimated dose-toxicity relationship and to provide supportive information in addition to the 3+3 design in the next escalation/de-escalation decision.

After the accelerated dose titration, subjects will be enrolled in a standard 3+3 dose escalation design. Dose escalation will continue until an RP2D is determined or until an MTD or a dose of 3000 mg twice-weekly is reached [Maximum Feasible Dose (MFD)]. After the RP2D (or MTD/MFD) has been determined in Part1, then Part 2 expansion cohorts will be opened. In Part 2, subjects with will be assigned to one of ~~two~~ four cohorts based on disease and EZH2 mutation status.

Safety assessments will be performed weekly for the first 4 weeks and then at regular intervals as outlined in the Time and Events Table (Section 7.1).

Disease response in lymphoma and solid tumor subjects will be assessed ~~every~~as described in the T&E table (Section 7.1).

3.3.2 3+3 Dose Escalation Phase

Paragraph 3

In the accelerated dose escalation cohorts and the 3+3 dose escalation cohorts, the dose will be escalated based on all available data, including PK data and the safety profile of prior cohorts, as well as the recommended dose from the N-CRM analysis described in Section 12.

Part 1 PK/PD cohorts: Any dose level may be expanded up to 12 subjects in order to collect adequate data on safety, pharmacokinetics, or pharmacodynamics. Urine, bile, and additional blood samples may be collected following repeated administration for drug metabolite profiling and to obtain information on renal excretion of GSK2816126. Initially, optional pre- and post-treatment tumor biopsies will be requested. At ~~MTDIf preliminary PD data warrant~~, mandatory collection of pre- and post-treatment tumor biopsies will~~may~~ be required for enrollment in a PK/PD ~~a~~ cohort. Mandatory biopsies may be instituted:at lower dose levels once evidence of target engagement has been demonstrated in surrogate tissue (e.g. H3K27me3 from PBMCs in blood); or if sufficient

3.3.2.1. Toxicity Leading to Termination of Accelerated Titration

The following events will result in an end to accelerated dose escalation:

REVISED POINT

- Any Grade 2 or higher adverse event that is considered related to the study medication except for alopecia, drug-related Grade 3 fatigue, or asthenia; diarrhea, nausea, and/or vomiting that respond to standard medical care within 48hrs; or Grade 3 or higher electrolyte abnormalities unrelated to underlying malignancy and corrected within in 48 hrs~~) that is considered related to the study medication~~.

3.3.3. Dose Limiting Toxicity

Table 3 Dose-Limiting Toxicity Criteria

REVISED ROW

Toxicity	DLT Definition
Hematologic	• Grade 4 absolute neutrophil count (ANC) for >7 days • Febrile neutropenia (~~defined as concurrent Grade 4 neutropenia and~~ • ~~fever >38.5°C and lasting >24 hrs)~~ (according to CTCAE v.4.0 criteria) • Grade 4 thrombocytopenia or anemia for > 7 days
Non-hematologic	• Grade 3 or greater nausea, vomiting, or diarrhea that does not respond to standard medical care within ~~72~~ 48 hours. • Grade 3 or greater clinically significant non-hematologic toxicity per NCI-CTCAE, v 4.0

1.4. Part 2: Expansion Cohort

Revised Text

Part 2: Expansion Cohorts in both wild type and EZH2 mutation-positive GCB-DLBCL and tFL subjects and subjects with MM

Lymphoma subjects will be enrolled based on EZH2 mutation status. There will be up to 30 subjects per group in both GCB-DLBCL cohorts, up to 16 subjects per group in both tFL cohort s, and up to 37 subjects with MM. Multiple myeloma subjects will be selected independent of their EZH2 mutation status.

~~Once preliminary PD data have been reviewed, the planned sample collection study day(s) may be revised based on newly available data to ensure appropriate monitoring. These changes must be approved and documented by GSK, but will not constitute a protocol amendment.~~

Further evaluation of futility:

The methodology is based on the predictive probability of success if enrollment continues until all planned subjects are recruited ~~to 30 subjects~~[Lee, 2008]. The predictive probability design is similar to a Green-Dahlberg design in that it allows for early stopping for futility. The differences are that the predictive probability design allows for evaluation of stopping rules after each subject, rather than at only two stages, once a minimum number of subjects are evaluable. In this particular study, we will stop only for futility. While the two designs have similar type I and type II error rates, the probability of early termination is greater with the predictive probability design.

In both EZH2 mutation status cohorts, after ~~After~~ 12 subjects have been enrolled in each cohort to examine safety and efficacy, the number of observed confirmed responses will guide further enrollment according to the rules summarized in Figure 1. A maximum of 30 subjects per cohort will be enrolled at the RP2D. All available data will be considered in making enrollment decisions.

Figure 1 Diagram of Stopping Rules for EZH2 Cohort Expansion: GSK2816126

	Number of Responses						
Number of Subjects	**0**	**1**	**2**	**3**	**4**	**5**	**≥6**
12	■						
13	■						
14	■	■					
15	■	■					
16	■	■					
17	■	■					
18	■	■					
19	■	■					
20	■	■	■				
21	■	■	■				
22	■	■	■				
23	■	■	■				
24	■	■	■	■			
25	■	■	■	■			
26	■	■	■	■			
27	■	■	■	■			
28	■	■	■	■	■		
29	■	■	■	■	■		
30	■	■	■	■	■	■	

Figure 1 Legend: The shaded regions are the specific regions for stopping the study for futility. For instance, if there is only one response in fourteen subjects, then the predictive probability for success will be 5.0% or less (the futility criterion) and the study will be stopped.

In the tFL cohort, after 12 subjects have been enrolled to examine safety and efficacy, the number of observed confirmed responses will guide further enrolment according to the rules summarized in Figure 2. A maximum of 16 subjects will be enrolled at the RP2D. All available data will be considered in making enrollment decisions.

Figure 2 Diagram of Stopping Rules for tFL Cohort Expansion: GSK2816126

	Number of Responses			
Number of Subjects	**0**	**1**	**2**	**>3**
12				
13				
14				
15				
16				

Figure 2 Legend: The shaded regions are the specific regions for stopping the study for futility. For instance, if there is no response in twelve subjects, then the predictive probability for success will be 1% or less (the futility criterion) and the study will be stopped.

For the MM cohort: After 13 subjects have been enrolled to examine safety and efficacy, the number of observed confirmed responses will guide further enrollment according to the rules summarized in Figure 3. A maximum of 37 subjects will be enrolled at the RP2D. All available data will be considered in making enrollment decisions.

Figure 3 Diagram of Stopping Rules for MM Cohort Expansion

Number of Subjects	0	1	2	3	4
13					
14					
15					
16					
17					
18					
19					
20					
21					
22					
23					
24					
25					

Number of Subjects	0	1	2	3	4
26					
27					
28					
29					
30					
31					
32					
33					
34					
35					
36					
37					

The shaded regions are the specific regions for stopping the study for futility. For instance, if there is no response in 13 subjects, then the predictive probability for success will be 1% or less (the futility criterion) and the study may be stopped.

3.5. Rationale

3.5.1. Rationale for Study

Enhancer of zeste homolog 2 (EZH2)), a component of the Polycomb Repressor Complex 2 (PRC2), mediates transcriptional repression of target genes through tri-methylation of histone H3 on lysine 27 (H3K27me3). EZH2 and H3K27me3 are dysregulated in many cancers through diverse pathways. While EZH2 mutation plays a significant role in progression of certain lymphomas, data from prostate, breast, and several other solid tumors have demonstrated that increased EZH2 expression correlates with increased aggressiveness of tumors and poor prognosis.

GSK2816126 is a selective and potent inhibitor of wild-type and mutant EZH2 capable of decreasing H3K27me3 levels in all cell types examined. EZH2 inhibition has been shown to decrease the growth of several cell lines derived from EZH2 wild type (WT) and mutant lymphomas, SNF5-mutant malignant rhabdoid tumors, multiple myeloma, AML, neuroblastoma, prostate, breast, skin and colon cancers.

Most of these cancers have an overall poor outlook either because of lack of any effective therapy or standard therapies do not result in a durable remission. This first study of this agent will be conducted in subjects with non-Hodgkin lymphomas, especially germinal center B-cell diffuse large B-cell lymphoma (GCB-DLBCL), ~~and transformed follicular lymphoma (t-FL),~~ tFL, and subjects with multiple myeloma and solid tumors who have

relapsed or are refractory to prior therapies and have a high degree of unmet medical need in terms of available treatment options.

~~Relapsed and/or refractory DLBCL and transformed FL have an overall poor outlook. This is the first study of this agent to be conducted in subjects with these relapsed and/or refractory lymphoma malignancies for which no standard therapies are anticipated to result in a durable remission. Current data from GSK2816126 preclinical development indicate a potential to inhibit the EZH2 enzyme component of the PRC2 and that this inhibition may have clinical utility in the treatment of certain cancers including DLBCL, SNF5-mutant malignant rhabdoid tumors, multiple myeloma, AML, neuroblastoma, prostate, breast, skin, and colon cancerslymphomas, including DLBCL and transformed FL.~~

3.5.2. Rationale for Population

Preclinical studies demonstrate that B-cell lymphomas of DLBCL origin with EZH2 activating mutations are the most sensitive to GSK2816126; however, the growth of a subset of EZH2 wild-typelymphomas, SNF5-mutant malignant rhabdoid tumors, multiple myeloma, AML, neuroblastoma, prostate, breast, skin, and colon cancers are also sensitive to EZH2 inhibition. There is increasing evidence that a large number of solid tumors or subtypes may be driven by EZH2 mutation or over expression. Often, these tumors have poor prognosis. Therefore, the study includes subjects with Non-Hodgkin's Lymphoma and enriched for subsets (GCB-DLBCL, tFL) as well as multiple myeloma and solid tumors that have relapsed or are refractory to prior treatment with standard of care or do not have standard of care available or refuse standard of care therapy.

~~Preclinical studies demonstrate that B-cell lymphomas of DLBCL origin with EZH2 activating mutations are the most sensitive to GSK2816126; however, the growth of a subset of EZH2 wild-type lymphomas, SNF5-mutant malignant rhabdoid tumors, multiple myeloma, AML, neuroblastoma, prostate, breast, skin, and colon cancers EZH2 WT DLBCL cell lines and primary DLBCL samples are sensitive to GSK2816126EZH2 inhibition treatment. Activating mutations in EZH2 occur in GCB-DLBCL and follicular lymphoma, but not lymphomas of ABC (Activated B cell phenotype) origin. These are post-germinal center B cells which are not dependent on EZH2. In addition, B-cell lymphoma cell lines of ABC origin are not sensitive to GSK2816126 [Beguelin, 2013].~~

Section 3.8.2. Infusion Reaction Stopping Criteria and Management

REVISED TEXT

~~3.8.3.~~ 3.8.2.1 Management of Infusion Site Reactions

Infusion Site Reaction

Infusion Site (Histamine) Reaction	**Grade 1**: Continue infusion and closely monitor the subject **Grade 2/3**: Temporarily interrupt study medication and: - Administer diphenhydramine 50 mg or similar anti-histamine - provide supportive care - may resume infusion once resolved to </= grade 1* - For grade 3 reactions, corticosteroids may be considered **Grade 4**: - Discontinue infusion. Administer diphenhydramine, corticosteroids and supportive care as above. - May consider restarting study treatment at a reduced dose or dose level pre-event based on discussion with GSK Medical Monitor.

*Recommend following institutional guidelines for re-starting after infusion reactions seen with cytotoxic therapy. A general guideline would be as follows:

- Restart under observation at a rate of 25% the original rate for the first 30 mins

- If no reaction, increase infusion rate by 25% of original rate every half hour till full dose administered

- If Grade 1 reaction, continue at the rate at which the reaction occurs

ADDED SECTIONS

3.8.3. Dose Adjustment for Non-Hematologic Toxicity

See Table 4 Dose Adjustment Guideline for drug related non-hematologic toxicities based on worst grade.

Table 4 Dose Adjustment Guideline for Drug Related Non-Hematologic Toxicity

Worst Grade	Dose Adjustment
G1	No change in dose
G2	Continue dosing with no change OR Consider holding for up to 2 weeks for toxicity to resolve to baseline or ≤ Grade 1, then continue at the same dose OR dose reduce by at least 25% if the toxicity is considered a DLT.
G3 and 4	Hold for up to 2 weeks for toxicity to resolve to baseline or ≤ Grade 1, then dose reduce by at least 25%. If no recovery to ≤Grade 1* or baseline after 14 days, patient should be withdrawn.

If the non-hematologic toxicity or event resolves to baseline or ≤ Grade 1 within 14 days of stopping therapy, treatment with GSK2816126 may be restarted with at least **25%** dose reduction. For a non-DLT, the treatment with GSK2816126 could restart at a full dose, if deemed appropriate.

If the non-hematologic toxicity does not resolve to ≤ Grade 1 or baseline within 14 days, the subject should be withdrawn from the treatment permanently (Section 6.3). However, if the investigator and GSK Medical Monitor agree that further treatment will benefit the subject, treatment can restart with at least **25%** dose reduction under weekly clinical monitoring. If the toxicity resolves to ≤ Grade 1 or baseline, the dose may be resumed to the initial dose level.

3.8.4. Dose Adjustment For Hematologic Toxicity

3.8.4.1. For subjects with lymphoma and multiple myeloma:

The treatment may be held for 2 weeks if:

- ~~≤5% myeloblasts in bone marrow AND~~
- neutrophil and platelet count did not recover to neutrophils ≥0.5 x 10^9/L and platelets ≥25 x 10^9/L

The treatment may resume as soon as count recovery has occurred (i.e., neutrophils ≥0.5 and platelets ≥25 x 10^9/L).

~~The treatment may be held for additional 1-2 weeks if the neutrophil and platelet count did not recover after 2 weeks.~~

When the treatment resumes, the dose may be adjusted based on platelet count, i.e., dose can be reduced by at least 25% increments up to twice when the platelet count ≤25 x 10^9/L (G4 thrombocytopenia) and it is not attributed to the disease. If a subject has persistent G4 thrombocytopenia for 4 weeks not attributed to disease or requires platelet transfusions for bleeding in the absence of the disease, the subject will be withdrawn from the study.

3.8.4.2. For subjects with solid tumors:

- Grade 1 & 2 (platelet count ≥ 50,000): Continue dosing at same dose level with weekly or more frequent monitoring as necessary

- Grade 3 (platelet count between 25,000 to <50,000): After discussion with medical monitor and using sound clinical judgement, continue at same dose or adjust dose (e.g. consider missing one dose or till count recovery to Grade 2). Monitor CBC at least twice a week, more frequently if necessary

- Grade 4 (platelet count below 25,000): Interrupt study medication and monitor CBC every 2-3 days. If platelet counts recover to Grade 2, discuss with medical monitor resuming treatment at the same or adjusted dose based on sound clinical judgement. Platelet transfusion is allowed based on institutional guidelines. In case of platelet transfusion, hold drug for at least 7 days from day of transfusion, and if platelet counts recover to Grade 2 consider initiating treatment at a lower dose using sound clinical judgement and after consulting with the GSK medical monitor. Discontinue treatment if drug has to be held for >14 days or greater than 2 dose reductions required.

Section 4: INVESTIGATIONAL PRODUCT

4.1. Description of Investigational Product

Table 5 Investigational Product

REVISED ROW

Route/ Regimen	Delivered as an intravenous solution over 2 - 4 hours Study drug can be diluted into saline or dextrose for a final volume of 250ml at ambient temperature and normal room lighting up to 48 hours prior to infusion. PVH, PE and PA bags and tubing are all acceptable. ~~Requires protection from light during administration.~~

Section 5: STUDY POPULATION

REVISED TEXT

5.1. Number of Subjects

A maximum of approximately 169 ~~Approximately 100~~ subjects will be enrolled. See Section 12.4 for sample size assumptions.

The number of dose levels and the level at which the RP2D (or MTD or MFD) is reached cannot be determined in advance. An adequate number of subjects will be enrolled into the study to establish the recommended dose(s) for further study. It is estimated that 40 subjects will be enrolled into Part 1 (dose-escalation) of the study. Up to ~~60~~ 129 subjects will be enrolled in Part 2 in five expansion cohorts: two GCB-DLBCL cohorts with up to 30 subjects from the EZH2 wild-type population, and up to 30 subjects from the EZH2 mutation positive population, and two tFL cohorts with up to 16 subjects from the EZH2 wild-type population and up to 16 subjects from the EZH2 mutation positive population and up to 37 subjects in the MM cohort. Additional subjects/cohorts may be enrolled to allow for evaluation of additional dose levels.

Section 5.2. Subject Selection Criteria

REVISED TEXT

5.2.1. Part 1 Inclusion Criteria

~~Specific information regarding warnings, precautions, contraindications, AEs, and other pertinent information on the GSK study treatment that may impact subject eligibility is provided in the IB and SPM [GlaxoSmithKline Document Number 2013N169204_00, 2013].~~

Inclusion criteria no 3:

Tumor type criteria:

- Relapsed/refractory NHL that meets one of the following criteria:
  - ~~GCB-~~Diffuse large B cell lymphoma (DLBCL) or transformed follicular lymphoma relapsed after, or refractory to at least one prior chemotherapy regimen (e.g., rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone [R-CHOP]) AND not a candidate for standard salvage regimens or autologous stem cell transplant (e.g., due to age, comorbid conditions or failure to respond to salvage chemotherapy). Local confirmation of lymphoma subtype (e.g. GCB-DLBCL) is allowed for enrollment but must be confirmed through central laboratory testing.
  - ~~GCB/ –~~DLBCL or transformed FL relapsed after or refractory to at least two prior chemotherapy regimens

- Other NHLs that have failed at least one prior line of therapy.

- Relapsed and/or refractory MM that have failed prior standard therapy and for which there is no standard salvage regimen.
- Solid tumors (RECIST evaluable, with the exception of castrate resistant prostate cancer (CRPC)) at least one and not more than three standard of care chemotherapeutic regimens, or tumor for which there is no approved therapy, or for which standard therapy is refused.

Inclusion criteria no.4:

DLBCL and tFL: Availability of archival tissue, or willingness to undergo fresh biopsy for: confirmation of GCB-DLBCL status (DLBCL subjects); retrospective central testing of EZH2 mutation status (DLBCL ,and tFL subjects),
For all other tumor types: availability of archival tissue or fresh biopsies as applicable. DLBCL and tFL: Availability of archival tissue, or willingness to undergo fresh biopsy for: confirmation of GCB-DLBCL status (DLBCL subjects); retrospective central testing of EZH2 mutation status (DLBCL, and tFL subjects),
For all other tumor types: availability of either archival tissue or fresh biopsies

Part 1 Cohort Expansion Tumor Type

Inclusion Criteria no 9

Adequate organ system function as defined below:

System	LABORATORY VALUES
Hematologic	
ANC	≥1.2 x 109/L
Hemoglobin	≥9 g//dL
Platelets	≥75x 109/L
Platelets for Subjects with MM	≥ 50,000 (transfusion independent)
PT/INR and PTT	≤1.5 x ULN
Hepatic	
Albumin	≥2.5 g/dL
Total bilirubin	≤1.5 times ULN
AST and ALT	≤2.5 times ULN without liver metastases ≤5 times ULN if documented liver metastases
Renal	
Serum Creatinine Calculate Creatinine Clearance [a, b] OR 24 hr urine Creatinine Clearance	≤1.5 mg/dL or ≥50 mL/min ≥50mL/min
Reproductive/Endocrine	
Testosterone	<50ng/dL (only for subjects with CRPC)

Cardiac	
Left Ventricular Ejection Fraction (LVEF)	≥LLN (minimum of 50% LVEF) by ECHO or MUGA[c]

Abbreviation(s): ANC, absolute neutrophil count; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ECHO, echocardiogram; INR, international normalization ratio, MUGA, multigated (radionuclide) angiogram; PT, prothrombin time, PTT, partial thromboplastin time, ULN, upper limit of normal , LLN, lower limit of normal.
Calculated by Cockcroft-Gault formula

6. For MM subjects, adequate renal function is defined as serum creatinine ≤ 2.5 mg/dL OR creatinine clearance (either calculated or obtained via 24 hr urine collection) ≥ 30 mL/minECHO is the preferred method
7. ECHO is the preferred method

5.2.2. Part 2 Inclusion Criteria

Inclusion criteria no. 1:

In addition to inclusion criteria listed for Part 1, Part 2 will enroll **GCB-DLBCL tFL and MM subjects only** and subjects will be required to undergo EZH2 mutation testing. Local mutation testing is allowed for enrollment but must be confirmed through central laboratory testing.~~testing by a central laboratory prior to enrollment~~ This will require availability of archival tissue, or willingness to undergo fresh biopsy, for central testing of EZH2 mutation status.

Inclusion criteria no. 2:

Based on the results of the mutation test, lymphoma subjects may be enrolled in one of four cohorts:

- GCB-DLBCL EZH2 mutan~~tion~~ cohort:
  - Tumors must contain one, or more, of the following EZH2 activating mutations: Y641F; Y641N; Y641S; Y641H; Y641C; A677G; and/or A687V
- GCB-DLBCL EZH2 wild type cohort:
  - Tumors that do not contain one of the above mutations
  - Subjects with tumors harboring EZH2 mutations other than the seven outlined above will be enrolled in the EZH2 wild type cohort
- tFL EZH2 mutant cohort:
  - Tumors must contain one, or more, of the following EZH2 activating mutations: Y641F; Y641N; Y641S; Y641H; Y641C; A677G; and/or A687V
- tFL EZH2 wild type cohort:
  - Tumors that do not contain one of the above mutations
  - Subjects with tumors harboring EZH2 mutations other than the seven outlined above will be enrolled in the EZH2 wild type cohort

- Subjects should have accessible tumor and willingness to undergo two biopsies. Subjects for whom biopsies are not feasible may be eligible for enrollment at the discretion of the GSK medical monitor; contact GSK medical monitor to discuss possible enrollment.

5.2.3. Exclusion Criteria

Exclusion criteria no.1

Currently receiving cancer therapy (chemotherapy, radiation therapy, immunotherapy or biologic therapy) (permitting corticosteroids to control systemic or local symptoms, up to a dose of 10 mg prednisolone or equivalent daily and stable for at least 7 days prior to enrollment).

- Hormonal (e.g., anti-androgen) therapies for prostate cancer must be stopped 4 to 6 weeks prior to enrolment. Subjects with prostate cancer may remain on luteinizing hormone releasing hormone (LHRH) agonists. Subjects with prostate cancer may also remain on low-dose prednisone or prednisolone (up to 10 mg/day) and still be eligible for this study.

Exclusion criteria no. 8:

Unresolved toxicity greater than Grade 1 National Cancer Institute – Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4 from previous anti-cancer therapy, with the exception of alopecia and peripheral neuropothy [NCI-CTCAE, 2009].

~~Unresolved toxicity greater than NCI-CTCAE version 4 (Grade 1 if marrow is clear, Grad 2 if not) from previous anti-cancer therapy, with the exception of alopecia and lymphopenia [NCI-CTCAE, 2009].~~

- Lymphoma subjects with ≤ Grade 3 lymphopenia can be enrolled at the discretion of the investigator

Section 6: COMPLETION OR WITHDRAWAL OF SUBJECTS

REVISED TEXT

6.3. Permanent Discontinuation from Study Treatment

Subjects will receive study treatment until disease progression, death or unacceptable toxicity, including meeting stopping criteria for liver chemistry defined in Section 8.3.1. In addition, study treatment will~~may~~ be permanently discontinued for any of the following reasons:

- Substantial d~~D~~eviation(s) from the protocol
- Request of the subject or proxy (withdrawal of consent by subject or proxy)
- Investigator's discretion

- A dose delay of > 21days unless the investigator and GSK Medical Monitor agree that further treatment may benefit the subject
- Intercurrent illness that prevents further administration of study treatment(s)
- Subject is lost to follow-up or study is closed or terminated.

The primary reason study treatment was permanently discontinued must be documented in the subject's medical records and eCRF.

If the subject voluntarily discontinues from treatment due to toxicity, 'adverse event' will be recorded as the primary reason for permanently discontinuation on the eCRF.

Once a subject has permanently discontinued from study treatment, the subject will not be allowed to be retreated.

~~If the subject voluntarily discontinues from treatment due to toxicity, 'AE' will be recorded as the primary reason for permanently discontinuation on the eCRF.~~

Section 7: STUDY ASSESSMENTS AND PROCEDURES

Table 6 Time and Events, Treatment Phase: Screening through Day 28 (See also PK sampling table for PK sampling schedule on Day 1 and Day 15)

Details added:

- Window period of '-1 Day' was added to the Safety Assessments heading under Study Phase column
- 'At Screening' was added under Visit Window for ECHO assessment
- The frequency of assessment was changed from 'Every 4 weeks' to Prior to every infusion' for Hematology parameters in Continuation phase
- Day 4 pre-dose and end of infusion was added for PK sampling for Part 1 at Day 1 and 4 Visit.
- Blood samples for Genetic research were added at screening and Day 1 and 4 Visit.
- The time points for blood samples obtained for assessing PD biomarkers were revised as prior to dosing on D1 (baseline), 2 hours after the end of the infusion on day 1, 4, 8, 11,15, and 18 and at day 21 and 28 visits (± 1-2 days).
- Archival Tissue for mutation testing will be for All DLBCL and tFL subjects.
- The time points for tumor biopsy was revised to be obtained at D1 (up to -14 days) and after 6th dose Day 18 (+3 day window)

- Clinical Activity Assessments sub-heading was changed to Disease Assessments for Lymphoma Subjects

- Footnote a. was changed as follows: A subject is to receive two doses per week which should be given 3 days apart. If there is a need to change scheduling <u>after Cycle 1</u>, the scheduled days of the week can change as long as there are 3-4 days between doses. ~~Up to 5 days between doses is permitted for exceptional circumstances.~~

Table 6 Time and Events, Treatment Phase: Screening through Day 28 (See also PK sampling table for PK sampling schedule on Day 1 and Day 15)

- Added rows are as follows:

STUDY PHASE		**SCREEN**	**First Treatment Period**				**Continuation Phase**	**Follow-Up**
VISIT		**Screen**	**Day 1 and 4[a]**	**Day 8 and 11 [a]**	**Day 15 and 18 [a]**	**Day 21**		
VISIT WINDOW (±days)		-14					±7	
Disease Assessments for Solid Tumors								
CT/MRI	Must be repeated every 8 weeks	X					X	X[d]
Positron emission tomography (PET)	The use of standalone PET or PET in combination with CT scan is optional. Standalone PET dose not replace CT	X[e]					X[e]	X[d,e]
Disease Assessments for Prostate Cancer								
Vitamin D_3 and PTH		X					X	X[d]
Urinalysis Urine microscopy UPC		X					X[e]	X[d,e]
Urine electrolytes		X						
PSA		X						

Tumor biopsy for PD optional for Part 1 and Part 2. Required for Part 1 PK/PD cohort at MTD	A tumor biopsy should be obtained at D1 (up to -14 days) and after 6th dose Day 18(+3 day window)		X		X (After 6th dose, Day 18)			

Disease Assessments for Multiple Myeloma (MM)								
Disease Characteristics	Every 6 weeks after Wk4, Including cytogenetics as appropriate	X						
Total Protein, CRP, β2 microglobulin	Every 6 weeks after Wk4	X						
Response Assessment	Every 6 weeks after Wk4; Response criteria in Appendix 6							
SPEP, FLC assay, quantitative immunoglobulins (IgG, IgA, IgM)	Not required for subjects with non-secretory MM	X						
UPEP	Only required if paraprotein is present in urine	X						
Extramedullary Disease Assessment	Only required for MM with extramedullary disease	X						
BM aspirate and biopsy	Required for non-secretory MM, or as appropriate for other subjects	X			Day 18		Week 10, Day 1	

Disease Assessments for Solid Tumors								
CT/MRI	Must be repeated every 8 weeks	X					X	X[d]
Positron emission tomography (PET)	The use of standalone PET or PET in combination with CT scan is optional. Standalone PET does not replace CT	X[e]					X[e]	X[d,e]
Disease Assessments for Prostate Cancer								
Vitamin D_3 and PTH		X					X	X[d]
Urinalysis Urine microscopy UPC		X					X[e]	X[d,e]
Urine electrolytes		X						
PSA	Wk 9 and every 8 weeks thereafter	X						
ECOG Performance status	See Appendix 2	X	X	X	X	X		

Table 7 Time and Events, PK Sampling Table for Part 1, Day 1 and Day 15

	Duration of Infusion in hours		
	2	**3**	**4**
From start of infusion - 60 mins	Predose	Predose	Predose
± 5 mins	0.5 hr	0.5 hr	0.5 hr
± 5 mins	1 hr	1 hr	1 hr
- 5 mins	2 hr (prior to end of infusion)	2 hr	2 hr
- 5 mins		3 hr (prior to end of infusion)	4 hr (prior to end of infusion)
From end of infusion ± 5 mins	0.5 h	0.5 h	0.5 h
± 5 mins	1 hr	1 hr	1 hr
± 5 mins	2 hr	2 hr	2 hr
± 15 mins	4 hr	4 hr	4 hr
± 15 mins	6 hr	6 hr	6 hr
From start of infusion ± 1hour	12 hr (Day 1 only)	12 hr (Day 1 only)	12 hr (Day 1 only)
± 1 hour	18 hr (Day 1 only)	18 hr (Day 1 only)	18 hr (Day 1 only)
± 1 hour	24 hr	24 hr	24 hr
2 hour	72 or 96 hr	72 or 96 hr	72 or 96 hr

* Stability has been established for up to 9 hours on wet ice or at 4°C for GSK2816126 in whole blood.

Section 7.2. Demographic/Medical History and Baseline Assessments

REVISED POINTS

- Ann Arbor stage of initial diagnosis for NHL
- Ann Arbor stage of relapse/refractory diagnosis for NHL
- For NHL, ~~U~~unilateral or bilateral bone marrow biopsy within 35 days prior to commencing study therapy.

- Baseline assessment for Subjects with multiple myeloma
    - International staging system (ISS) stage at initial diagnosis and screening
    - Type (active or smoldering)
    - Presence of plasmacytoma
    - Cytogenetics
    - Presence of extramedullary disease
    - Laboratory assessment: Total protein, paraprotein, CRP and β2-microglobulin; for secretory MM: SPEP, UPEP, IgG, IgA, IgM, FLC assay

Section 7.5. Pharmacodynamics

REVISED TEXT

Changes from baseline H3K27me3 will be assessed in pre- and post-treatment samples ~~by immunohistochemistry (IHC)~~ for tumor or surrogate tissue/body fluid (e.g. PBMCs, blood, skin or hair)~~., and Enzyme-linked immunosorbent assay for peripheral blood mononuclear cells (PBMCs [blood]), or other tissue or body fluid~~.

Section 7.6. Translational Research

REVISED TEXT

Translational or biomarker research may be performed on archival tissue, tumor biopsies, blood samples or other surrogate tissue (e.g. skin or hair) collected on study, to better understand DLBCL, transformed FL, MM, mechanism of action ~~of~~ and response to GSK2816126.

Comparative examination of pre-dosing profiles of participants may uncover known or novel candidate biomarkers/profiles which could be used to predict response to treatment with GSK2816126 or provide new insights into lymphoma, other cancers,~~DLBCL~~ and medically related conditions. Comparative examination of post-dosing profiles in conjunction with pre-dosing profiles may yield known and novel candidate biomarkers/profiles and new insights which relate to the action of GSK2816126.

Performance of these investigations may be conditional on the results of the clinical trial principally, but not exclusively, on the primary measures of the clinical trial outcome and samples may be selected for analysis on the basis of the clinical outcome.

Unless stated otherwise, these investigations may be performed irrespective of whether a response to GSK2816126 is observed.

All samples may be retained for a maximum of ~~or~~ 15 years after the last subject completes the trial.

Novel candidate biomarkers and subsequently discovered biomarkers of the biological response associated with lymphoma, other cancers, or medically related conditions and/or the action of GSK2816126 may be identified by application of the following. DNA/gene, RNA and protein analysis of blood and tumor tissue including but not limited to the following analyses:

- Confirmation of GCB-subtype DLBCL status by ~~analysis~~ IHC analysis using the ~~Choi~~ standard methods or ~~of~~ tumor GEP signature

7.6.1. Tumor Biomarker Analysis

DLBCL/tFL patients: A requirement for inclusion in this study is availability of archival tissue, or willingness to undergo fresh biopsy for the following:

- Confirmation of GCB-subtype DLBCL status by analysis of tumor by IHC using the standard methods (DLBCL subjects)
- Confirmation of EZH2 WT status by targeted sequencing of EZH2 gene (DLBCL and tFL subjects)
- DNA, RNA or protein measurements to identify predictors of sensitivity or resistance to GSK2816126
- All other patients will be asked to submit an archival tumor specimen for retrospective DNA, RNA or protein testing of potential markers of sensitivity and/or resistance; however this will not be an eligibility requirement.

7.6.1.2. EZH2 Mutation Analysis (required for study entry Part 2 for GCB-DLBCL and tFL subjects only)

Screening for eligibility for Part 2 of the study will be conducted using a custom quantitative real time polymerase chain reaction (RT-PCR) test based on TaqMan PCR chemistry. The test detects 7 known activating mutations in the EZH2 gene: Y641F (c.1937A>T); Y641N (c.1936T>A); Y641S (c.1937A>C); Y641H (c.1936T>C); Y641C (c.1937A>G); A677G (c.2045C>G); and A687V (c.2075C>T) (Althea^{DX} 2014).

7.6.2. Circulating cell free DNA Analysis

Paragraph 1:

Plasma samples ~~collected~~ will be analyzed to investigate mutations, including but not limited to EZH2, in cfDNA.

7.6.3. Circulating biomarker analysis

Paragraph 1:

Levels of circulating biomarkers, may be assessed to determine relationships between biomarker expression and response to GSK2816126, as well as to better understand the expression of circulating biomarkers in ~~DLBCL and transformed FL~~ lymphoma and other tumor types.

7.6.4. RNA Expression Research of a Subset of RNA Species

Paragraph 3

RNA expression studies may be conducted using RNA-seq, quantitative RT-PCR, and/or alternative equivalent technologies, which can facilitate the simultaneous measurement of the relative abundances of RNA species resulting in a RNA expression profile for each blood and tumor tissue sample. The RNAs assayed may be those involved in tumor pathogenesis, the absorption, distribution, metabolism, or excretion of GSK2816126, or in the subject's response to GSK2816126. In addition, continuing research may identify other proteins or regulatory RNAs that may be involved in response to GSK2816126 or tumor ~~the~~ pathogenesis. The RNAs that code for these proteins and/or regulatory RNAs may also be studied. This will enable the evaluation of changes in RNA expression profiles that may correlate with biological response relating to ~~DLBCL~~ lymphoma, other cancers, and medically related conditions or the action of GSK2816126.

7.6.5. Tumor Tissue collection

Paragraphs 1, 2 and 3

The availability of archived tissue (or willingness to undergo fresh biopsy) is required for all screened lymphoma subjects for determination of EZH2 mutation status, and/or ~~for~~ GCB-~~subtyping~~subtype of DLBCL subjects.

~~Pre-treatment (baseline), and Post-treatment (Day 18 11) tumor biopsies are required for all subjects in Part 2 (optional for Part 1). Subjects for whom biopsies are not feasible will be eligible for enrollment and participation in study at the discretion of the GSK medical monitor. Contact GSK medical monitor for confirmation of enrollment and study entry if biopsies are not feasible.~~

A tumor biopsy at progression for biomarker research is recommended for all subjects.

For Part 1 PK/PD cohorts, pre-treatment and post-treatment tumor biopsies will be initially optional. At MTD, mandatory collection of pre- and post-treatment tumor biopsies will be required for further enrollment of subjects in a PK/PD cohort. Mandatory biopsies may be instituted: at lower dose levels once evidence of target engagement has been demonstrated in surrogate tissue (H3K27me3 from PBMCs in

blood); or if sufficient evidence of target engagement (e.g. dose dependence) is not observed in PD assay from surrogate tissue. Optional tumor biopsies may be requested for all or a portion of subjects in Part 2. Subjects for whom biopsies are not feasible will be eligible for enrollment and participation in study at the discretion of the GSK medical monitor. Contact GSK medical monitor for confirmation of enrollment and study entry if biopsies are not feasible.

7.6.6. Blood collection

Blood samples will be collected at multiple time points from all subjects on study (Parts 1 and 2) for pharmacodynamic and exploratory biomarker testing (Section 7.1).

Further details on sample requirements and collection will be provided in the SPM.

Section 7.7. Evaluation of Anti-Cancer Activity

REVISED TEXT

Disease assessment may include imaging and physical examination (as indicated for palpable/superficial lesions). Refer to Appendix 4 (Section 15.4) for more details on response assessment criteria. Disease assessment for lymphomas will be ~~completed within 4 weeks prior to the first dose of GSK2816126 then every 8 weeks thereafter,~~ completed within 4 weeks of first dose of GSK2816126 and repeated 8 weeks after dosing is initiated, every 12 weeks thereafter, and at the final study visit. Disease assessment for solid tumors will be completed at 8 weeks of first dose of GSK2816126 and repeated every 8 weeks thereafter, and at the final study visit. . Disease assessment for MM will be completed within 4 weeks of first dose of GSK2816126 and repeated every 6weeks thereafter. See the Time and Events Table (Section 7.1) for the schedule of assessments of anti-cancer activity. Assessments must be performed on a calendar schedule and should not be affected by dose interruptions/delays. For post-baseline assessments, a window of ±7 days is permitted to allow for flexible scheduling. If the last radiographic assessment was more than 8 weeks prior to the subject's withdrawal from study and progressive disease has not been documented, a disease assessment should be obtained at the time of withdrawal from study.

For subjects with NHL, ~~T~~the following B symptoms should be assessed at the time points in the Time and Events Table (Section 7.1):

- night sweats without signs of infection
- unintentional weight loss of ≥10% within the previous 6 months
- recurrent, unexplained fever of great than 38^{o}C for 2 weeks without signs of infection

If a subject had involvement of bone marrow at baseline, and a CR is suspected, a b~~B~~one marrow biopsy must be obtained as described in Section 7.2.1. ~~If a subject had involvement of bone marrow at baseline, and a CR is suspected,~~A ~~a~~ repeat bone marrow

biopsy will be performed within 8 weeks of the imaging confirmed CR in accordance with the response guidelines (Appendix 4: Section 15.4).

ADDED SECTION

7.8 Genetic Research

The information regarding genetic research is included in Appendix 6.

Section 8.2: Definition of an SAE

REVISED TEXT

~~g. Protocol-Specific SAEs:~~

Section 9.4 Drugs and QT Prolongation

Completely updated Table 13 and Table 14

Table 13 Drugs with a Risk of Torsades de Pointes that are not permitted for Co-Administration with GSK2816126

Generic Name	Drug Class	Generic Name	Drug Class
Amiodarone	Anti-arrhythmic	Halofantrine	Anti-malarial
Anagrelide	Phosphodiesterase 3 inhibitor	Haloperidol	Anti-psychotic
Arsenic trioxide	Anti-cancer	Ibutilide	Anti-arrhythmic
Astemizole (Removed from US Market)	Antihistamine	Levofloxacin	Antibiotic
Azithromycin	Antibiotic	Levomethadyl (Removed from US Market)	Opiate
Bepridil (Removed from US Market)	Anti-anginal	Mesoridazine (Removed from US Market)	Anti-psychotic
Chloroquine	Anti-malarial	Methadone	Opiate
Chlorpromazine	Anti-psychotic / Anti-emetic	Moxifloxacin	Antibiotic
Cisapride (Removed from US Market)	GI stimulant	Ondansetron	Anti-emetic
Citalopram	Anti-depressant, SSRI	Pentamidine	Antibiotic
Clarithromycin	Antibiotic	Pimozide	Anti-psychotic
Cocaine	Local anesthetic	Probucol (Removed from US Market)	Antilipemic
Disopyramide	Anti-arrhythmic	Procainamide (Oral off US mkt)	Anti-arrhythmic

Generic Name	Drug Class	Generic Name	Drug Class
Dofetilide	Anti-arrhythmic	Quinidine	Anti-arrhythmic
Domperidone (On non US Market)	Anti-nausea	Sevoflurane	Anesthetic, general
Dronedarone	Anti-arrhythmic	Sotalol	Anti-arrhythmic
Droperidol	Anti-psychotic / Anti-emetic	Sparfloxacin (Removed from US Market)	Antibiotic
Erythromycin	Antibiotic	Sulpiride (On non US Market)	Anti-psychotic, atypical
Escitalopram	Anti-depressant, SSRI	Terfenadine (Removed from US Market)	Antihistamine
Flecainide	Anti-arrhythmic	Thioridazine	Anti-psychotic
Grepafloxacin (Off market worldwide)	Antibiotic	Vandetanib	Anti-cancer

Data Source: www.crediblemeds.org (27 February 2015)

Table 14 Drugs with a Possible Risk of Torsades de Pointes that are Prohibited

Generic Name	Drug Class	Generic Name	Drug Class
Alfuzosin	Alpha1-blocker	Norfloxacin	Antibiotic
Apomorphine	Dopamine agonist	Ofloxacin	Antibiotic
Aripiprazole	Anti-psychotic, atypical	Olanzapine	Anti-psychotic, atypical
Atazanavir	Anti-viral	Oxytocin	Oxytocic
Bedaquiline	Antibiotic	Paliperidone	Anti-psychotic, atypical
Bortezomib	Proteasome inhibitor	Pasireotide	Somatostatin analog
Bosutinib	Tyrosine kinase inhibitor	Pazopanib	Tyrosine kinase inhibitor
Clozapine	Anti-psychotic, atypical	Perflutren lipid microspheres	Imaging contrast agent
Crizotinib	Kinase inhibitor	Pipamperone (On non US Market)	Antipsychotic
Dabrafenib	Anti-cancer	Promethazine	Anti-psychotic / Anti-emetic
Dasatinib	Tyrosine kinase inhibitor	Quetiapine	Anti-psychotic, atypical
Dexmedetomidine	Sedative	Ranolazine	Anti-anginal
Dihydroartemisinin+ piperaquine	Anti-malarial	Rilpivirine	Anti-viral
Dolasetron	Anti-nausea	Risperidone	Anti-psychotic, atypical
Eribulin	Anti-cancer	Roxithromycin (On non US Market)	Antibiotic
Famotidine	H2-receptor antagonist	Saquinavir	Anti-viral
Felbamate	Anti-convulsant	Sertindole (On non US Market)	Anti-psychotic, atypical
Fingolimod	Sphingosine phospate receptor modulator	Sorafenib	Tyrosine kinase inhibitor
Foscarnet	Anti-viral	Sunitinib	Anti-cancer
Fosphenytoin	Anti-convulsant	Tacrolimus	Immunosuppressant
Gatifloxacin (Removed from US	Antibiotic	Tamoxifen	Anti-cancer

Generic Name	Drug Class	Generic Name	Drug Class
Market)			
Gemifloxacin	Antibiotic	Telavancin	Antibiotic
Granisetron	Anti-nausea	Telithromycin	Antibiotic
Iloperidone	Anti-psychotic, atypical	Tetrabenazine (Orphan drug in US)	Monoamine Transporter Inhibitor
Isradipine	Anti-hypertensive	Tizanidine	Muscle relaxant
Lapatinib	Anti-cancer	Tolterodine	Muscle relaxant
Lithium	Anti-mania	Toremifene	Estrogen agonist/antagonist
Mifepristone	Progesterone antagonist	Vardenafil	Phosphodiesterase inhibitor
Mirabegron	Beta3 adrenergic antagonist	Vemurafenib	Kinase inhibitor
Mirtazapine	Anti-depressant, Tetracyclic	Venlafaxine	Anti-depressant, SNRI
Moexipril/HCTZ	Anti-hypertensive	Vorinostat	Anti-cancer
Nicardipine	Anti-hypertensive	Ziprasidone	Anti-psychotic, atypical
Nilotinib	Anti-cancer		

Data Source: www.crediblemeds.org (27 February 2015)

Section 11 Data Management

REVISED TEXT

Paragraph 1

For this study, data will be collected using defined eCRFs in the validated data system, InForm. Some data (i.e. Biomarker, PK, Holter ECG) will be transmitted electronically to GSK from an external vendor via a validated data system~~, the External Alliance Portal.~~

Section 12.4. Sample Size Determination

REVISED TEXT

The sample size planned for Part 1 arises from the predefined criteria for dose selection and is not driven by statistical considerations.

The additional 129 subjects in Part 2 of the study (which includes approximately 30 subjects each for the EZH2 mutant and EZH2 WT GCB-DLBCL populations and 16 subjects each for the EZH2 mutant and EZH2 WT tFL populations, as well as up to 37 MM subjects) will provide additional safety and tolerability information about the treatment and a better precision around the response rate estimate.

12.4.1. Part 1: Dose-Escalation Phase

The total number of subjects to be enrolled in Part 1 will depend on the number of subjects needed to characterize individual dose cohorts. The sample size is not driven by statistical considerations. However, it is anticipated that approximately 40 subjects will be enrolled. Given true incidence rates of DLTs, the associated probabilities of

escalating to the next dose in a 3+3 scheme are provided for reference below in ~~Section 12.4.1.~~ Table 15.

12.4.2. Part 2: Expansion Cohort

An initial dose escalation will be used to establish the RP2D for GSK2816126. Once the final dose is confirmed, at least 12 and up to 30 subjects in both GCB-DLBCL mutation status cohorts, up to 16 subjects in both tFL mutation status cohorts and up to 37 subjects with MM will be enrolled at that dose, using decision rules defined in Figure 1, Figure 2 and Figure 3. The sample size and stopping rules are based on the methodology of Lee & Liu [Lee, 2008].

~~The assumptions underlying the design are detailed below.~~

The assumptions underlying the design are detailed below for both GCB-DLBCL~~EZH2~~ cohorts. The null hypothesis is:

H_0: p≤10%

The alternative hypothesis is:

H_A:p>10 ~~30~~%

For GCB-DLBCL cohorts, starting with 12 subjects and allowing for a maximum sample size of 30, this design will have a type I error rate (α) of 0.062 and 88.9% power when the true response rate is 30%. The trial is not designed to stop early for efficacy, but is designed to stop early for futility if the predictive probability of success is 5.0% or less. The type I error rate, power, and predictive probability of success to stop early for futility were derived from explicitly stating the minimum and maximum sample size, futility stopping rate and selection of the optimizing criterion as the maximization of power under the alternative hypothesis. The Bayesian prior used in determining the design was Beta (0.15, 0.85), a distribution with a mean response rate of 15%. Under the null hypothesis, if the true response rate is 10%, the expected sample size of the design is 18~~.0~~ subjects per expansion cohort and probability of early termination (PET) is 88.7%. Under the alternative hypothesis, if the true response rate is 30%, the expected sample size of the design is 29~~.0~~ subjects per expansion cohort and PET is 8.8%.

The assumptions underlying the design are detailed below for both ~~the~~ tFL cohorts. The null hypothesis is:

H_0: p≤5%

The alternative hypothesis is:

H_A:p>5%

Starting with 12 subjects and allowing for a maximum sample size of 16, this design will have a type I error rate (α) of 0.043 and 80.1% power when the true response rate is 25%.

The trial is not designed to stop early for efficacy, but is designed to stop early for futility if the predictive probability of success is about 1.0% or less. The type I error rate, power, and predictive probability of success to stop early for futility were derived from explicitly stating the minimum and maximum sample size, futility stopping rate and selection of the optimizing criterion as the minimization of the expected sample size under the null hypothesis. The Bayesian prior used in determining the design was Beta (0.05, 0.95), a distribution with a mean response rate of 5%. Under the null hypothesis, if the true response rate is 5%, the expected sample size of the design is 14 subjects per expansion cohort and probability of early termination (PET) is 83.3%. Under the alternative hypothesis, if the true response rate is 30%, the expected sample size of the design is 16 subjects per expansion cohort and PET is 8.5%.

The assumptions underlying the design are detailed below for MM subjects. The null hypothesis is:

H_0: $p \leq 5\%$

The alternative hypothesis is:

H_A; $p > 5\%$

Starting with 13 subjects and allowing for a maximum sample size of 37, this design will have a type I error rate (α) of 0.032 and about 85% power when the true response rate is 20%. The trial is not designed to stop early for efficacy, but is designed to stop early for futility if the predictive probability of success is about 1.0% or less. The type I error rate, power, and predictive probability of success to stop early for futility were derived from explicitly stating the minimum and maximum sample size, futility stopping rate and selection of the optimizing criterion as the minimization of the power under the alternative hypothesis. The Bayesian prior used in determining the design was Beta (0.20, 0.80), a distribution with a mean response rate of 20%. Under the null hypothesis, if the true response rate is 5%, the expected sample size of the design is 22 subjects and probability of early termination (PET) is 91%. Under the alternative hypothesis, if the true response rate is 20%, the expected sample size of the design is 36 subjects per expansion cohort and PET is 10%.

Section 12.5 Data Analysis Considerations

REVISED TEXT

12.5.3. Treatment Comparisons

No formal hypothesis testing will be performed between dose cohorts. Safety, PK, PD marker, and efficacy summaries will be provided by dose cohort and planned time of assessment in Part 1 and by expansion cohort and planned time of assessment in Part 2.

12.5.3.2. Other Comparisons of Interest

- PK: PK parameters will be evaluated and summarized for each dose cohort in Part 1.
- PD marker: Changes from baseline in PD markers will be evaluated and summarized for each dose cohort in Part 1 and for each cohort ~~(EZH2 WT and EZH2 mutant)~~ in Part 2.
- Clinical anti-cancer activity: The number of subjects with ~~a~~ complete responses, partial responses, stable disease, and progressive disease for each dose cohort in Part 1 and for each expansion cohort in Part 2 will be listed and summarized if data warrant.

12.5.5.4. Efficacy Analyses

Paragraph 1

Anti-tumor activity for lymphoma subjects will be assessed based on the Response Criteria listed in 15.4. Anti-tumor activity for subjects with solid tumors will be assessed based on the Response Criteria listed in 15.5. Anti-tumor activity for subjects with MM will be assessed based on the Response Criteria listed in 15.6. The response data will be summarized by study part, and cohort within Part 2. Full details will be specified in the RAP.

Section 13: STUDY CONDUCT CONSIDERATIONS

REVISED TEXT

13.2. Regulatory and Ethical Considerations, Including the Informed Consent Process

ADDED TEXT

In approving the clinical protocol the IEC/IRB and, where required, the applicable regulatory agency are also approving the optional assessments, e.g. genetic research described in Appendix 5, unless otherwise indicated. Where permitted by regulatory authorities, approval of the optional assessments can occur after approval is obtained for the rest of the study. If so, then the written approval will clearly indicate approval of the optional assessments is being deferred and the study, except for the optional assessments, can be initiated. When the optional assessments are not approved, then the approval for the rest of the study will clearly indicate this and therefore, the optional assessments will not be conducted.

Section 14: REFERENCES

ADDED REFERENCES

Althea^{DX} Design validation report for the EZH2 mutation detection assay panel for clinical testing. CO-121613-001. Report Date: 27-JAN-2014.

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Chung WH, Hung SL, Chen YT. Genetic predisposition of life-threatening antiepileptic-induced skin reactions. Expert Opin. Drug Saf. 2010; 9: 15-21.

McCabe MT & Creasy CL. EZH2 as a potential target in cancer therapy. Epigenomics 2014;6:341-51.

RECIST guidelines (version 1.1). Europena Journal of Cancer. 2009; 45: 228-247.

www.crediblemeds.org (27 February 2015)

Section 15: APPENDICES

REVISED TEXT

15.5. Appendix 5: RECIST 1.1

I. Efficacy Assessment

Disease progression and response evaluations will be determined according to the definitions established in the Response Evaluation Criteria in Solid Tumors (RECIST 1.1) [Chung, 2010; Eisenhauer, 2009].

See the Time and Events Table for the schedule of efficacy assessments. Assessments must be performed on a calendar schedule and should not be affected by dose interruptions/delays. For post baseline assessments, a window of ±14 days is permitted to allow for flexible scheduling.

- The following are required at baseline: CT for Chest/Abdomen/Pelvis or MRI for Abdomen/Pelvis and clinical disease assessment for palpable lesions, brain scan and bone scan. At each post baseline assessment, evaluations of the sites of disease identified by these scans are required except for brain scan and bone scans. Brain and Bone scans should be performed as clinically indicated.

Confirmation of CR and PR are required per protocol. Confirmation assessments must be performed no less than 4 weeks after the criteria for response have initially been met and may be performed at the next protocol scheduled assessment. If a confirmation assessment is performed prior to the next protocol schedule assessment, the next protocol scheduled evaluation is still required (e.g. evaluations must occur at each protocol scheduled timepoint regardless of unscheduled assessments).

A baseline bone scan is required for all subjects. For subjects without bone disease at baseline, subsequent bone scans should only be performed as clinically indicated (e.g. presentation of bone pain). For subjects with bone disease at baseline, a bone scan is required as clinically indicated. In addition, in order to assign a response of CR in a subject with bone disease at baseline, a bone scan must be performed 1 week prior to 4 weeks after

A baseline brain scan is required for all subjects. For subjects without CNS disease at baseline, subsequent brain scans should only be performed as clinically indicated (e.g. symptoms suggestive of CNS progression). For subjects with CNS disease at baseline, a brain scan is required as clinically indicated. In addition, in order to confirm a CR in a subject with brain disease at baseline, a brain scan must be performed 1 week prior to the 1st set of images showing CR to 4 weeks after the next protocol specified assessment.

Ia. Baseline documentation of target and non-target lesions

- All baseline lesion assessments must be performed within 28 days of randomizations.
- Lymph nodes that have a short axis of <10mm are considered non-pathological and should not be recorded or followed.
- Pathological lymph nodes with <15mm and but ≥10mm short axis are considered non measurable.
- Pathological lymph nodes with ≥15mm short axis are considered measurable and can be selected as target lesions, however lymph nodes should not be selected as target lesions when other suitable target lesions are available.
- Measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions, and recorded and measured at baseline. These lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically).

Note: Cystic lesions thought to represent cystic metastases should not be selected as target lesions when other suitable target lesions are available.

Note: Measurable lesions that have been previously irradiated and have not been shown to be progressing following irradiation should not be considered as target lesions.

- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by CT or MRI can be considered measurable. Bone scans, FDG-PET scans or X-rays are not considered adequate imaging techniques to measure bone lesions.
- All other lesions (or sites of disease) should be identified as non-target and should also be recorded at baseline. Non-target lesions will be group by organ. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

Ib. Assessment Guidelines

Please note the following:

- The same diagnostic method, including use of contrast when applicable, must be used throughout the study to evaluate a lesion.
- All measurements should be taken and recorded in millimeters (mm), using a ruler or calipers.

- Ultrasound is not a suitable modality of disease assessment. If new lesions are identified by ultrasound, confirmation by CT or MRI is required.
- Fluorodeoxyglucose (FDG)-PET is generally not suitable for ongoing assessments of disease. However FDG-PET can be useful in confirming new sites of disease where a positive FDG-PET scans correlates with the new site of disease present on CT/MRI or when a baseline FDG-PET was previously negative for the site of the new lesion. FDG-PET may also be used in lieu of a standard bone scan providing coverage allows interrogation of all likely sites of bone disease and FDG-PET is performed at all assessments.
- If PET/CT is performed then the CT component can only be used for standard response assessments if performed to diagnostic quality, which includes the required anatomical coverage and prescribed use of contrast. The method of assessment should be noted as CT on the CRF.

Clinical Examination: Clinically detected lesions will only be considered measurable when they are superficial (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler/callipers to measure the size of the lesion, is required. [Chung, 2010; Eisenhauer, 2009].

CT and MRI: Contrast enhanced CT with 5mm contiguous slices is recommended. Minimum size of a measurable baseline lesion should be twice the slice thickness, with a minimum lesion size of 10 mm when the slice thickness is 5 mm. MRI is acceptable, but when used, the technical specification of the scanning sequences should be optimised for the evaluation of the type and site of disease and lesions must be measured in the same anatomic plane by use of the same imaging examinations. Whenever possible the same scanner should be used. [Chung, 2010; Eisenhauer, 2009].

X-ray: In general, X-ray should not be used for target lesion measurements owing to poor lesion definition. Lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung; however chest CT is preferred over chest X-ray [Chung, 2010; Eisenhauer, 2009].

Brain Scan: Baseline brain scans are required, then contrast enhanced MRI is preferable to contrast enhanced CT.

Bone Scan (typically bone scintigraphy): If a bone scan is performed and a new lesion(s) is equivocal, then correlative imaging (i.e.X-ray, CT, or MRI) is required to demonstrate malignant characteristics of the lesion(s).

Note: PET [FDG or fluoride] may be used in lieu of a standard bone scan providing coverage allows interrogation of all likely sites of bone disease and PET is performed at all assessments.

Ic. Follow-up Assessments for Subjects Permanently Discontinued from Study Treatment

Refer to 8.3.1.1 and the Time and Events Tables found in the protocol for follow-up assessment of subjects who are to be followed up for disease progression and/or survival after permanently discontinue from study treatment

Id. Assessment of Subject Completion

If the last radiographic assessment was more than 8 weeks prior to withdrawal from study and progressive disease has not been documented, a disease assessment should be obtained at the time of withdrawal from study.

II. Guidelines for Evaluation of Disease

IIa. Measurable and Non-measurable Definitions

Measurable lesion:

A non nodal lesion that can be accurately measured in at least one dimension (longest dimension) of

- ≥10 mm with MRI or CT when the scan slice thickness is no greater than 5mm. If the slice thickness is greater than 5mm, the minimum size of a measurable lesion must be at least double the slice thickness (e.g., if the slice thickness is 10 mm, a measurable lesion must be ≥ 20 mm).
- ≥10 mm calliper/ruler measurement by clinical exam or medical photography.
- ≥20 mm by chest x-ray.

Additionally lymph nodes can be considered pathologically enlarged and measurable if

- ≥15mm in the short axis when assessed by CT or MRI (slice thickness recommended to be no more than 5mm). At baseline and follow-up, only the short axis will be measured [Chung, 2010; Eisenhauer, 2009].

Non-measurable lesion:

All other lesions including lesions too small to be considered measurable (longest diameter <10 mm or pathological lymph nodes with ≥ 10 mm and <15 mm short axis) as well as truly non-measurable lesions, which include: leptomeningeal disease, ascites, pleural or pericardial effusions, inflammatory breast disease, lymphangitic involvement of the skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques [Eisenhauer, 2009].

Measurable disease: The presence of at least one measurable lesion. Palpable lesions that are not measurable by radiologic or photographic evaluations may not be utilized as the only measurable lesion.

Non-Measurable only disease: The presence of only non-measurable lesions. Note: non-measurable only disease is not allowed per protocol.

III. Response Criteria

IIIa. Evaluation of target lesions

Definitions for assessment of response for target lesion(s) are as follows:

- Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes must be <10mm in the short axis.
- Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as a reference, the baseline sum of the diameters (e.g. percent change from baseline).
- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease.
- Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as a reference, the smallest sum of diameters recorded since the treatment started (e.g. percent change from nadir, where nadir is defined as the smallest sum of diameters recorded since treatment start). In addition, the sum must have an absolute increase from nadir of 5mm.
- Not Applicable (NA): No target lesions at baseline.
- Not Evaluable (NE): Cannot be classified by one of the five preceding definitions.

Note:

- If lymph nodes are documented as target lesions the short axis is added into the sum of the diameters (e.g. sum of diameters is the sum of the longest diameters for non-nodal lesions and the short axis for nodal lesions). When lymph nodes decrease to non-pathological size (short axis <10mm) they should still have a measurement reported in order not to overstate progression.
- If at a given assessment time point all target lesions identified at baseline are not assessed, sum of the diameters cannot be calculated for purposes of assessing CR, PR, or SD, or for use as the nadir for future assessments. However, the sum of the diameters of the assessed lesions and the percent change from nadir should be calculated to ensure that progression has not been documented. If an assessment of PD cannot be made, the response assessment should be NE.
- All lesions (nodal and non-nodal) should have their measurements recorded even when very small (e.g 2 mm). If lesions are present but too small to measure, 5 mm should be recorded and should contribute to the sum of the diameters, unless it is likely that the lesion has disappeared in which case 0 mm should be reported.
- If a lesion disappears and reappears at a subsequent time point it should continue to be measured. The response at the time when the lesion reappears will depend upon the status of the other lesions. For example, if the disease had reached a CR status then PD would be documented at the time of reappearance. However, if the response

status was PR or SD, the diameter of the reappearing lesion should be added to the remaining diameters and response determined based on percent change from baseline and percent change from nadir.

IIIb. Evaluation of non-target lesions

Definitions for assessment of response for non-target lesions are as follows:

- Complete Response (CR): The disappearance of all non-target lesions. All lymph nodes identified as a site of disease at baseline must be non-pathological (e.g. <10 mm short axis).
- Non-CR/Non-PD: The persistence of 1 or more non-target lesion(s) or lymph nodes identified as a site of disease at baseline ≥ 10 mm short axis.
- Progressive Disease (PD): Unequivocal progression of existing non-target lesions.
- Not Applicable (NA): No non-target lesions at baseline.
- Not Evaluable (NE): Cannot be classified by one of the four preceding definitions.

Note:

- In the presence of measurable disease, progression on the basis of solely non-target disease requires substantial worsening such that even in the presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy.
- Sites of non-target lesions, which are not assessed at a particular timepoint based on the assessment schedule, should be excluded from the response determination (e.g. non-target response does not have to be "Not Evaluable").

IIIc. New lesions

New malignancies denoting disease progression must be unequivocal. Lesions identified in follow-up in an anatomical location not scanned at baseline are considered new lesions.

Any equivocal new lesions should continue to be followed. Treatment can continue at the discretion of the investigator until the next scheduled assessment. If at the next assessment the new lesion is considered to be unequivocal, progression should be documented.

IIId. Evaluation of overall response

The table below presents the overall response at an individual time point for all possible combinations of tumor responses in target and non-target lesions with or without the appearance of new lesions for subjects with measurable disease at baseline.

Evaluation of Overall Response for Subjects with Measurable Disease at Baseline

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR or NA	No	CR
CR	Non-CR/Non-PD or NE	No	PR
PR	Non-PD or NA or NE	No	PR
SD	Non-PD or NA or NE	No	SD
NE	Non-PD or NA or NE	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR=complete response, PR = partial response, SD=stable disease, PD=progressive disease, NA= Not applicable, and NE=Not Evaluable

Note:

- Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration." Objective response status is determined by evaluations of disease burden. Every effort should be made to document the objective progression even after discontinuation of treatment.
- In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of CR depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the CR.
- The dosing schedule, dosing interruptions and unique design (see Table 2 of the protocol) should be considered when assessing tumor response. Thus, subjects with PD before Week 8, but without rapid clinical deterioration, may continue planned dosing schedule to allow detection of antitumor response. It is recommended that subjects who experience investigator-determined PD at the week 8, at the discretion of the investigator, may receive additional tumor assessment before the initiation of alternative anticancer therapy.
- During Part 1 or Part 2, is recommended that subjects who experience investigator-determined PD at any time, at the discretion of the investigator, may receive additional tumor assessment before the initiation of alternative anticancer therapy.

IIIe. Evaluation of best overall response

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

- To be assigned a status of SD, follow-up disease assessment must have met the SD criteria at least once after first dose at a minimum interval of 4 weeks.
- If the minimum time for SD is not met, best response will depend on the subsequent assessments. For example if an assessment of PD follows the assessment of SD and SD does not meet the minimum time requirement the best response will be PD. Alternative subjects lost to follow-up after an SD assessment not meeting the minimum time criteria will be considered not evaluable.

IIIf. Confirmation Criteria (recommended):

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

IIIg. Independent Review

Disease progression and response evaluations will be collected centrally during the study and may be reviewed or analyzed by an independent central reviewer. Details will be provided in the SPM.

15.6. Appendix 6: Genetic Research

Genetic Research Objectives and Analyses

The objectives of the genetic research are to investigate the relationship between genetic variants and:

- Response to medicine, including [GSK2816126] or any concomitant medicines;
- [Disease susceptibility, severity, and progression and related conditions

Genetic data may be generated while the clinical study is underway or following completion of the study. Genetic evaluations may include focused candidate gene approaches and/or examination of a large number of genetic variants throughout the genome (whole genome analyses). Genetic analyses will utilize data collected in the clinical study and will be limited to understanding the objectives highlighted above. Analyses may be performed using data from multiple clinical studies to investigate these research objectives.

Appropriate descriptive and/or statistical analysis methods will be used. A detailed description of any planned analyses will be documented in a Reporting and Analysis Plan (RAP) prior to initiation of the analysis. Planned analyses and results of genetic investigations will be reported either as part of the clinical RAP and study report, or in a separate genetics RAP and report, as appropriate.

Study Population

Any subject who is enrolled in the clinical study, can participate in genetic research. Any subject who has received an allogeneic bone marrow transplant must be excluded from the genetic research.

Study Assessments and Procedures

A key component of successful genetic research is the collection of samples during clinical studies. Collection of samples, even when no *a priori* hypothesis has been identified, may enable future genetic analyses to be conducted to help understand variability in disease and medicine response.

- A 6 ml blood sample will be taken for Deoxyribonucleic acid (DNA) extraction. Blood sample is collected at the baseline visit, after the subject has been randomized and provided informed consent for genetic research. If a subject initially declines to participate in genetic research and then changes their mind, a sample should be obtained at the earliest opportunity. Instructions for collection and shipping of the genetic sample are described in the laboratory manual. The DNA from the blood sample may undergo quality control analyses to confirm the integrity of the sample. If there are concerns regarding the quality of the sample, then the sample may be destroyed. The blood sample is taken on a single occasion unless a duplicate sample is required due to inability to utilize the original sample.

The genetic sample is labelled (or "coded") with the same study specific number as used to label other samples and data in the study. This number can be traced or linked back to the subject by the investigator or site staff. Coded samples do not carry personal identifiers (such as name or social security number).

Samples will be stored securely and may be kept for up to 15 years after the last subject completes the study or GSK may destroy the samples sooner. GSK or those working with GSK (for example, other researchers) will only use samples collected from the study for the purpose stated in this protocol and in the informed consent form. Samples may be used as part of the development of a companion diagnostic to support the GSK medicinal product.

Subjects can request their sample to be destroyed at any time.

Informed Consent

Subjects who do not wish to participate in the genetic research may still participate in the clinical study. Genetic informed consent must be obtained prior to any blood being taken for genetic analysis.

Subject Withdrawal from Study

If a subject who has consented to participate in genetic research withdraws from the clinical study for any reason other than being lost to follow-up, the subject will be given a choice of one of the following options concerning the genetic sample, if already collected:

- Continue to participate in the genetic research in which case the genetic DNA sample is retained

- Discontinue participation in the genetic research and destroy the genetic DNA sample

If a subject withdraws consent for genetic research or requests sample destruction for any reason, the investigator must complete the appropriate documentation to request sample destruction within the timeframe specified by GSK and maintain the documentation in the site study records.

Genotype data may be generated during the clinical study or after completion of the clinical study and may be analyzed during the clinical study or stored for future analysis.

- If a subject withdraws consent for genetic research and genotype data has not been analyzed, it will not be analyzed or used for future research.

- Genetic data that has been analyzed at the time of withdrawn consent will continue to be stored and used, as appropriate.

Screen and Baseline Failures

If a sample for genetic research has been collected and it is determined that the subject does not meet the entry criteria for participation in the clinical study, then the investigator should instruct the participant that their genetic sample will be destroyed. No forms are required to complete this process as it will be completed as part of the consent and sample reconciliation process. In this instance a sample destruction form will not be available to include in the site files.

Provision of Study Results and Confidentiality of Subject's Data

GSK may summarize the genetic research results in the clinical study report, or separately and may publish the results in scientific journals.

GSK may share genetic research data 'with other scientists to further scientific understanding in alignment with the informed consent. GSK does not inform the subject, family members, insurers, or employers of individual genotyping results that are not known to be relevant to the subject's medical care at the time of the study, unless required by law. This is due to the fact that the information generated from genetic studies is generally preliminary in nature, and therefore the significance and scientific validity of the results are undetermined. Further, data generated in a research laboratory may not meet regulatory requirements for inclusion in clinical care.

Section 15.6 Appendix 6: Response Criteria for Multiple Myeloma

Consensus Recommendations [Rajkumar, 2011] **for the Uniform Reporting of Clinical Trials: Report of the International Myeloma Working Group (IMWG) Consensus Panel**

Response Criteria [Durie, 2006]

sCR (stringent complete response):

Complete response as defined below plus:

- normal free light chain (FLC) ratio and
- absence of clonal cells in bone marrow by immunohistochemistry or 2-4 color flow cytometry.

CR (complete response):

- Negative serum and urine immunofixation, and
- Disappearance of any soft tissue plasmacytomas, and
- ≤ 5% plasma cells in bone marrow.

VGPR (very good partial response):

- Serum and urine M-component detectable by immunofixation but not on electrophoresis **OR**
- 90% or greater reduction in serum M-component plus urine M-component < 100mg/24h.

PR (partial response):

- ≥ 50% reduction of serum M-protein and reduction in 24 hour urinary M-protein by ≥ 90% or to < 200mg/24h, and
- If the serum and urine M-protein are not measurable, a ≥ 50% decrease in the difference between involved and uninvolved free light chain levels is required in place of the M-protein criteria. If serum and urine M-protein are not measurable, and serum free light chain assay is also not measurable, ≥ 50% reduction in bone marrow plasma cells is required in place of M-protein, provided baseline bone marrow plasma cell percentage was ≥ 30%, and
- In addition to the above listed criteria, if present at baseline, a ≥ 50% reduction in the size of the soft tissue plasmacytomas is also required.

MR (minimal response):

- ≥25% but ≤49% reduction of serum M-protein and reduction in 24 hour urinary M-protein by 50% to 89%, AND
- If present at baseline, 25% to 49% reduction in the size of soft tissue plasmacytomas is also required.
- No increase in size or number of lytic bone lesions (development of compression fracture does not exclude response).

SD (stable disease):

- Not meeting criteria for CR, VGPR, PR, MR or Progressive Disease.

Progressive Disease:

Requires any one or more of the following:

- Increase of ≥ 25% from lowest response value in any one or more of the following:
  - serum M-component (absolute increase must be ≥ 0.5 g/dl), or
  - urine M-component (absolute increase must be ≥ 200 mg/24h), or
  - the difference between involved and uninvolved free light chain levels (absolute increase must be > 10mg/dl): only for subjects without measurable serum and urine M-protein levels, or
  - bone marrow plasma cell percentage (the absolute % must be ≥10%) – only for subjects without measurable serum and urine M-protein levels and without measurable disease by FLC level.
  - definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas.
  - development of hypercalcemia (corrected calcium > 11.5 mg/dl or 2.65 mmol/l) that can be attributed solely to the plasma cell proliferative disorder.

a. All response categories (CR, sCR, VGPR, PR, MR and Progressive Disease) require two consecutive assessments made at any time before the institution of any new therapy; CR, sCR, VGPR, PR, MR, and SD categories also require no known evidence of progressive or new bone lesions if radiographic studies were performed. VGPR and CR categories require serum and urine studies regardless of whether disease at baseline was measurable on serum, urine, both, or neither. Radiographic studies are not required to satisfy these response requirements. Bone marrow assessments need not be confirmed. For Progressive Disease, serum M-component increases of more than or equal to 1 g/dL are sufficient to define relapse if starting M-component is ≥ 5 g/dL.

b. Clarifications to IMWG criteria for coding CR and VGPR in subjects in whom the only measurable disease is by serum FLC levels: CR in such subjects indicates a

normal FLC ratio of 0.26 to 1.65 in addition to CR criteria listed above. VGPR in such subjects requires a > 90% decrease in the difference between involved and uninvolved FLC levels.

c. Clarifications to IMWG criteria for coding Progressive Disease: Bone marrow criteria for Progressive Disease are to be used only in subjects without measurable disease by M protein and by FLC levels; "25% increase" refers to M protein, FLC, and bone marrow results, and does not refer to bone lesions, soft tissue plasmacytomas, or hypercalcemia and the "lowest response value" does not need to be a confirmed value.

AMENDMENT [4]

Where the amendment applies

This amendment applies to all investigator sites participating in this study

Summary of Amendment Changes with Rationale

Based on emerging data and guidance from ANSM following the submission of our CTA, GSK agreed to update the protocol for the following:

- Update the instructions for investigational product to restrict the storage duration of the final diluted solution to not more than 12 hours at ambient temperature (Protocol previously noted storage up to 48 hours),
- Instruct the investigators to inform their patients that they should: minimize or avoid prolonged exposure to natural or artificial sunlight; to wear sunglasses and loose fitting clothing to protect the skin; and to use a broad spectrum sunscreen on any uncovered areas of the body if outdoors.
- Amend the protocol to extend the period of post treatment contraception for women to 2 weeks (14 days).

In addition, updates to the timing and frequency of pregnancy testing were updated to align with current GSK SOP. Text was added to protocol to clarify those females who become pregnant while on study should be immediately withdrawn from study treatment and withdrawn from the study.

Lastly, the administration of ondansetron and palonosetron was clarified to allow oral doses up to 8mg TID and exclude IV.

AUTHORS:

PPD

Sponsor/medical monitor Information Page

Medical Monitor and Sponsor Contact Information:

Role	Name	Day Time Phone Number	After-hours Phone/Cell/ Pager Number	Fax Number	GSK Address
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~~Seconda ry~~ Primary Medical Monitor	PPD PPD MD, PhD	PPD			1250 South Collegeville Road, Mailstop UP 4410 Collegeville, PA 19426, USA PPD
Seconda ry Medical Monitor	PPD MD	Office: PPD Cell: PPD	PPD		1250 South Collegeville Road, Mailstop UP 4410 Collegeville, PA 19426, USA PPD

PROTOCOL SYNOPSIS

REVISED TEXT

INCLUSION/EXCLSUION CRITERIA:

Part 1: Inclusion Criteria

8. Women of childbearing potential must have a negative serum pregnancy test within ~~14~~7 days of first dose of study treatment and agree to use effective contraception, as defined in Section 10.1, during the study and for at least ~~one~~ two weeks (14 days) following the last dose of study treatment.

Section 4. INVESTIGATIONAL PRODUCT

REVISED TEXT

4.1: Description of Investigational Product

Table 5 Investigational Product

Product name:	GSK2816126 Injection,15 mg/mL, 30 mL vial with 25 mL fill volume
Formulation description:	Solution containing 15 mg/mL GSK2816126 in water for Injection, methanesulfonic acid, Captisol and acetic acid
Dosage form:	A solution stored at 2-8°C, protected from light
Unit dose strength(s)	15 mg/mL
Route/ Regimen	Delivered as an intravenous solution over 2 - 4 hours Study drug can be diluted into saline or dextrose for a final volume of 250ml at ambient temperature and normal room lighting up to ~~4~~8<u>12</u> hours prior to infusion. PVH, PE and PA bags and tubing are all acceptable
Physical description:	A clear, pale yellow coloured solution, essentially free from visible particles of foreign matter

Section 5 STUDY POPULATION

REVISED TEXT

Section 5.2 Subject Selection Criteria

5.2.1 Part 1 Inclusion Criteria

8. Women of childbearing potential must have a negative serum pregnancy test within ~~14~~ <u>7</u> days of first dose of study treatment and agree to use effective contraception, as defined in Section 10.1, during the study and for at least ~~one~~ <u>two weeks (14 days)</u> following the last dose of study treatment.

Section 6.3 PERMANENT DISCONTINUATOIN FROM STUDY TREATMENT

REVISED TEXT

<u>Female subject who becomes pregnant while on study treatment</u>

Section 7 STUDY ASSESSMENTS AND PROCEDURES

REVISED TEXT

Table 6 Time and Events, Treatment Phase: Screening through Day 28 (See also PK sampling table for PK sampling schedule on Day 1 and Day 15)

Details added:

- In females of child bearing potential, a serum pregnancy test is required ~~at screening if performed~~ within ~~14~~ 7 days of first dose of study drug; ~~and repeat as clinically indicated~~ urine or serum test thereafter.
- Urine or serum pregnancy tests were added to Continuation Phase 'Every 4 Weeks' and at time of Follow Up Visit

- Section 7.3.6 Laboratory Assessments

- Table 8 List of Clinical Laboratory Tests

Hematology			
Platelet Count		*RBC Indices*:	*Automated WBC Differential:*
RBC Count		MCV	Neutrophils
WBC Count (absolute)		MCH	Lymphocytes
Reticulocyte Count		MCHC	Monocytes
Hemoglobin			Eosinophils
Hematocrit			Basophils
Clinical Chemistry			
BUN	Potassium	AST	Total and direct bilirubin
Creatinine	Chloride	ALT	Uric Acid
Sodium	Calcium	Alkaline phosphatase	Total Protein
Magnesium	Glucose	LDH	PO4
FSH and estradiol (as needed in women of non-child bearing potential only) Pregnancy test for females (serum at screening, Urine or serum during Continuation Phase)			

Abbreviation(s): ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; FSH, follicle stimulating hormone; LDH, lactate dehydrogenase; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; PO_4, phosphate; RBC, red blood cell; WBC, white blood cell.

Section 7.3.7 Pregnancy Testing and Reporting

The need for a screening pregnancy test depends on whether a female subject is of childbearing potential or non-childbearing potential.

If a female subject is of childbearing potential, she must have a serum β-HCG pregnancy test performed within ~~14~~ 7 days prior to the first dose of study treatment. Subjects with positive pregnancy test result must be excluded from the study. Subjects with negative pregnancy test result must agree to use an effective contraception method as described in

Section 10.1 during the study until at least ~~1~~ 2 weeks (14 days) after permanent discontinuation of study treatment.

Any pregnancy that occurs during study participation must be reported using a clinical trial pregnancy form. To ensure subject safety, each pregnancy must be reported to GSK within 2 weeks of learning of its occurrence. The pregnancy must be followed up to determine outcome (including premature termination) and status of mother and child. While pregnancy itself is not considered to be an AE or SAE, pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous abortions must be reported as an SAE.

Any SAE occurring in association with a pregnancy brought to the investigator's attention after the subject has completed the study and considered by the investigator as possibly related to the study treatments, must be promptly reported to GSK.

Any female subject who becomes pregnant while participating in the study will be withdrawn from the study. Study treatment should be immediately withdrawn from a subject who becomes pregnant during the study in order to eliminate further exposure of the embryo to the study treatment.

Section 9 CONCOMITANT MEDICATIONS AND NON DRUG THERAPIES

REVISED TEXT

Section 9.4 Drugs and QT Prolongation

If a subject requires medication for hyperemesis, due to the potential of serotonin 5-HT3 receptor antagonists to increase QTcF, palonosetron and ondansetron at a maximum oral dose of 8 mg TID are the only allowed drugs in this class. Intravenous administration of these drugs are not permitted

Section 10 LIFESTYLE AND/OR DIETARY RESTRICTIONS

REVISED TEXT

Section 10.1.1 Female Subjects

Abstinence

Sexual inactivity by abstinence must be consistent with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

Complete abstinence from sexual intercourse for 14 days prior to first dose of study treatment, through the dosing period, and for at least two ~~one~~ weeks (14 days) after the last dose of study treatment.

Section 10.2 Lactation Restrictions

Female subjects who are lactating must discontinue nursing prior to the first dose of study treatment and must refrain from nursing throughout the treatment period and for at least ~~one~~ two weeks (14 days) after last dose of study treatment.

Section 10.4 Sun and UV Exposure Restrictions

Prior to starting study drug, subjects should be instructed to:

- Minimize or avoid prolonged exposure to natural or artificial sunlight (e.g., tanning beds, sunlamps, UVA or UVB treatments)
- Wear loose fitting clothing with long sleeves, sunglasses, and broad rim hat that protect the skin from sun exposure AND use a broad spectrum sunscreen (e.g., UVA and UVB protective with minimum SPF 30) on any uncovered areas of the body if outdoors

	STUDY PHASE	**SCREEN**	**First Treatment Period Cycle 1**				**Continuation Phase Cycle 2 and beyond**	**Follow-Up[j]**
	VISIT	**Screen**	**Day 1 and 4[a]**	**Day 8 and 11[a]**	**Day 15 and 18[a]**	**Day 21**		
	VISIT WINDOW (±days)	-14					±7[l]	±7[l]
Assessments (notes)								
Informed consent		X						
Demographic data		X						
Record subject using IVRS system		X	X					
Height/Weight (Refer to Section 7.3.1)	Measurements in metric scale. Height measured only at screening	X	X				Every 4weeks (Cycle Day 1)	X
Pregnancy test	In females of child bearing potential, a serum[i] B-HCG pregnancy test is required within 7 days of first dose of study drug; urine or serum[n] B-HCGtest thereafter.	X					Every 4 weeks (Cycle Day 1)	X
Disease characteristics (Refer to Section 7.2)	Record date of diagnosis, primary tumor type, histology, stage, etc.	X						
Prior anti-cancer therapy & radiation	Record date of therapies	X						
Prior surgical procedures		X						
Past and current medical conditions		X						
Alcohol consumption		X						
Past and current tobacco use		X						
Physical examination		X	Day 1	Day 8	Day 15	X	Every 4 weeks Cycle Day 1	
ECOG PS	See Appendix 2	X	X	X	X	X	X	X

	STUDY PHASE	**SCREEN**	**First Treatment Period Cycle 1**				**Continuation Phase Cycle 2 and beyond**	**Follow-Up[j]**
	VISIT	**Screen**	**Day 1 and 4[a]**	**Day 8 and 11[a]**	**Day 15 and 18[a]**	**Day 21**		
	VISIT WINDOW (±days)	-14					±7[l]	±7[l]
Vital signs	BP, body temperature, pulse rate, respirations Cycle 1 Day 1 vitals should be taken at same time points as PK draws on PK Table 7	X	X (Day 1 follow PK Table 7)	X	X	X	Prior to each infusion	X
ECG[b]	Pre-infusion and at the end of infusion except on Day 1 (Section 7.3.4). Two copies of the ECG tracing should be obtained at the time of the ECG, one to be kept in the study file for retrospective collection by the sponsor if necessary. ECG data should be reviewed by qualified personnel with experience in this study population	X	X[b]	X	X		On Day 4 of each cycle	X

	STUDY PHASE	**SCREEN**	**First Treatment Period Cycle 1**				**Continuation Phase Cycle 2 and beyond**	**Follow-Up[j]**
	VISIT	**Screen**	**Day 1 and 4[a]**	**Day 8 and 11[a]**	**Day 15 and 18[a]**	**Day 21**		
	VISIT WINDOW (±days)	-14					±7[l]	±7[l]
Holter Monitoring	Continuous 12-lead Holter ECGs (obtained via a Holter monitor) will be acquired for a total of approximately 24 hours beginning an hour before infusion on **Day 1 only**		X (Day 1)					
ECHO /MUGA	At Screening	X						
Concomitant medications	See Section 9.2 for list of prohibited and cautionary medications	X	X	X	X	X	continuous	X
Adverse events (Refer to Section 8)	Adverse event assessment should be continuous	X	X	X	X	X	continuous	X
Blood Sampling: on dosing days, collect blood samples prior to dosing unless otherwise noted								
Chemistry	No need to repeat at pre-dose Day 1 if screening assessments were performed within 72 hours of first dose (- 1 day visit window after screening)	X	X	X	X	X	Prior to every infusion	X

	STUDY PHASE	**SCREEN**	**First Treatment Period Cycle 1**				**Continuation Phase Cycle 2 and beyond**	**Follow-Up[j]**
	VISIT	**Screen**	**Day 1 and 4[a]**	**Day 8 and 11[a]**	**Day 15 and 18[a]**	**Day 21**		
	VISIT WINDOW (±days)	-14					±7[l]	±7[l]
Hematology	No need to repeat at pre-dose Day 1 if screening assessments were performed within 72 hours of first dose (- 1 day visit window after screening)	X	X	X	X	X	Prior to every infusion	X
Coagulation	PT/PTT/INR. No need to repeat at pre-dose Day 1 if screening assessments were performed within 72 hours days of first dose(- 1 day visit window after screening)	X						
Blood sample for circulating biomarkers	A blood sample for circulating biomarkers should be obtained on Day 1 (prior to treatment), Day 21and at the time of disease progression		X			X		X (at progression)

	STUDY PHASE	**SCREEN**	**First Treatment Period Cycle 1**				**Continuation Phase Cycle 2 and beyond**	**Follow-Up[j]**
	VISIT	**Screen**	**Day 1 and 4[a]**	**Day 8 and 11[a]**	**Day 15 and 18[a]**	**Day 21**		
	VISIT WINDOW (±days)	-14					±7[l]	±7[l]
Blood sample for Genetic research	A 6mL blood sample should be collected after screening (preferably on day 1) if informed consent has been obtained for Genetic research		X					
Whole Blood for Biomarkers[g]	Whole blood should be obtained prior to dosing on day 1,day 18 and C2D1 (sample taken prior to dosing)		X (Day 1)		X (Day 18)		X (C2W1D1 pre dose only)	
PK sampling for Part 1	For details, see Table 7		Day 1 (Table 7) Day 4pre-dose and end of infusion	Soon after ECG collection	Day 15 (Table 7)	At the time of circulating biomarker collection	Cycle 2, 4, 6 and 12 – pre-dose and within 5 min prior to end of infusion on Day 4	

	STUDY PHASE	**SCREEN**	**First Treatment Period Cycle 1**				**Continuation Phase Cycle 2 and beyond**	**Follow-Up[j]**
	VISIT	**Screen**	**Day 1 and 4[a]**	**Day 8 and 11[a]**	**Day 15 and 18[a]**	**Day 21**		
	VISIT WINDOW (±days)	-14					±7[l]	±7[l]
PK sampling for Part 2	Three samples to be collected on Day 1 and Day 11: Predose within 60 minutes prior to start of infusion, single draw between 0.5 and 1.9 h from start of infusion, single draw between 3-6h following end of infusion.		Day 1 and pre-dose on Day 4	X (after 4th dose, Day 11)	pre-dose on Day 15		Cycle 2, 4, 6 and 12 – pre-dose and within 5 min prior to end of infusion on Day 4	
Translational Research								
Tumor Tissue for EZH2 mutation and GCB confirmation testing (required: for all GCB DLBCL and tFL subjects)[c]	Availability of archival tissue (or fresh biopsy) is required for central testing of GCB-subtype and EZH2 mutation status	X						
Tumor tissue for solid tumors (including prostate subjects)[c]	Availability of archival tissue (or fresh biopsy)	X						
Tumor biopsy for PD optional for Part 1 and Part 2Required for PK/PD cohort	A tumor biopsy should be obtained at D1 (up to -14 days) and after 6th dose Day 18(+3 day window)		X		X (After 6th dose, Day 18)[h]			

	STUDY PHASE	**SCREEN**	**First Treatment Period Cycle 1**				**Continuation Phase Cycle 2 and beyond**	**Follow-Up[j]**
	VISIT	**Screen**	**Day 1 and 4[a]**	**Day 8 and 11[a]**	**Day 15 and 18[a]**	**Day 21**		
	VISIT WINDOW (±days)	-14					±7[l]	±7[l]
Tumor biopsy for biomarker research	Recommended for all subjects							X (at pro-gression)
Additional Assessments for PD/PK Cohort[m]								
Blood for metabolite evaluation (Part 2 PK/PD expansion cohort only			Day 1 (Table 7)		Day 15 (Table 7)			
Urine for Metabolite (Part 2 PK/PD expansion cohort only)	On Day 15, urine samples should be collected while subject is in the office		Day 1 prior to first dose and from 0 to 24h		Day 15 from 0 to 8 h			
Bile for metabolite (Part 2 PK/PD expansion cohort only) – at least 4 subjects)					Day 15			
Plasma for 4β-hydroxycholesterol and cholesterol assay (Part 2 PK/PD expansion cohort only)			X (Day 1 prior to First Dose)			X		

	STUDY PHASE	**SCREEN**	**First Treatment Period Cycle 1**				**Continuation Phase Cycle 2 and beyond**	**Follow-Up[j]**
	VISIT	**Screen**	**Day 1 and 4[a]**	**Day 8 and 11[a]**	**Day 15 and 18[a]**	**Day 21**		
	VISIT WINDOW (±days)	-14					±7[l]	±7[l]
Disease Assessments for Lymphoma Subjects: *Baseline disease assessments at screening and repeated 8 weeks after dosing is initiated and every 12 weeks thereafter*								
CT[k]	Must be completed within 4 weeks of first dose of GSK2816126 and repeated 8 weeks after dosing is initiated. Every 12 weeks thereafter	X					X	X[d]
Positron emission tomography (PET)	The use of standalone PET or PET in combination with CT scan is optional. Standalone PET does not replace CT	X[e]					X[e]	X[d,e]
Bone Marrow biopsy)	See Section 7.7	X					X[f]	X[f]
B symptoms	See Section 7.7	X	X	X	X	X	X	
Disease Assessments for Multiple Myeloma (MM) subjects: Baseline disease assessments at screening, week 4 and then every 6 weeks there after unless otherwise noted								
Disease Characteristics	Every 6 weeks after Wk4, Including cytogenetics as appropriate	X					X	
Total Protein, CRP, β2 microglobulin	Every 6 weeks after Wk4	X					X	
Response Assessment	Every 6 weeks after Wk4; Response criteria in Appendix 6						X	

	STUDY PHASE	**SCREEN**	**First Treatment Period Cycle 1**				**Continuation Phase Cycle 2 and beyond**	**Follow-Up[j]**
	VISIT	**Screen**	**Day 1 and 4[a]**	**Day 8 and 11[a]**	**Day 15 and 18[a]**	**Day 21**		
	VISIT WINDOW (±days)	-14					±7[l]	±7[l]
SPEP, FLC assay, quantitative immunoglobulins (IgG, IgA, IgM)	Not required for subjects with non-secretory MM	X					X	
UPEP	Only required if paraprotein is present in urine	X						
Extramedullary Disease Assessment	Only required for MM with extramedullary disease	X						
BM aspirate and biopsy	Required for non-secretory MM, or as appropriate for other subjects	X			Day 18		Week 10, Day 1	
Disease Assessments for Solid Tumors: Baseline disease assessments at screening and repeated every 8 weeks after dosing is initiated								
CT/MRI[k]	Must be completed within 4 weeks of first dose of GSK2816126 and repeated every 8 weeks	X					X[d]	X[d]
Positron emission tomography (PET)	The use of standalone PET or PET in combination with CT scan is optional. Standalone PET does not replace CT	X[e]					X[d,e]	X[d,e]

	STUDY PHASE	**SCREEN**	**First Treatment Period Cycle 1**				**Continuation Phase Cycle 2 and beyond**	**Follow-Up[j]**
	VISIT	**Screen**	**Day 1 and 4[a]**	**Day 8 and 11[a]**	**Day 15 and 18[a]**	**Day 21**		
	VISIT WINDOW (±days)	-14					±7[l]	±7[l]
Disease Assessments for Prostate Cancer: (in addition to those assessments for all solid tumor subjects): Baseline disease assessments at screening and repeated as noted below after dosing is initiated								
PSA	Wk 9 and every 4 weeks thereafter	X					Every 4 weeks (Cycle Day 1)	X
Study Medication								
GSK2816126 Dosing	Dosed 2x weekly with at least 2-3 non-dosing days in between dosing days (3 weeks on/1 week off)							

AMENDMENT [5]

Where the Amendment Applies

Amendment 5 applies to all global sites.

Summary of Amendment Changes with Rationale

Updates were made throughout the protocol to correct minor inconsistencies, spelling errors and provide further clarification. The following updates have been made to the this amendment to align with updated GSK SOPs and Guidance documents, as well as, to include expansion cohorst in Part 1 of the study to explore further efficacy and safety data:

- Updates made to the Part 1 and Part 2 Objectives, Endpoints and study hypothesis to align with the added Part 1 expansion cohorts of GCB DLBCL and solid tumors containing EZH2 inhibitor sensitizing mutations or prostate cancer to support MTD/RP2D and initiation of planned part 2 analysis
- Study design and number of subjects updated to include the added Part 1 expansion cohorts and update Part 2 expansion cohort
- Inclusion and exclusion criteria updated to define eligibility of GCB DLBCL and solid tumor subjects in Part 1 expansion cohort. Exclusion for Central nervous system metastases, invasive malignancy other than disease under study and prior allogeneic transplant added.
- Male and female contraception use and pregnancy information updated in inclusion criteria and Section 10 to align with GSK written standards
- Statistical methods/Section 12 updated to include Part 1 interim analysis of futility and efficacy for GCB DLBCL subjects. Part 2 updated to further clarify that expansion design is planned based on predictive probability methodology. Rather than early stop for either futility or efficacy, Part 2 allows early stop for futility only. Number of subjects to be enrolled into the Part 2 expansion cohorts updated accordingly
- Risk Assessment updated to include: updated list of medications with risk and possible risk of tpd that are prohibited or to be used with caution; drugs that are to be used with caution will require additional ECG monitoring; clarify instructions for the treatment of infusion reactions; new drug interaction data; additional data and instructions for phototoxicity; and data and mitigation strategy for increased ALT levels seen in higher doses.
- PK/PD cohort moved from Part 1 to Part 2
- Study rationale updated to include supporting rationale for inclusion of GCB-DLBCL and solid tumor subjects (to include prostate cancer)
- Safety management guidelines updated to clarify QTcF to be used for eligibility and stopping criteria

- Time and Events tables updated to clarify required assessments. Added clarification that brain scans are required for all subjects at screening and bone scans should be completed as clinically indicated. Collection of Blood for PD biomarkers removed and collection of whole blood for biomarkers added
- Response criteria added for subjects with prostate cancer in Appendix 7 of the protocol
- Adverse event and serious adverse event Section 8 updated to align with latest GSK written standards, to include: further definition of events which would meet liver stopping and monitoring criteria, as well as, definition and process for study treatment restart and rechallenge after a liver event and removal of Section 8.4 addressing disease related event
- Section 9 updated with latest list of prohibited medications and those to be used with caution

List of Specific Changes

- **Author (s):**

- PPD
- Global Clinical Operations Sciences, USA
- Drug Metabolism and Pharmacokinetics, USA
- Cancer Epigenetics, USA
- Non--Clinical Safety, USA
- Cancer Research Epigenetics Management,
- Non-Clinical Safety, USA
- Statistics, Oncology TA Group, USA
- Global Clinical Operations Sciences, USA
- Clinical Oncology, USA
- Clinical Oncology, USA
- Cancer Epigenetics DPU, USA
- Clinical Pharmacology Modeling & Simulation,
- Statistics, Oncology TA Group, USA

Sponsor/Medical Monitor Information Page

REVISED TEXT

Medical Monitor and Sponsor Contact Information:

Role	Name	Day Time Phone Number	After-hours Phone/Cell/ Pager Number	GSK Address
Primary Medical Monitor	PPD MD, PhD	PPD	PPD	1250 South Collegeville Road, Mailstop UP 4410 Collegeville, PA 19426, USA PPD
Secondary Medical Monitors	PPD MD	Office: PPD PPD Cell: PPD	PPD	1250 South Collegeville Road, Mailstop UP 4410 Collegeville, PA 19426, USA PPD
	PPD	Office PPD PPD		1250 South Collegeville Road, Mailstop UP 4410 Collegeville, PA 19426, USA PPD

LIST OF ABBREVIATIONS

Added the abbreviations TdP (Torsades de Pointe)

Section Protocol Synopsis: Study Rationale

Rationale for Change:

- Clarified that subjects with castrate resistant prostate cancer are included in the cohort of subjects with solid tumors.

- Clarified the patient population to be enrolled under this amendment to include patients with GCB DLBCL and solid tumors containing EZH2 inhibitor sensitizing mutations or prostate cancer

REVISED TEXT

- Most of these cancers have an overall poor outlook either because of lack of any effective therapy or standard therapies do not result in a durable remission. This first study of this agent will be conducted in subjects with non-Hodgkin lymphomas, especially germinal center B-cell diffuse large B-cell lymphoma (GCB-DLBCL) and transformed follicular lymphoma (t-FL), and subjects with solid tumors (-including castrate resistant prostate cancer) and multiple myeloma (MM) who have relapsed or are refractory to prior therapies and have a high degree of unmet medical need in terms of available treatment options.

Section Protocol Synopsis: Study Objectives, Endpoints And Hypotheses

Rationale for Change:

- Moved Part 1 objectives for the PD/PK cohort to Part 2 of the study

- Included the hypothesis and statistical analysis plan for the Part 1 expansion of GCB DLBCL and solid tumor subjects. GCB-DLBCL cohort expansion was added into Part 1 dose escalation phase. The study design was based on predictive probability methodology (Liu, 2008) to allow interim futility/efficacy assessment by comparing the overall responses with the pre-specified futility and efficacy stopping criteria, in order to enabling early decision of opening Part 2 expansion phase or terminating the trial.

- Due to the improvement of response rates of cancer treatments over time, the study designs in Part 2 expansion phase based on predictive probability method were revised by updating the null and alternative hypothesis, to align with the current typical response rates. The sample size and futility stopping criteria for each cohort (GCB-DLBCL mutant and wild type, tFL mutant and wild type, and MM) are updated

- Update Part 1 and Part 2 exploratory objectives and endpoints

REVISED TEXT

Part 1 Objectives		Part 1 Endpoints
Secondary	• 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 (Cτ), maximum observed concentration (Cmax), time of occurrence of Cmax (tmax), terminal phase half-life (t1/2), 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~~ PD response assessed by change from baseline in tri-methylation of Histone H3K27 (H3K27me3)
	• To determine clinical activity of GSK2816126 in GCB DLBCL and solid tumors containing EZH2 inhibitor sensitizing mutations or prostate cancer	• Best Overall Response rate (complete response [CR] + partial response [PR])
	•	
	~~• Evaluate the relationship between GSK2816126 exposure markers and safety/efficacy/PD responses~~	~~• Samples to characterize the metabolites in blood, bile and/or urine~~
	~~• To generate samples (data reported separately) with which to characterize the metabolic profile of GSK2816126 after repeat-dosing (In the PK/PD~~	~~• Concentration of GSK2816126 in urine measured with an investigational bio-analytical~~

Part 1 Objectives		Part 1 Endpoints
	~~expansion cohort only)~~ • ~~To determine the amount of GSK2816126 excreted in urine after dosing at steady state~~	~~method and extrapolated to total amount excreted in urine over time using urine volume~~
Exploratory	• To confirm tumor EZH2 and GCB-DLBCL status • To investigate the mechanism of action ~~and additional indicators of sensitivity and resistance to~~ of GSK2816126 • To identify biomarkers predictive of response or resistance to GSK2816126 • ~~To generate samples (data reported separately) with which to investigate the potential for GSK2816126 to affect cytochrome P450 (CYP) 3A4 enzyme activity~~	• IHCfor confirmation of GCB-DLBCL status • PCR or NGS to determine EZH2 mutation status • Evaluate transcriptional and/or protein changes upon GSK2816126 treatment • Correlate baseline tumor genomic (DNA), protein and/or transcription (RNA) profiles with response • ~~Tumor baseline genetic profiles, response~~ • ~~Samples to assess a potential change in 4b-OH cholesterol to cholesterol ratio in plasma following repeat dosing of GSK2816126 (data reported separately)~~
Hypothesis	~~No formal statistical hypotheses are being tested in Part 1: Phase I dose escalation. Analysis of the data obtained from Part 1 will only utilize descriptive methods~~	

Part 1 Objectives	Part 1 Endpoints
	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 utilize descriptive methods only. The cohort expansion of GCB-DLBCL patients in Part 1 will assess the overall response rate (p) of GCB-DLBCL patients. The null and alternative hypotheses for the overall response rate are detailed below: The null hypothesis is: H_0: $p \leq 20\%$ The alternative hypothesis is: H_A: $p \geq 40\%$ For cohort expansion of solid tumor subjects in Part 1, there is no formal statistical hypothesis being tested. Analysis of the data obtained from solid tumor expansion cohort will utilize descriptive methods only.

	Part 2 Objectives	Part 2 Endpoints
Primary	• 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~~Overall response rate (% of subjects achieving CR and PR per response criteria)
Secondary	• 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 GSK2816126 exposure and PD parameters	• GSK2816126 exposure markers (dose, concentration, Cmax or AUC) and PD responses. PD response assessed by change from baseline in tri-methylation of Histone H3K27 (H3K27me3)
	• 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

	Part 2 Objectives	Part 2 Endpoints
	•	using urine volume
	• 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)
	•	•
	• 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)
Exploratory	• 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~~	• Correlate baseline tumor genomic (DNA), protein and/or transcription (RNA) profiles with response
	• To investigate the relationship between genetic variants in candidate genes and the pharmacokinetics (PK) and safety profile of GSK2816126 based on Part 1 and 2 data combined	• Evaluate transcriptional and/or protein changes upon GSK2816126 treatment • ~~Deoxyribonucleic acid (DNA), ribonucleic acid (RNA) and protein markers in tumor and blood~~ • Pharmacogenomic (PGx) analysis of whole blood

	Part 2 Objectives	**Part 2 Endpoints**
Hypothesis	In Part 2, the overall response rate (p) of GCB-DLBCL and tFL patients will be assessed for each EZH2 mutation status cohort (wild type and mutant), and also for MM patients. • For each of the GCB-DLBCL and tFL cohort, the null and alternative hypotheses of the overall response rate are as following: The null hypothesis is: H_0: p≤20% The alternative hypothesis is: H_A: p≥40% • For MM cohort: The null hypothesis is: H_0: p≤10% The alternative hypothesis is: H_A: p≥25% ~~The primary objective of Part 2 is to determine whether administration of GSK2816126 has a potentially clinically meaningful response rate.~~ • ~~In subjects with GCB-DLBCL, this will be determined in each EZH2 mutation status cohort (wild type and mutant) by testing the null hypothesis that the response rate is ≤10%, with about 90% power when the true response rate is 30%.~~ • ~~In subjects with tFL, this will be determined in each EZH2 mutation status cohort by testing the null hypothesis that the response rate is ≤5%, with about 80% power when the true response rate is 25%.~~ • ~~In subjects with MM, this will be determined by testing the null hypothesis that the response rate is ≤5%, with about 85% power when the true response rate is 20%.~~	

Section Protocol Synopsis

Rationale for Change: Included expansion cohort in Part 1 of the study to enroll at the MTD an additional 27 GCB-DLBCL and 15 solid tumor subjects to collect additional safety and efficacy data in these patient populations. Clarified that solid tumor cohort in Part 1expansion will include subjects with solid tumors containing EZH2-inhibitor sensitizing mutations or metastatic castrate resistant prostate cancer (mCRPC, regardless of mutation status). Updated the total number of subjects expected to be enrolled based on addition of the Part 1 expansion cohort and updated Part 2 cohort subject numbers.

REVISED TEXT

- **Study Design:**This study is divided into 2 parts; Part 1 of the study is a dose escalation phase to identify MTD and 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~~ non-Hodgkin~~'s~~ lymphomas (NHL), Multiple Myeloma (MM) and solid tumors will be enrolled in the dosing cohorts until a RP2D is established. One or more dose level/s during Part 1 escalation may be expanded up to 12 subjects to explore safety and preliminary efficacy. At the identified MTD, approximately 27 GCB-DLBCL subjects and approximately 15 subjects with solid tumors containing EZH2-inhibitor sensitizing mutations or metastatic castrate resistant prostate cancer (mCRPC, regardless of mutation status), may be enrolled to explore safety and preliminary efficacy. Subjects may continue treatment in the study until disease progression, unacceptable toxicity, or withdrawal of consent. Expansion cohorts (Part 2) are planned in subjects with MM, and in subjects with both EZH2 mutant positive and EZH2 WT GCB-DLBCL and tFL to further explore clinical activity at the RP2D.

- **NUMBER OF SUBJECTS:** ~~Approximately~~ Up to approximately 250~~169~~ subjects worldwide (inclusive both Parts 1 and 2).

INCLUSION/EXCLUSION CRITERIA:

Rationale for Change: In line with the added Part 1 expansion cohort, updated that the NHL tumor types to be enrolled under this amendment will include GCB-DLBCL subjects and the inclusion criteria for these subjects. Removed criteria for tFL and other NHLs. Updated the tumor type criteria for solid tumor subjects including subjects with CRPC. Updated the inclusion of women who are of child bearing potential and male and female contraception use per GSK document standards. Updated the adequate organ funcation table to clarify renal parameters and clarify footnotes.

Part I: Inclusion Criteria

Subjects eligible for enrollment in the study must meet all of the following criteria:

3. Tumor type criteria:
   - Relapsed/refractory NHL that meets ~~one of~~ the following criteria:
     - Germinal C~~c~~enter B cell Diffuse large B cell lymphoma (GCB-DLBCL) ~~or transformed follicular lymphoma~~ relapsed ~~after~~, or refractory to at least one prior ~~chemotherapy~~ regimen (e.g., rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone [R-CHOP]) AND not a candidate for standard salvage regimens or autologous or allogeneic stem cell transplant. ~~(e.g., due to age, comorbid conditions or failure to respond to salvage chemotherapy).~~ Local confirmation of lymphoma subtype ~~(e.g.~~ GCB-DLBCL~~)~~ is allowed for enrollment but must be confirmed through central laboratory testing.
     - ~~DLBCL or transformed FL relapsed after or refractory to at least two prior chemotherapy regimens.~~
     - ~~Other NHLs that have failed at least one prior line of therapy and for which there is no standard salvage regimen.~~
   - ~~Relapsed and/or refractory MM that have failed prior standard therapy and for which there is no standard salvage regimen.~~
   - ~~Solid tumors [RECIST evaluable, with the exception of castrate resistant prostate cancer (CRPC) at least one and not more than three standard of care chemotherapeutic regimens, or tumor for which there is no approved therapy, or for which standard therapy is refused.~~
   - Solid tumors that meet the following criteria:
     - Measurable disease by RECIST 1.1 in at least 1 site
       - For Castrate Resistant Prostate Cancer (CRPC) measurable disease can also include PSA level (see below)
     - Disease progression with the last line of therapy and at least one prior standard of care regimens, or tumor for which there is no approved therapy, or for which standard therapy is unsuitable or refused.
     - Mutation Status:
       - Solid tumor types, other than prostate, must have~~a~~ one of the following EZH2 inhibitor sensitizing mutations as determined via local testing:
         - An activating mutation in EZH2 (Y641F/C/S/H/N, A677V/G, and/or A687V
         - Loss of a component of the SWI/SNF complex, including, but not limited to, ARID1A, SMARCB1 (aka SNF5/INI1/BAF47), SMARCA4 (aka BRG1), or PBRM1 (aka PB1) as determined by molecular testing (bi-allelic loss or mutation) or immunohistochemistry
         - Loss of BAP1 (ubiquitin carboxy-terminal hydrolase) as determined by molecular testing (bi-allelic loss or mutation) or immunohistochemistry

- CRPC subjects:
  - Must have measurable disease by either:
    - RECIST1.1 (Appendix 5), or
    - a minimum PSA of 5 ng/mL
  - Disease progression on last line of therapy and must have progressed on abiraterone, enzalutamide, or taxane chemotherapy
  - Subjects may continue GnRH agonists
  - Small cell prostate cancer is eligible

~~DLBCL and tFL: Availability of archival tissue, or willingness to undergo fresh biopsy for: confirmation of GCB-DLBCL status (DLBCL subjects); retrospective central testing of EZH2 mutation status (DLBCL, and tFL subjects). For all other tumor types: availability of either archival tissue or fresh biopsies.~~

4. For all subjects: Availability of archival tissue, or willingness to undergo fresh biopsy if archival tissue is not available, as described in Section 7.6.1.1, Section 7.6.1.2 and Section 7.6.5.
5. Must have a pre-existing central venous access such as a port, Hickmann catheter, or a peripherally inserted central catheter (PICC line) or be willing and able to have one inserted.
6. ECOG Performance Status of 0 or 1 (see Appendix 2).
7. Men with a female partner of childbearing potential must have either had a prior bilateral vasectomy with resultant azoospermia, bilateral orchiectomy, or must agree to use one of the contraception methods listed in Section 10.1 from the time of the first dose of study medication until at least 2 weeks (14 days) ~~3 months~~ after the last dose of study treatment due to the long elimination phase of study drug.~~for clearance of any altered sperm.~~
8. A female subject is eligible to participate if~~s~~ she is of:
   - Non-child bearing potential as defined in Section 10.1.1.
     i. ~~Women of childbearing potential must have a negative serum pregnancy test within 7 days of first dose of study treatment and agree to use effective contraception, as defined in Section 10.1, during the study and for at least two weeks (14 days) following the last dose of study treatment.~~
   - Child bearing potential as defined in Section 10.1.1 and agrees to use effective contraception, as defined in Section 10.1, for an appropriate period of time (as determined by the product label) prior to the start of dosing to sufficiently minimize the risk of pregnancy and for at least 2 weeks (14 days) following the last dose of study treatment. Women of childbearing potential must have a negative serum pregnancy test within 7 days of first dose of study treatment followed by negative urine or serum pregnancy test once every 4 weeks (prior to next dose cycle) thereafter.

9. Adequate organ system function as defined below:

System	LABORATORY VALUES
Hematologic	
ANC	≥1.2 x 10^9/L
Hemoglobin	≥9 g//dL
Platelets	≥75x 10^9/L
~~Platelets for Subjects with MM~~	~~≥ 50,000 (transfusion independent)~~
PT/INR and PTT	≤1.5 x ULN
Hepatic	
Albumin	≥2.5 g/dL
Total bilirubin	≤1.5 times ULN
AST and ALT	≤2.5 times ULN without liver metastases ≤5 times ULN if documented liver metastases
Renal	
~~Serum Creatinine~~ Calculate Creatinine Clearance[a, b] ~~OR 24 hr urine Creatinine Clearance~~	~~≤1.5 mg/dL~~ ~~or~~ ≥50 mL/min ~~≥50mL/min~~
Reproductive/Endocrine <u>for CRPC only</u>	
Testosterone	<50 ng/dL (only for subjects with CRPC)
Cardiac	
Left Ventricular Ejection Fraction (LVEF)	≥LLN (minimum of 50% LVEF) by ECHO or MUGA[c]

Abbreviation(s): ANC, absolute neutrophil count; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ECHO, echocardiogram; INR, international normalization ratio, MUGA, multigated (radionuclide) angiogram; PT, prothrombin time, PTT, partial thromboplastin time, ULN, upper limit of normal , LLN, lower limit of normal.

a. Calculated by Cockcroft-Gault formula
b. For MM subjects, adequate renal function is defined as ~~serum creatinine ≤ 2.5 mg/dL OR~~ <u>calculated</u> creatinine clearance ~~(either calculated or obtained via 24 hr urine collection)~~ ≥30 mL/min~~ECHO is the preferred method~~
c. ECHO is the preferred method <u>and should always be used if available.</u>

NOTE: Laboratory results obtained during Screening should be used to determine eligibility criteria. In situations where laboratory results are outside the permitted range, the investigator may opt to retest the subject and the subsequent within range screening result may be used to confirm eligibility. ~~Subjects requiring transfusions to meet eligibility criteria are not eligible.~~

Rationale for Change: Included the tumor type inclusion criteria for tFL and MM patients to be enrolled into Part 2 of the study.

Part 2: Inclusion Criteria

1. In addition to inclusion criteria listed for Part 1, Part 2 will enroll GCB-DLBCL, tFL and MM subjects only.
    a. Relapsed and/or refractory MM or tFL that have failed prior standard therapy and for which there is no standard salvage regimen

Rationale for Change:

- Clarified the exclusion of cancer therapies received prior to first dose.
- Added the exclusion of subjects with prior allogeneic transplant.
- To manage exposure to another investigational product, clarified the time period between use of another investigational product and first dose of study treatment.
- Concurrent use of therapeutic warfarin is allowed. Added in Section 9.2 additional monitoring for INR and bleeding. Clarified that anticoagulants that do not have reversal agents available are prohibited .
- Included exclusion for use of packed red blood cell or platelet transfusion within 7 days of screening laboratory tests to ensure that the subject has relatively stable bone marrow function and does not have any serious condition that would lead to dependency on frequent transfusions.
- To further clarify subject population, added criteria to exclude subjects with CNS involvement and other invasive malignancies.

Part 1 and 2: Exclusion Criteria

Subjects meeting any of the following criteria must not be enrolled in the study:

1. ~~Currently r~~Receiving any cancer therapy within 2 weeks of first dose (~~chemotherapy, radiation therapy, immunotherapy or biologic therapy~~including surgery, and/or tumor embolization) ~~(permitting corticosteroids to control systemic or local symptoms, up to a dose of 10 mg prednisolone or equivalent daily and stable for at least 7 days prior to enrollment).~~

    Note: the following are allowed:

    - Corticosteroids to control systemic or local symptoms, up to a dose of 10 mg prednisone or equivalent daily and stable for at least 7 days prior to enrolment.
    - Subjects with prostate cancer may remain on GnRH agonists. Other hormonal therapies (e.g., bicalutamide, abiraterone and enzlutimide) for prostate cancer must be stopped 4 weeks prior to enrolment

Note: the following are NOT allowed:

- Chemotherapy regimens with delayed toxicity within the last 3 weeks
- Nitrogen mustards, Melphalan, Monoclonal antibody or Nitrosourea within the last 6 weeks

- ~~Hormonal (e.g., anti-androgen) therapies for prostate cancer must be stopped 4 to 6 weeks prior to enrolment. Subjects with prostate cancer may remain on luteinizing hormone releasing hormone (LHRH) agonists. Subjects with prostate cancer may also remain on low-dose prednisone or prednisolone (up to 10 mg/day) and still be eligible for this study.~~

2. Any major surgery, radiotherapy or immunotherapy within the 4 weeks prior to first dose of study drug, or palliative radiotherapy to a single symptomatic lesion within the 2 weeks prior to first dose of study drugs.
3. Subjects with prior allogeneic transplant are excluded: however, subjects who have previously received an autologous stem cell transplant are allowed if a minimum of 100 days has elapsed from the time of transplant and the subject has recovered from transplant-associated toxicities prior to the first dose of GSK2816126

   - ~~Subjects who have previously received an autologousstem cell transplant are allowed if a minimum of 100 days has elapsed from the time of transplant and the subject has recovered from transplant-associated toxicities prior to the first dose of GSK2816126~~

4. Received an investigational anti-cancer drug within ~~4~~ 6 weeks, or within 5 half-lives (whichever is shorter) of the first dose of study drug. ~~At least~~ A minimum of 14 days must have passed between the last dose of prior investigational agent and the first dose of study drug.
5. Current use of a prohibited medication or expected to require any of these medications during treatment with study drugs (Section 9).
6. Known HIV, or serological evidence for Hepatitis B (positive HBsAg), or chronic Hepatitis C infection.

   - For s~~S~~ubjects who are negative for HBsAg, but HBcAb positive, a HBV DNA (viral load) test will be performed and if negative are eligible.~~positive will be excluded~~.
   - Subjects with positive Hepatitis C antibody serology with a~~but~~ negative HCV RNA test results are eligible.

7. Concurrent use of therapeutic warfarin is allowed. However, anticoagulants that do not have reversal agents available are prohibited (see Section 9.2). ~~Current use of therapeutic warfarin. Therapeutic dosing of warfarin is defined as resulting in an International Normalization Ratio (INR) low molecular weight heparin is permitted.~~
8. Unresolved toxicity greater than Grade 1 National Cancer Institute – Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4 from previous anti-cancer therapy, with the exception of alopecia and peripheral neuropathy [NCI-CTCAE, 2009].

- Lymphoma subjects with ≤Grade 3 lymphopenia can be enrolled at the discretion of the investigator

9. Packed red blood cell or platelet transfusion within 7 days of screening laboratory tests.
10. Psychological, familial, sociological or geographical conditions that do not permit compliance with the protocol.
11. Cardiac exclusion criteria:
    - History of acute coronary syndromes (including myocardial infarction and unstable angina), coronary angioplasty, or stenting within the past 6 months prior to first dose of study drug.
    - QTcF interval >450msec.
    - Uncontrolled arrhythmias. Subjects with rate controlled atrial fibrillation for >1 month prior to first dose of study drugs may be eligible.
    - Class II, III or IV heart failure as defined by the New York Heart Association (NYHA) functional classification system.
12. Known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to the study drug or their excipients.
13. Pregnant or lactating female.
14. Unwillingness or inability to follow the procedures outlined in the protocol.
15. Uncontrolled diabetes or other medical condition that may interfere with assessment of toxicity.
16. Central nervous system (CNS) metastases, with the following exception:
    - Subjects who have previously treated CNS metastases, are asymptomatic, and have no requirement for steroids at least 14 days prior to first dose of study drug.
    - Subjects with carcinomatous meningitis are excluded regardless of clinical stability.
17. Invasive malignancy or history of invasive malignancy other than disease under study, except as noted below:
    - Any other invasive malignancy from which the subject has been disease-free for more than 2 years and, in the opinion of the principal investigator and GSK Medical Monitor, will not affect the evaluation of the effects of this clinical trial treatment on currently targeted malignancy, can be included in this clinical trial.
    - Curatively treated non-melanoma skin cancer and any carcinoma-in-situ.

Rationale for Change: **STATISTICAL METHODS** - GCB-DLBCL cohort expansion was added into Part 1 dose escalation phase. The study design was based on predictive probability methodology (Liu, 2008) to allow interim futility/efficacy assessment by comparing the overall responses with the pre-specified futility and efficacy stopping criteria, in order to enabling early decision of opening Part 2 expansion phase or terminating the trial. Due to the improvement of response rates of cancer treatments over

time, the study designs in Part 2 expansion phase based on predictive probability method were revised by updating the null and alternative hypothesis, to align with the current typical response rates. The sample size and futility stopping criteria for each cohort (GCB-DLBCL mutant and wild type, tFL mutant and wild type, and MM) are updated

- **STUDY TREATMENT DOSAGE/DOSAGE FORM, ROUTE, AND DOSE REGIMEN**: Starting dose will be 50 mg, IV, twice weekly, with one 28 day cycle being defined as twice weekly dosing for three consecutive weeks and one week off. Dose escalations will be performed in Part 1 and dose adjustments are allowed to address tolerability and safety issues. Alternative schedules may be evaluated if emerging data suggest that twice weekly administration with 2 hour infusions will result in excessive toxicity. In addition, alternative dosing schedules may be considered if the safety, pharmacokinetic (PK), and pharmacodynamic (PD) data suggest that a sufficient therapeutic exposure cannot be achieved using the initial schedule and after a protocol amendment.
- **SAFETY ASSESSMENTS**: Routine physical examinations, vital sign measurements, echocardiograms, and monitoring of adverse events. Cardiac safety monitoring will be required, consisting of triplicate 12-lead electrocardiograms (ECGs) pre-infusion of drug, at the end of infusion of drug, one at night prior to going to sleep (*e.g.*, 10 pm) and one prior to discharge from the unit for Day 1, dose one only. The subject will not be discharged from the unit unless the QTc**F** is <500 msec. In addition, 24 hours of high fidelity 12-lead Holter monitoring will be performed for dose one. Tracings from this will be used for concentration QT analysis as well. Pre-infusion and end of infusion ECGs will be recorded for all other ECG timepoints. Laboratory testing includes at least hematology and clinical chemistry. Additional safety assessments may be necessary based on emerging data.

- **PHARMACOKINETIC/PHARMACODYNAMIC MEASUREMENTS:** There will be extensive serial blood sampling for PK and PD measurements in Part 1 of this study with limited blood sampling performed on all subjects in Part 2. Urine and bile may be collected in some subjects in the Part 2~~1~~ PK/PD expansion cohort. Single safety PK blood draws may be collected for subjects with severe adverse events or adverse events of concern. Mandatory collection of pre-treatment and post-treatment biopsies will be implemented in Part 2~~1~~ PK/PD cohorts. ~~based on outcome of preliminary PD data in surrogate tissue (e.g. Peripheral blood mononuclear cells (PBMCs) from blood).~~

- **TRANSLATIONAL RESEARCH:** Translational or biomarker research may be performed on archival tissue, tumor biopsies and blood samples collected on study, to better understand DLBCL, transformed FL, and the mechanism of action ~~of~~ and response to GSK2816126. Performance of these investigations may be conditional on the results of the clinical trial principally, but not exclusively, on the primary measures of the clinical trial outcome and samples may be selected for analysis on the basis of the clinical outcome. Unless stated otherwise, these investigations may be performed irrespective of whether a response to GSK2816126 is observed and will be categorized as exploratory. Findings may be reported independently of any final clinical study report. .

- **STATISTICAL METHODS**: Subject demographic and safety data will be collected on electronic case report forms (eCRFs). All data will be pooled and descriptive safety analyses summarized and listed by cohort at study conclusion.
  - Part 1 in GCB-DLBCL subjects is designed to evaluate preliminary efficacy at the MTD/RP2D or other dose level. Futility and efficacy assessments will be conducted after 13 GCB-DLBCL subjects are enrolled, using overall response rate (ORR) as the efficacy endpoint, until up to 27 subjects are enrolled. The design allows interim analysis (IA) of futility and efficacy to be performed at any point in between. The futility and efficacy stopping rules are defined based on pre-specified type I error rate and power of the hypothesis testing of ORR. If the thresholds for futility are met, enrollment to Part 1 cohort/s may be stopped based upon the evaluation of the totality of the data. If the efficacy thresholds are reached, and the totality of the data support opening Part 2, then Part 2 will start. If neither futility nor efficacy thresholds are met at an interim analysis, and the totality of the data does not support continuation of the trial, then Part 1 may be stopped.

    For the cohort expansion of solid tumor subjects in Part 1, there is no formal statistical hypothesis testing. Analysis of the data obtained from the solid tumor expansion cohort will only utilize descriptive methods.
- Part 2 expansion phase of the study is designed to investigate clinical activity of GCB-DLBCL and tFL patients with EZH2 mutant and wild type, and MM patients, using ORR as the primary endpoint. Secondary endpoints such as PFS, TTR, TTP, DOR and OS will be evaluated. In Part 2, for patients with GCB-DLBCL and tFL, futility assessment will be conducted on an ongoing basis after data are available from the first 10 subjects and until up to 32 patients. For patients with MM, futility assessment will be conducted on an ongoing basis after data are available from the first 14 subjects and until up to 40 subjects.

- ~~A futilityassessment will be conducted after data are available from the first 12 subjects in Part 2 and after that until up to 30 GCB-DLBCL subjects and 16 tFL subjects have been enrolled in each of the EZH2 WT and EZH2 mutant cohorts. Also, in the MM cohort a futility assessment will be conducted after data are available from the first 13 subjects in Part 2 and after that until up to 37 subjects.~~

Section 1.2.2 Pre-Clinical Pharmacology & Safety of GSK2816126

Rationale for Change:

Nonclinical Pharmacology - Added clarification of treatment options for possible infusion reactions. Updated to be in line with changes throughtout the protocol. Included updated data and guidance for human subjects based on preclinical data from ongoing phototoxicity testing. Updated to be in line with Risk Section of the protocol.

REVISED TEXT

Nonclinical Pharmacology: Human subjects will be monitored during the infusion for evidence of histamine release related symptoms/infusion reactions and treated as needed with supportive care per local standard of care. (e.g., corticosteroids, oxygen, epinephrine, diuretics, IV fluid~~with anti-histamines~~). . ~~Subsequent subjects may be treated prophylactically with antihistamine and/or by lengthening the infusion duration. .~~ The infusion duration can be lengthened with restart of the infusion or at the next infusion. Premedications (antihistamines or similar) may be provided at the next infusion or prior to treatment of new subjects.

In dogs, a mild, reversible dose dependent decrease in minute (up to 128 mL/min/kg; 49%) and tidal volume (8 mL/kg; 56%) at 100 mg/kg and an elevation in QTc interval at 30 (maximum increase of 12 msec or 5%) and 100 (maximum increase of 18 msec or 8%) mg/kg were observed following the end of a single 8 hour infusion. These effects did not directly correlate with peak GSK2816126 blood levels as the onset was 4-7 hours following the end of the infusion. QTc interval elevations were not observed following repeat dosing.

A direct effect on human ether à go-go-related gene (hERG) channel repolarization is unlikely (IC_{25} of 54.2 µM; 28.61 µg/mL), however, GSK2816126 did block hERG current density in vitro consistent with an effect on hERG channel trafficking. The mechanism for this change is unclear. Evaluation of the QTc interval has been incorporated into this clinical study protocol.

GSK2816126 has evidence of absorbance within the 290-700 nm wavelength range of concern for photosafety. While GSK2816126A has no absorbance peaks (λmax) > than 290 nm, there is an absorbance peak at 285 nm with a small tail of absorbance that extends to ~380 nm and therefore, has a potential risk for phototoxicity. To date, no *in vivo* phototoxicity or Bio-distribution studies of the product in the skin or the eyes have been completed. No photosafety concerns have been observed in humans at doses up to 3000 mg/day, however, only a limited number of patients have received GSK2816126.

To minimize the risk for potential phototoxicity, human subjects will be instructed to minimize or avoid prolonged exposure to natural or artificial sunlight (e.g., tanning beds, sunlamps, UVA or UVB treatments) and wear loose fitting clothing with long sleeves, sunglasses, and broad rim hat that protect the skin from sun exposure AND use a broad spectrum sunscreen (e.g., UVA and UVB protective with minimum SPF 30) on any uncovered areas of the body if outdoors from the time of first dose of study medication until at least 2 weeks (14 days) following last dose of study medication due to long elimination phase.

Section 1.3 Benefit/Risk Assessment

Rationale for Change: Updated text based on new preclinical and human data, as well as, to to be in line with changes throughtout the protocol.

REVISED TEXT

Summaries of findings from ~~pre-~~nonclinical studies conducted with GSK2816126 can be found in Section 1.2.2 of the protocol and the Investigator's Brochure (IB) [GlaxoSmithKline Document Number 2013N16904_04, 2017~~2013N169204_00, 2013~~]. ~~GSK2816126 has not yet been administered to human subjects and~~ Ttoxicology studies performed in dogs and rats suggest that the primary toxicities of GSK2816126 are cardiovascular, hemolytic and allergic (see Section ~~4~~3, GSK2816126 IB [GlaxoSmithKline Document Number 2013N16904_04, 2017~~, 2013N169204_00, 2013)~~].

This section outlines the risk assessment and mitigation strategy for this protocol based on nonclinical and clinical findings. Additional information on clinical findings can be found in Section 1.3.1 of the protocol and Section 5 and Section 6 of the Investigator's Brochure [GlaxoSmithKline Document Number 2013N16904_04, 2017].

Section 1.3.1 Risk Assessment

Rationale for Change:

Cardiovascular – QT prolongation- Based on review of QTc data from the study with the GSK co-chairs of the QT panel and Global Safety Board, it was agreed that the restriction on the administration of drugs possibly associated with Torsade de Pointes could be relaxed and will be included as medications to be used with caution (Table 14). Additional ECG assessments will be recommended when these medications are initiated after Cycle 1. Exclusion and withdrawal criteria for cardiac monitoring will remain as stated in the protocol (e.g., patients with a QTc > 450 msec are excluded from entry and patients > 500 msec will be withdrawn as dictated by the protocol).

Histamine Reaction/InfusionReaction – Added that this risk/mitigation includes infusion reactions/histamine reactions and that mitgaton strategy that should be used per local standard of care. Updates made in line with changes through the protocol.

Drug Interactions – Included most recent DDI data.

Phototoxicity – Included updated data and guidance for human subjects based on preclinical data from ongoing phototoxicity testing. Updated to be in line Section 1.2.2 of the protocol.

Hepatic Toxicity – Nonclinical and current clinical data, possible risks and mitigation strategy added for possible increased liver function tests/ALT.

REVISED TEXT

Potential Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy
Cardiovascular – QT prolongation	**QTc prolongation** was observed (up to 8%; 18 msec in dog) following the end of a single 8 hour infusion Effect did not directly correlate with peak GSK2816126 blood levels; onset was 4-7 hours following the end of the infusion; reversed within 3-8 hours following onset Effects not observed following repeat dosing in dogs No arrhythmias were detected in preclinical studies The mechanism for the QTc prolongation is unlikely due to a direct effect on hERG repolarization as GSK2816126 weekly inhibited hERG tail current (IC25 of 54.2 µM; 28.61 µg/mL). However, GSK2816126 was shown to block hERG current density in vitro consistent with an effect on hERG channel traffickin	Protocol includes cardiovascular eligibility criteria, laboratory assessments (potassium and magnesium), cardiac monitoring (electrocardiograms [ECGs], Holter monitoring during the study, and dose stopping/modification criteria for the management of QT prolongation) Co-administration of medications that are known to prolong the QT interval and have a risk of causing Torsades de Pointes (TdP) are prohibited. ~~and d~~Drugs that have a possible risk of TdP~~Torsades de Pointes are prohibited~~will be used with caution and additional ECG monitoring required. All subjects will remain in the clinical research unit (CRU) after receiving their first dose of study medication (Week 1, Day 1) with periodic ECGs and Holter monitoring for 24 hours. Subjects will not be discharged from the unit unless their last

Potential Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy
		measured QTc on an ECG performed immediately prior to discharge after the first dose is <500 msec. Timings for in-house on-drug ECGs are pre-infusion, at the end of infusion, before bed, and before discharge the next morning for Day 1 of cycle 1 only. Refer to Section 7.1 (T&E) for other ECG timings
Local Infusion Site Reaction	**Vascular/perivascular inflammation and necrosis** (in rats at all dose levels, including controls, and in dogs given ≥100 mg/kg) Dose-limiting vascular damage (necrosis, inflammation, edema and/or hemorrhage) at the local infusion and/or indwelling catheter sites was observed in rats and dogs following twice weekly IV infusions of GSK2816126 (vehicle containing 5% Captisol) (6 to 16 hours) for 2 to 4 weeks Inflammation at the infusion site led to secondary histopathologic changes in multiple peritoneal and retroperitoneal tissues/organs and clinical pathology findings; morbidity/mortality observed in rats (≥30 mg/kg; Cmax ≥2.97 μg/mL; AUC0-24h ≥23.5 μg.h/mL) and dogs (≥100 mg/kg; Cmax=9.88 μg/mL and AUC0-24h=80.1 μg.h/mL) was attributable to vascular or extravascular irritant (vesicant) effects of GSK2816126 and prolonged intravenous catheterization Infusion site and secondary histopathologic findings were partially reversible and secondary clinical pathology effects were reversible	Subjects will be dosed via a central venous access device with a formulation including 10% Captisol Subjects will be monitored closely for infusion site reactions (during infusion and for one hour post infusion) and if reaction occurs, infusion will be interrupted and the appropriate clinical intervention commenced. See Management of Infusion Site Reaction (Section 3.8.2) Laboratories will be monitored as well, including liver function tests (LFTs), other chemistries, and hematology

Potential Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy
Histamine Reaction/InfusionReaction	**Acute histamine-like reactions seen in rats and dogs** which began within minutes of dosing were observed at ≥300 mg/kg in dogs (C_{max} 66.5 to 130 µg/mL) and 300 mg/kg (C_{max} 33.9 to 54.2 µg/mL) in rats. In dogs, histamine reactions resulted in discontinuation of dosing. In rats, histamine-related decreased body temperature, along with increased HR and decreased BP likely led to mortality in restrained, but not in unrestrained animals	Subjects will be monitored during the infusion for evidence of ~~histamine release related symptoms~~ histamine release related symptoms/infusion reactions and treated as needed with ~~anti-histamines and~~supportive care per local standard of care (e.g., corticosteroids, oxygen, epinephrine, diuretics, IV fluid).~~Severe cases will also be treated with corticosteroids. . Subsequent subjects treated at that dose or higher doses will be treated prophylactically with anti-histamines. If necessary based on emerging clinical data, t~~The infusion duration can be lengthened with restart of the infusion or at the next infusion. Premedications (antihistamines or similar) may be provided at the next infusion or prior to treatment of new subjects.
Drug Interactions	~~No *in vivo* drug-drug interaction studies have been performed. Based on in vitro data, GSK2816126 has a potential to inhibit cytochrome P450 (CYP) 2C8, 2C9, 2C19 and 3A4 enzymes and to induce CYP3A enzymes. In addition, *in vitro* data suggests that GSK2816126 is a substrate for CYP3A enzymes and for P-gp, BCRP, and may be a substrate for OAT **transporters**~~. No in vivo drug-drug interaction (DDI) studies have been performed. GSK2816126 is metabolized by CYP3A enzymes in vitro. GSK2816126 has also been shown to be a substrate of P-gp and BCRP transporters. Therefore, substances that potently inhibit or	The potential for drug-drug interactions will be monitored in clinical trials and some concomitant medications are prohibited or to be used with caution (see Section 9).

Potential Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy
	induce CYP3A, P-gp or BCRP could lead to higher/lower exposure in subjects, potentially leading to alterations of the pharmacologic effects of GSK2816126. On the other hand, GSK2816126 was shown to inhibit CYP2C8, CYP2C9, CYP2C19 and CYP3A4 with IC_{50} values <5 μM. GSK2816126 activate human PXR (EC_{50} = 10 μM) and, therefore, may have the potential to induce CYP enzymes. A further in vitro study in cultured human hepatocytes (n=3 donors) showed induction of CYP3A4 mRNA with a calculated EC_{50} of 4.22-5.43 μM and E_{max} of 3.22-16.5-fold. In vitro studies demonstrated that GSK2816126 (up to 100 μM) has the potential to inhibit human transporters BCRP, OATP1B1, OATP1B3, OCT2, MATE1 and MATE2-K (IC_{50} values of 21, 13, 34, 2.88, 0.025 and 0.95 μM, respectively), however, GSK2816126 did not inhibit P-gp (up to 100 μM) or OAT1 and OAT3 (up to 25 μM). Based upon the current average clinical C_{max} of 58 μM (30.6 μg/mL) at 3000 mg dose, mathematical model simulations suggest that GSK2816126 has the potential to perpetrate a clinical DDI when co-administered with sensitive substrates of transporters OATP1B1, BCRP, OCT2, MATE1 and MATE2-K upon inhibition, and CYP2C8, 2C9, 2C19 upon inhibition, and CYP3A4 upon inhibition or induction.	

Potential Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy
Phototoxicity	GSK2816126 has recently been demonstrated to be phototoxic in an in vitro assay for phototoxicity (3T3 Neutral Red Uptake Phototoxicity Test). To date, no photosafety concerns have been observed in humans at doses up to 3000 mg/day, however, only a limited number of patients have received GSK2816126.	Subjects will be instructed to minimize or avoid prolonged exposure to natural or artificial sunlight (e.g., tanning beds, sunlamps, UVA or UVB treatments) and wear loose fitting clothing with long sleeves, sunglasses, and broad rim hat that protect the skin from sun exposure AND use a broad spectrum sunscreen (e.g., UVA and UVB protective with minimum SPF 30) on any uncovered areas of the body if outdoors from the time of first dose of study medication until at least 2 weeks (14 days) following last dose of study medication due to long elimination phase.
Hepatic Toxicity	In first in human study EZH117208 (present study), an increase in level of ALT has been noted in the group of subjects receiving doses of 1800 mg to 3000 mg (single infusion dose) None of these ALT increases have been associated with increase in total bilirubin or INR and all have shown improvement following either withholding or discontinuing GSK2816126. The 3000 mg dose has been declared to exceed the MTD. The highest dose being explored in this study is 2400 mg . In nonclinical species given GSK2816126, twice weekly for 2 and/or 4 weeks, changes in liver pathology (inflammation, hyperplasia) in dogs and clinical chemistry parameters (i.e. increases in ALT, AST, ALP, bilirubin and decreases in albumin) in rats and dogs were observed and were	Dosing at 3000 mg has been discontinued, with the highest dose being explored is at 2400 mg. Continued laboratory and clinical moniotoring for liver dysfunction (LFT, coagulation parameters INR/PTT, other blood chemistry, clinical observation for jaundice). Dose management and stopping criteria as per guidelines for non-hematologic toxicity (Section 3.8.3 and Table 4) and hepatic safety monitoring (Section 8.3.1)

Potential Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy
	consistent with systemic inflammation. These effects were considered secondary to vascular damage at the infusion and/or surgical site and attributable to vascular or extravascular irritant (vesicant) effects of GSK2816126 and prolonged intravenous catheterization. No current evidence suggests the presence of reactive metabolites. No glutathione conjugates were identified in the *in vitro, ex vivo* studies that were conducted. GSK2816126 is not a CYP metabolism-dependent inhibitor. Based on in vivo dosing to rats twice weekly for 2 weeks at doses up to 300 mg/kg, no evidence of induction of PXR panel genes was noted. This is in agreement with the observation that GSK2816126 is not a rat PXR activator. It is however a human PXR activator, and an in vitro inducer of CYP3A4 in human hepatocytes, suggesting species differences between rat and human. GSK2816126 is an in vitro inhibitor against hepatic transporters OATP1B1, OATP1B3 and BCRP with a moderate in vitro potency (IC_{50}: 13-34 µM). With the high clinic concentration, a potential risk for inhibiting hepatobiliary excretion of substrates of these transporters cannot be excluded.	

Section 1.3.3 Overall Benefit: Risk Conclusion

Rationale for Change: Included mention of clinical data generated from the GSK2816126 study.

REVISED TEXT

Current data from GSK2816126 clinical study and ~~pre~~nonclinical development indicate a potential for clinical utility in the treatment of subjects with relapsed and/or refractory DLBCL and/or transformed FL, NHL, multiple myeloma, and other solid tumors. Considering the overall poor outlook of these subjects on failing prior therapy and recognizing the measures taken to minimise risk to subjects participating in the Phase I clinical trials, the potential risks identified in association with GSK2816126 are justified by the anticipated benefits that may be afforded to subjects with the previously mentioned tumor types that have been shown in non~~pre~~clinical models to respond to GSK2816126.

Section 1.4.1 Contraindications, Warnings and Precautions

Rationale for Change: Updated section in line with Section 1.2.2 and Section 1.3.1.

REVISED TEXT

Contraindications:

Any known hypersensitivity to agents structurally similar to GSK2816126 or the constituents of the vehicle would contraindicate GSK2816126 use.

Precautions: ~~Until clinical safety information for GSK2816126 is available,~~ ECG monitoring for evidence of QTc prolongation must be conducted. Co-administration of medications that are known to prolong the QT interval and have a risk of causing ~~Torsades de Pointes~~(TdP~~)~~ are to be avoided beginning 14 days prior to the first dose of study drug or longer if necessary, as determined by the primary investigator or medical monitor until discontinuation from the study. Co-administration of medications that are known to prolong the QT interval and have a possible risk of causing TdP are to be used with caution. Subjects will be instructed to minimize or avoid prolonged exposure to natural or artificial sunlight (e.g., tanning beds, sunlamps, UVA or UVB treatments) and wear loose fitting clothing with long sleeves, sunglasses, and broad rim hat that protect the skin from sun exposure AND use a broad spectrum sunscreen (e.g., UVA and UVB protective with minimum SPF 30) on any uncovered areas of the body if outdoors from the time of first dose of study medication until at least 2 weeks (14 days) following last dose of study medication due to long elimination phase.

Section 2.1 Part 1: Phase I Dose Escalation

Rationale for Change – See rationale for change to Part 1 and Part 2 objectives and endpoints under Synopsis.

REVISED TEXT

	Part 1 Objectives	Part 1 Endpoints
Secondary	• 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 (Cτ), maximum observed concentration (Cmax), time of occurrence of Cmax (tmax), terminal phase half-life (t1/2), 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~~ PD response assessed by change from baseline in tri-methylation of Histone H3K27 (H3K27me3)
	• To determine clinical activity of GSK2816126 in GCB DLBCL and solid tumors containing EZH2 inhibitor sensitizing mutations or prostate cancer	• Best Overall Response rate (complete response [CR] + partial response [PR])
	•	
	~~• Evaluate the relationship between GSK2816126 exposure markers and safety/efficacy/PD responses~~	~~• Samples to characterize the metabolites in blood, bile and/or urine~~
	~~• 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)~~	~~• 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~~
	~~• To determine the amount of GSK2816126 excreted in urine after dosing at steady state~~	

Part 1 Objectives		Part 1 Endpoints
Exploratory	• To confirm tumor EZH2 and GCB-DLBCL status • ~~To investigate the mechanism of action and additional indicators of sensitivity and resistance to~~ of GSK2816126 • To identify biomarkers predictive of response or resistance to GSK2816126 • ~~To generate samples (data reported separately) with which to investigate the potential for GSK2816126 to affect cytochrome P450 (CYP) 3A4 enzyme activity~~	• IHCfor confirmation of GCB-DLBCL status • PCR or NGS to determine EZH2 mutation status • Evaluate transcriptional and/or protein changes upon GSK2816126 treatment • Correlate baseline tumor genomic (DNA), protein and/or transcription (RNA) profiles with response • ~~Tumor baseline genetic profiles, response~~ • ~~Samples to assess a potential change in 4b-OH cholesterol to cholesterol ratio in plasma following repeat dosing of GSK2816126 (data reported separately)~~
Hypothesis	~~No formal statistical hypotheses are being tested in Part 1: Phase I dose escalation. Analysis of the data obtained from Part 1 will only utilize descriptive methods~~ 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 utilize descriptive methods only. The cohort expansion of GCB-DLBCL patients in Part 1 will assess the overall response rate (p) of GCB-DLBCL patients. The null and alternative hypotheses for the overall response rate are detailed below: The null hypothesis is: H_0: p≤20% The alternative hypothesis is: H_A: p≥40%		

Part 1 Objectives	Part 1 Endpoints
	For cohort expansion of solid tumor subjects in Part 1, there is no formal statistical hypothesis being tested. Analysis of the data obtained from solid tumor expansion cohort will utilize descriptive methods only.

Section 2.2 Part 2: Expansion

	Part 2 Objectives	Part 2 Endpoints
Primary	• 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~~Overall response rate (% of subjects achieving CR and PR per response criteria)
Secondary	• 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 GSK2816126 exposure and PD parameters	• GSK2816126 exposure markers (dose, concentration, Cmax or AUC) and PD responses. PD response assessed by change from baseline in tri-methylation of Histone H3K27 (H3K27me3)
	• 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

	Part 2 Objectives	Part 2 Endpoints
		urine volume
	• 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)
	• 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	• 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~~	• Correlate baseline tumor genomic (DNA), protein and/or transcription (RNA) profiles with response
	• To investigate the relationship between genetic variants in candidate genes and the pharmacokinetics (PK) and safety profile of GSK2816126 based on Part 1 and 2 data combined	• Evaluate transcriptional and/or protein changes upon GSK2816126 treatment • ~~Deoxyribonucleic acid (DNA), ribonucleic acid (RNA) and protein markers in tumor and blood~~ • Pharmacogenomic (PGx) analysis of whole blood

	Part 2 Objectives	Part 2 Endpoints
Hypothesis	In Part 2, the overall response rate (p) of GCB-DLBCL and tFL patients will be assessed for each EZH2 mutation status cohort (wild type and mutant), and also for MM patients. • For each of the GCB-DLBCL and tFL cohort, the null and alternative hypotheses of the overall response rate are as following: The null hypothesis is: H_0: p≤20% The alternative hypothesis is: H_A: p≥40% • For MM cohort: The null hypothesis is: H_0: p≤10% The alternative hypothesis is: H_A: p≥25% ~~The primary objective of Part 2 is to determine whether administration of GSK2816126 has a potentially clinically meaningful response rate.~~ • ~~In subjects with GCB-DLBCL, this will be determined in each EZH2 mutation status cohort (wild type and mutant) by testing the null hypothesis that the response rate is ≤10%, with about 90% power when the true response rate is 30%.~~ • ~~In subjects with tFL, this will be determined in each EZH2 mutation status cohort by testing the null hypothesis that the response rate is ≤5%, with about 80% power when the true response rate is 25%.~~ • ~~In subjects with MM, this will be determined by testing the null hypothesis that the response rate is ≤5%, with about 85% power when the true response rate is 20%.~~	

Section 3.1 Study Schematic

Rationale for Change: Upated study schematic to include Part 1 expansion cohort.

REVISED TEXT

Part 1
Accelerated Dose Titration followed by 3+3 Dose Escalation

To determine the safety and tolerability of GSK2816126 in subjects with relapsed/refractory DLBCL, transformed FL, other NHLs, solid tumors and MM

Part 1 will include a cohort expansion at MTD or any dose level to enroll subjects with GCB-DLBCL and solid tumors with EZH2 inhibitor sensitizing mutations or prostate cancer

↓

Section 3.2 Discussion of Study Design

Rationale for Change – Updated to include expansion of any dose level during dose escalation to 12 subjects. At MTD, included Part 1 expansion cohort/analysis plan to include approximately 27 GCB-DLBCL subjects and approximately 15 subjects with solid tumors containing EZH2-sensitive mutations or prostate cancer to explore additional safety and preliminary efficacy. Updated in line with updates made through the protocol.

REVISED TEXT

After the accelerated dose titration, subjects will be enrolled in a standard 3+3 dose escalation design. Dose escalation will continue until a recommended Phase 2 dose (RP2D) is determined or until a maximum tolerated dose (MTD) or a dose of 3000 mg twice-weekly is reached ~~[Maximum Feasible Dose (MFD)]. After the RP2D (or MTD/MFD) has been determined in Part1, then~~. Any dose level during Part 1 dose escalation may be expanded up to 12 subjects to explore safety and preliminary efficacy. At MTD/RP2D the cohort may be expanded to enroll approximately 27 GCB-DLBCL subjects and approximately 15 subjects with solid tumors containing EZH2-sensitive mutations or prostate cancer to explore additional safety and preliminary efficacy. Based on results of the Part 1 analysis in totality, Part 2 expansion cohorts may ~~will~~ be opened~~.~~ ~~In Part 2,~~ and subjects ~~with~~ will be assigned to ~~one of four~~ cohorts based on disease and EZH2 mutation status.

Safety assessments will be performed weekly for the first 4 weeks and then at regular intervals as outlined in the Time and Events Table (Section 7.1).

Disease response in lymphoma and solid tumor subjects will be assessed as described in the T&E table (Section 7.1).

Futility and Efficacy analysis will be performed on GCB-DLBCL subjects enrolled at the MTD/RP2D in cohort expansion of Part 1 as listed in Section 12.2.1.2.

Section 3.3.2 3+3 Dose Escalation Phase

Rationale for Change: Added definition of evaluable subject during dose escalation andmoved text for PK/PD cohort to Part 2 of the study.

REVISED TEXT

An evaluable subject in Table 2 is defined as a subject who has been on study for at least 28 days (one cycle). Evaluation of safety data from at least 1 subject during the accelerated dose titration or at least 3 subjects in the standard dose titration who have completed 28 days of dosing on study (one cycle) is required prior to defining a new dose and starting the next cohort. Once a higher dose has been cleared, subjects at lower dose levels who remain on study drug and have not experienced dose limiting toxicity will be allowed to escalate up to that level.

Reverting from 3+3 Dose Escalation to Accelerated Dose Titration: Once Grade 2 toxicity is seen in one subject, there are 2 scenarios where the accelerated dose escalation may be resumed.

1) If two additional subjects are added at the dose where Grade 2 toxicity was seen in the initial subject and if no Grade 2 or higher toxicity is seen in either of the 2 new subjects, the accelerated dose escalation may be resumed, or
2) If the 3+3 method is used and, at the next higher dose, the 3 subjects do not have a grade 2 or higher toxicity, the accelerated dose escalation may be resumed. (Before any decision is made to reinitiate accelerated dose titration a discussion between the investigators and the GSK medical monitor is required)

~~**Part 1 PK/PD cohorts:** Any dose level may be expanded up to 12 subjects in order to collect adequate data on safety, pharmacokinetics, or pharmacodynamics. Urine, bile, and additional blood samples may be collected following repeated administration for drug metabolite profiling and to obtain information on renal excretion of GSK2816126. Initially, optional pre- and post-treatment tumor biopsies will be requested. At MTD, mandatory collection of pre- and post-treatment tumor biopsies will be required for enrollment in a PK/PD cohort. Mandatory biopsies may be instituted at lower dose levels once evidence of target engagement has been demonstrated in surrogate tissue (e.g. H3K27me3 from PBMCs in blood); or if sufficient evidence of target engagement (e.g. dose dependence) is not observed in PD assay from surrogate tissue. Additional 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 data. These subjects may have the dose escalated to a higher completed dose level (not exceeding the MTD) once the necessary PK/PD procedures have been completed.~~

Section 3.3.5 Intra-subject Dose Escalation

Rationale for Change: Included additional text to clarify PK/PD and safety assessments for subjects who are approved for intra-subject dose escalation

REVISED TEXT

Decision on intra-subject dose escalation will be made after review of all safety data and approval by a GSK Medical Monitor and discussion with the investigator. In this case, the subject may begin dosing at the higher dose level as it will have already been demonstrated to be tolerable and monitoring will be performed as described in the protocol. Subjects approved for intra-subject dose escalation may require additional limited PK and/or PD sampling as determined by GSK Clinical Pharmacology. Additional safety assessments may be specified at the time of the dose escalation or schedule modification based on the safety profile in previous subjects at the higher dose level.

Section 3.3.7 Part 1: Futility and Efficacy Analysis for GCB-DLBCL Subjects

Rationale for Change: Text added to Section 3.3.7 and Section 3.4 include the patient populations to be enrolled in Part 1 expansion cohort and Part 2 and the statistical analysis that will be performed. GCB-DLBCL cohort expansion was added into Part 1 dose escalation phase. The study design was based on predictive probability methodology (Lee, 2008) to allow interim futility/efficacy assessment by comparing the overall responses with the pre-specified futility and efficacy stopping criteria, in order to enabling early decision of opening Part 2 expansion phase or terminating the trial. Additional details were moved to Section 12, Data Analysis and Statistical Considerations, of the protocol.

REVISED TEXT

There will be a GCB-DLBCL expansion cohort enrolled after the completion of dose escalation in Part 1. For the GCB-DLBCL expansion cohort in Part 1, futility and efficacy evaluation of overall response data will be performed in order to support the early decision regarding opening Part 2 dose expansion. The methodology is based on the Bayesian predictive probability of success if enrollment continues until all planned subjects are recruited [Lee, 2008]. Details of the predictive probability methodology, futility and efficacy evaluation are explained in Section 12.2.1.2. In summary, a minimum of 13 and maximum of 27 GCB-DLBCL patients will be enrolled. Once 13 GCB-DLBCL patients at MTD/RP2D have been enrolled (including patients in dose escalation phase) and have completed response assessments of safety and efficacy, response data will be reviewed on an ongoing basis for evidence of futility or efficacy.

For futility/efficacy analysis, subjects evaluable for response assessment will be defined by any or all of the following criteria:

- Subjects who have at least two post-baseline radiological disease assessments and have been on study for at least 28 days (one cycle.)

- Subjects who have progressed or have died or have withdrawn for study treatment due to any reason.

Interim analysis (IA) of futility and efficacy can be conducted at any time after 13 GCB-DLBCL subjects have enrolled and are evaluable for response assessment. If the thresholds for futility are met, the Part 1 expansion cohort may be stopped based upon the evaluation of the totality of the data. If the efficacy thresholds are reached, then Part 2 expansion may be opened. If neither futility nor efficacy thresholds are met at any interim analysis, and the totality of the data does not support continuation of the trial, then the trial may be terminated. All available data will be considered in making decision of termination or continuation of the trial.

Section 3.4 Part 2: Expansion Cohorts

Rationale for Change: Due to the improvement of response rates of cancer treatments over time, the study designs in Part 2 expansion phase based on predictive probability method were revised by updating the null and alternative hypothesis, to align with the current typical response rates. The sample size and futility stopping criteria for each cohort (GCB-DLBCL mutant and wild type, tFL mutant and wild type, and MM) are updated. Additional details were moved to Section 12, Data Analysis and Statistical Considerations, of the protocol.

REVISED TEXT

Part 2: Expansion Cohorts in both wild type and EZH2 mutation-positive GCB-DLBCL and tFL subjects, and subjects with MM

The primary objective of Part 2 is to investigate whether administration of GSK2816126 at the RP2D has a potentially clinically meaningful activity for more tumor types, if notable response rate is observed in Part 1 expansion cohort of GCB-DLBCL patients. Expansion cohorts will be enrolled in Part 2, including GCB-DLBCL and tFL patients with mutant and wild type EZH2 and patients with MM. Similar to Part 1 expansion design, Part 2 expansion design is planned based on predictive probability methodology. Rather than early stop for either futility or efficacy, Part 2 allows early stop for futility only. For each expansion cohort of GCB-DLBCL and tFL patients, a minimum of 10 and maximum of 32 patients will be enrolled at the RP2D. For MM cohort, a minimum of 14 and maximum of 40 patients will be enrolled at the RP2D. Interim analysis of response data will start from minimum number of patients enrolled and at any time thereafter. Details of Part 2 designs and stopping criteria are elaborated in Section 12.2. All available data will be considered in making decision of termination or continuation of the trial.

It is noted that patients with GCB-DLBCL, tFL and MM enrolled at MTD/RP2D in the previous stages of the trial (dose escalation and cohort expansion in Part 1) will be included for the Part 2 analysis.

~~Lymphoma subjects will be enrolled based on EZH2 mutation status. There will be up to 30 subjects per group in both GCB-DLBCL cohorts, up to 16 subjects per group in both tFL cohort s, and up to 37 subjects with MM. Multiple myeloma subjects will be selected independent of their EZH2 mutation status.~~

~~Further evaluation of futility:~~

~~The methodology is based on the predictive probability of success if enrollment continues until all planned subjects are recruited [Lee, 2008]. The predictive probability design is similar to a Green-Dahlberg design in that it allows for early stopping for futility. The differences are that the predictive probability design allows for evaluation of stopping rules after each subject, rather than at only two stages, once a minimum number of subjects are evaluable. In this particular study, we will stop only for futility. While the two designs have similar type I and type II error rates, the probability of early termination is greater with the predictive probability design.~~

~~In both GCB-DLBCL mutation status cohorts, after, 12 subjects have been enrolled in each cohort to examine safety and efficacy, the number of observed confirmed responses will guide further enrollment according to the rules summarized in Figure1..A maximum of 30 subjects per cohort will be enrolled at the RP2D. All available data will be considered in making enrollment decisions.~~

~~Figure 1 Diagram of Stopping Rules for GCB-DLBCL Cohort Expansion: GSK2816126~~

	~~Number of Responses~~						
~~Number of Subjects~~	**~~0~~**	**~~1~~**	**~~2~~**	**~~3~~**	**~~4~~**	**~~5~~**	**~~≥6~~**
~~12~~							
~~13~~							
~~14~~							
~~15~~							
~~16~~							
~~17~~							
~~18~~							
~~19~~							
~~20~~							
~~21~~							
~~22~~							
~~23~~							
~~24~~							
~~25~~							
~~26~~							
~~27~~							
~~28~~							
~~29~~							
~~30~~							

Figure 1Legend: The shaded regions are the specific regions for stopping the study for futility. For instance, if there is only one response in fourteen subjects, then the predictive probability for success will be 5.0% or less (the futility criterion) and the study may be stopped.

In both tFL mutation status cohorts, after 12 subjects have been enrolled to examine safety and efficacy, the number of observed confirmed responses will guide further enrolment according to the rules summarized in Figure 2. A maximum of 16 subjects will be enrolled at the RP2D. All available data will be considered in making enrollment decisions.

Figure 2 Diagram of Stopping Rules for tFL Cohort Expansion: GSK2816126

	Number of Responses			
Number of Subjects	**0**	**1**	**2**	**≥3**
12				
13				
14				
15				
16				

Figure2 Legend: The shaded regions are the specific regions for stopping the study for futility. For instance, if there is no response in twelve subjects, then the predictive probability for success will be 1% or less (the futility criterion) and the study may be stopped.

For the MM cohort: After 13 subjects have been enrolled to examine safety and efficacy, the number of observed confirmed responses will guide further enrollment according to the rules summarized in Figure 3 . A maximum of 37 subjects will be enrolled at the RP2D. All available data will be considered in making enrollment decisions.

Figure 3 Diagram of Stopping Rules for MM Cohort Expansion

Number of Subjects	**0**	**1**	**2**	**3**	**4**
13					
14					
15					
16					
17					
18					
19					
20					
21					
22					
23					

~~Number of Subjects~~	~~0~~	~~1~~	~~2~~	~~3~~	~~4~~
~~24~~					
~~25~~					
~~26~~					
~~27~~					
~~28~~					
~~29~~					
~~30~~					
~~31~~					
~~32~~					
~~33~~					
~~34~~					
~~35~~					
~~36~~					
~~37~~					

~~The shaded regions are the specific regions for stopping the study for futility. For instance, if there is no response in 13 subjects, then the predictive probability for success will be 1% or less (the futility criterion) and the study may be stopped.~~

Section 3.4.1 Part 2 PK/PD cohort

Rationale for Change: Part 1 will focus on completion of the Part 1 expansion cohort. Potential to enroll subjects into a PK/PD cohort was moved to Part 2 of the study. Text was added to clarify that this cohort may be enrolled at the RP2D.

REVISED TEXT

In Part 2 a cohort of up to 12 subjects may be enrolled at RP2D to collect adequate data on safety, pharmacokinetics, or pharmacodynamics. Urine, bile, and additional blood samples may be collected following repeated administration for drug metabolite profiling and to obtain information on renal excretion of GSK2816126. Mandatory collection of pre- and post-treatment tumor biopsies will be required for enrollment in a PK/PD cohort.

Section 3.5.2 Rationale for Population

Rationale for Change: Included text to add Part 1 expansion cohorts of GCB-DLBCL and solid tumor subjects and rationale for inclusion of these tumor types.

REVISED TEXT

Therefore, the study includes subjects with nNon-Hodgkin's Lymphoma and enriched for subsets (GCB-DLBCL, tFL) as well as multiple myeloma and solid tumors that have relapsed or are refractory to prior treatment with standard of care or do not have standard of care available or refuse standard of care therapy.

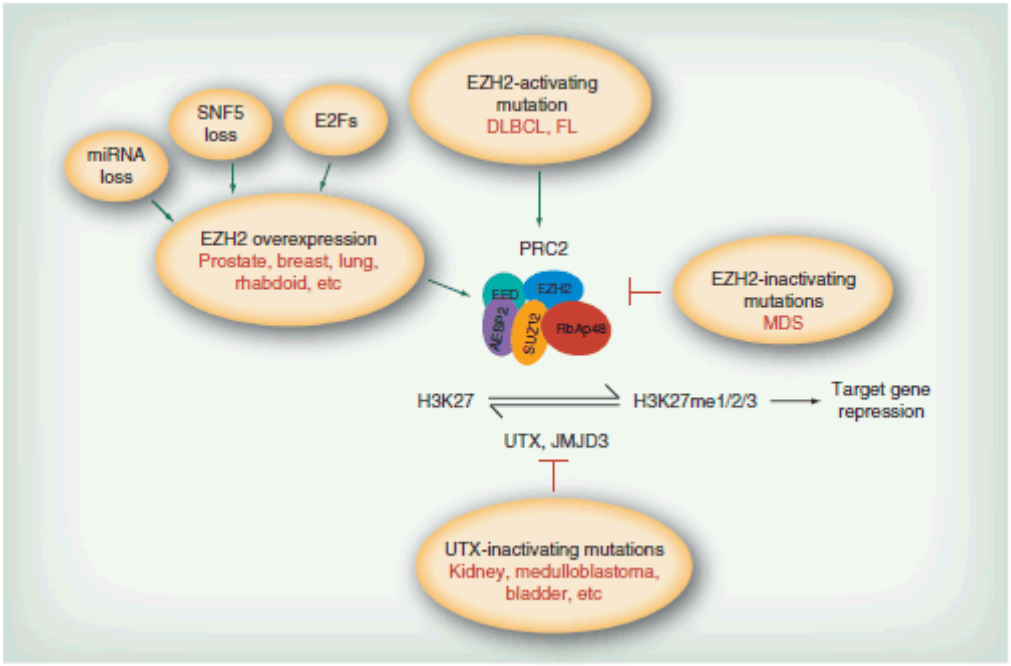
Part 1 will be comprised of 2 phases:

- Part 1 dose escalation which will include subjects with MM, relapsed/refractory tFL andDLBCL, other NHLs and solid tumors , and

- Part 1 cohort expansion at the highest tolerated dose/MTD which will include a cohort ofsubjects with relapsed/refractory GCB-DLBCL and a cohort of subjects with prostate cancer or solid tumors containing EZH2 inhibitior sensitizing mutations.

Part 2 will be comprised of cohort expansions in subjects with GCB-DLBCL, transformed follicular lymphoma and multiple myeloma.

EZH2 and H3K27me3 are dysregulated in nearly all cancers through numerous pathways including 1) recurrent gain-of-function heterozygous mutations in germinal center B-cell (GCB) DLBCL, FL, melanoma, and parathyroid adenoma, 2) EZH2 over-expression in numerous other aggressive tumors including those from prostate, breast, lung, liver, bladder, head and neck, skin, and kidney, and 3) inactivating mutations in UTX. H3K27 demethylase that acts in opposition to EZH2, described in numerous tumor types including transitional cell bladder carcinoma, esophageal squamous cell carcinoma, renal cell carcinoma, multiple myeloma, and subgroup 4 medulloblastoma (McCabe, 2014). Furthermore, data from prostate, breast, and several other tumor types have demonstrated that increased EZH2 expression correlates with increased aggressiveness of tumors and poor prognosis [GlaxoSmithKline Document Number 2013N169204_04, 2017]



McCabe **2014**

Table 1. Tumor types harboring EZH2-activating mutations.

Tumor type	Tumor subtype	Mutated	Total	Frequency (%)	Mutations observed	Ref.
Lymphoma	NHL	33	127	26.0	*1 A677G* *1 A687V* *31 Y641X*	[28]
	DLBCL	4	25	16.0	*Y641X*	[32]
		5	35	14.3	*Y641X*	[33]
		5	41	12.2	*1 A677G* *4 Y641X*	[12]
		31	320	9.7	*Y641X*	[13]
		1	73	1.4	*Y641X*	[34]
	GCB DLBCL	18	83	21.7	*Y641X*	[13]
	ABC DLBCL	0	42	0.0	*Y641X*	[13]
	FL	101	366	27.6	*7 A677G* *5 A687V* *50 Y641X*	[26]
		12	55	21.8	*Y641X*	[33]
		9	60	15.0	*Y641X*	[32]
		26	221	11.8	*Y641X*	[10]
		18	251	7.2	*Y641X*	[13]
	Burkitt lymphoma	0	23	0.0	*Y641X*	[33]

With regard to haematological indications for GSK2816126, preclinical studies demonstrate that B-cell lymphomas of DLBCL with EZH2 activating mutations are the most sensitive to GSK2816126. Approximately 22% of GCB-DLBCL tumors have an EZH2-activating mutation, whereas ABC DLBCL does not contain EZH2- activating mutations (McCabe MT & Creasy 2014). Early follicular lymphoma lesions have been

shown to have EZH2 mutations, as well as mutations in other genes that disrupt chromatin structure [Friedberg Blood. 2015;125(1):40-47].

Of particular interest is that there is some data to suggest that certain tumor types may respond to EZH2 inhibitors regardless of EZH2 inhibitor sensitizing status. Data presented at ASH Lymphoma Biology 2016 (Morschhauser F 2016) suggests that patients who have DLBCL(both GCB or nonGCB) and EZH2 mutated FL who are treated with the EZH2 targeted agent tazemetostat can achieve responses, providing proof of concept in DLBCL. Patients with GCB-DLBCL were analysed by EZH2-mutation status. Of patients with EZH2 mutation 1/5 had a PR (ORR=20%). Of those without a mutation, 3/19 had PR or CR (ORR=15.7%; 2 with CR). Therefore, Part 1 cohort expansion in GCB-DLBCL will enroll patients regardless of EZH2 related mutation status.

Neuroendocrine prostate cancer (NEPC) is a subtype of castration-resistant prostate cancer associated with aggressive clinical features and poor overall survival (Wang 2014). Mounting evidence suggests that NEPC evolves from prostate adenocarcinoma as one mechanism of resistance to androgen. Data from metastatic biopsies obtained from patients progressing on abiraterone or enzalutamide suggests that at least 10% of patients with late-stage castration-resistant prostate adenocarcinoma (CRPC) eventually develop small-cell NEPC. NEPC cancer is driven by N-Myc. N-Myc in turn drives EZH2, making neuroendocrine prostate cancer sensitive to inhibition (Dardenne 2016). Additionally, EZH2 has been described as an epigenetic driver of aggressive prostate cancer. EZH2 dysregulation may be involved in the progression from early prostate cancer to late (Yang, 2013). One of the most prevalent genetic modifications observed in prostate cancer is the fusion between the TMPRSS2 and ERG genes, resulted from an abnormal translocation on chromosome 21. Detected in more than half of all prostate tumors, this fusion gene consisting of the androgen-responsive TMPRSS2 promoter and the ERG coding region is able to substantially upregulate ERG expression, which has been proven to induce cell proliferation and invasion (Kumar-Sinha, 2008). Notably, it has been demonstrated that ERG can directly activate EZH2, which synergistically result in cancer progression through histone methylation linked de-differentiation (Yu, 2010b). Several studies have also confirmed that expression of EZH2 shows a correlated pattern with the stage of prostate cancer development (Berezovska, 2006; Saramaki., 2006; Hoffmann, 2007).Therefore, subjects with prostate cancer will be enrolled regardless of EZH2 related mutation status.

This study of GSK2816126 will focus primarily on the GCB-DLBCL NHL in order to ascertain a clinical benefit in a defined tumor type, for which there is high probability of potential benefit. However, solid tumors with changes to EZH2 inhibitor sensitizing mutations will be evaluated. These will be targeted as it is felt that they are most likely to show benefit. The exception in the solid tumor cohort will be prostate cancer, for which no mutation status will be required.

Section 3.5.3 Rationale for Dose and Schedule

Rationale for Change: Restructured section. Included text to update monitoring and risk mitigation strategy for infusion reactions in line with updates made through the protocol.

REVISED TEXT

The doses of GSK2816126 for evaluation in this study were selected based on available preclinical biology, toxicology, and pharmacokinetic data as well as predicted pharmacokinetic and response information for humans. Refer to the IB for more information [GlaxoSmithKline Document Number 2013N169204_04**, 2017** ~~2013N169204_00, 2013~~].

~~Predicted Effective Dose~~

~~The potential therapeutic dose for GSK2816126 in human was derived using available preclinical, PK and efficacy data from Karpas-422 and Pfeiffer tumor xenograft studies. Based on PK/PD modeling of Karpas-422 and Pfeiffer xenograft data, tumor eradication with GSK2816126 could be achieved in mice with an average total blood concentration target over the dosing interval of 1 ug/mL or an average free concentration of 16ng/mL. This free concentration is similar to the in vitro exposure producing 50% of the maximum effect (EC_{50}) obtained in Karpas-422 or Pfeiffer cell lines and to the average free concentration obtained with 50 mg/kg dosed daily in Karpas-422 xenograft model where more than 90% tumor growth inhibition was observed. This average free concentration could be achieved on average with twice-weekly administration of 950 mg in humans. Due to species differences in protein binding and blood to plasma partitioning, a dose of up to 2700 mg could be needed to achieve the average total blood concentration target of 1 ug/mL.~~

Starting Dose and Infusion Duration

Three approaches have been considered to establish the starting dose for GSK2816126 in ~~heme~~ hematological malignancies assuming a 70 kg adult with a surface area of 1.7 m^2.

An infusion duration of 2-hours is proposed for this clinical study. This infusion duration is shorter than the infusion duration used in animals but can be justified based on the following points:

- With infusion of a volume of 250 mL over 2 hours, GSK2816126 doses up to 1250 mg will provide infusion concentration up to the infusion concentration of 5 mg/mL used in dogs while doses up to 2500 mg will provide infusion concentration up to the concentration of 10 mg/mL used in rats. A 3000 mg dose would provide an infusion concentration of 12 mg/mL.
- The infusion will be performed into a larger (central) vein in humans than in animals. A shorter infusion duration and higher local blood flow would lead to a shorter exposure of the local area of the vein to high concentrations of GSK2816126.
- The main factor for the long infusion duration in animals was the histamine-

release like reaction. Subjects will be monitored during the infusion for evidence of histamine release related symptoms/infusion reactions and treated as needed with supportive care per local standard of care (e.g., corticosteroids, oxygen, epinephrine, diuretics, IV fluid). The infusion duration can be lengthened with restart of the infusion or at the next infusion. Premedications (antihistamines or similar) may be provided at the next infusion or prior to treatment of new subjects.~~Subjects will be monitored during the infusion for evidence of histamine release related symptoms and treated as needed with anti-histamines. Subsequent subjects treated at that dose or higher doses will be treated . If necessary based on emerging clinical data, the infusion duration can be lengthened.~~

Taking all three approaches into consideration and the shorter infusion duration of 2-hours, a starting dose of 50 mg twice-weekly as a 2-hour infusion is proposed. This dose provides a predicted total blood AUC of 1.43µg.h/mL and a total blood Cmax of 0.428 µg/mL. The AUC is 38-fold lower than the AUC (0-24hr) for the rat STD10 of 100 mg/kg, 18-fold lower than the AUC at the lowest tested dose in rat (30 mg/kg), and 56-fold lower than the AUC for the dog HNSTD of 100 mg/kg. The Cmax is 18-fold lower than the Cmax for the rat STD10 of 100mg/kg, 6.9-fold lower than the Cmax at the lowest tested dose in rat (30 mg/kg), and 23-fold lower than the Cmax for the dog HNSTD of 100 mg/kg. The starting dose of 50 mg will provide a suitable safety margin for the anticipated toxicities, while minimizing the number of subjects with aggressive lymphomas exposed to sub-therapeutic doses.

Predicted Effective Dose and Dosing Frequency

The potential therapeutic dose for GSK2816126 in human was derived using available preclinical, PK and efficacy data from Karpas-422 and Pfeiffer tumor xenograft studies. Based on PK/PD modeling of Karpas-422 and Pfeiffer xenograft data, tumor eradication with GSK2816126 could be achieved in mice with an average total blood concentration target over the dosing interval of 1 ug/mL or an average free concentration of 16ng/mL. This free concentration is similar to the in vitro exposure producing 50% of the maximum effect (EC_{50}) obtained in Karpas-422 or Pfeiffer cell lines and to the average free concentration obtained with 50 mg/kg dosed daily in Karpas-422 xenograft model where more than 90% tumor growth inhibition was observed. This average free concentration could be achieved on average with twice-weekly administration of 950 mg in humans. Due to species differences in protein binding and blood to plasma partitioning, a dose of up to 2700 mg could be needed to achieve the average total blood concentration target of 1 ug/mL.

The rationale for the proposed schedule of twice weekly, 3 weeks on / 1 week off for each 28-day cycle is based on preclinical *in vivo* observations. Briefly, mice with Pfeiffer tumor xenograft were treated daily with 50 mg/kg for 10 days. Tumor H3K27 tri-methylation levels were measured and tri-methylation inhibition was observed up to 5 days after the last administration. Using *in vivo* murine tumor xenograft models, schedules with progressively longer dosing intervals (i.e., from daily to once or twice-weekly to intermittent twice-weekly dosing with 2 weeks on/ 1 week off) were evaluated. Similar tumor growth inhibition were observed for the same total weekly dose, regardless of dosing frequency, except for lower tumor growth inhibition being observed with once weekly dosing. ~~Taken together, these data support a schedule of 3 weeks on / 1 week off.~~

~~Additional schedules may be explored based on safety, tolerability, PK and pharmacodynamics.~~

Taken together, these data support a schedule of twice weekly, 3 weeks on / 1 week off. ~~Additional schedules may be explored based on safety, tolerability, PK and pharmacodynamics.~~

Section 3.7 Dosage and Administration of Study Treatment

Rationale for change: Administrative change to clarify infusion duration per protocol.

REVISED TEXT

Investigational product (IP) details are provided in Table 5. It will be diluted in saline or D5W to a fixed 250 mL volume. This volume will be infused over a minimum of 2 hours (~~and/or~~ up to 4 hours). Additional details are provided in the SPM.

Section 3.8.1 QTcF Stopping Criteria

Rationale for Change: Clarified that QTcF would be used for eligibility and stopping criteria decision making. QT corrected by Friedericia's method provides a better assessment of QT interval at the extremes of heart rate. This is a more accepted correction method that is being employed in Oncology studies and the ECG machines centrally provided for GSK studies provides the QTcF values on the reads. This leads to uniform correction of QT and standardization across studies.

REVISED TEXT

The QTcF is the QT interval corrected for heart rate according Fridericia's formula (QTcF).

- For eligibility and withdrawal, subjects QTcF value will be used.
- For purposes of data analysis, QTcF values will be used.

If a subject that meets the corrected ~~QT (~~QTcF~~)~~[1] interval duration criteria below, study treatment(s) will be withheld.

- QTcF interval ~~(corrected for HR)~~ ≥500 msec; ~~IP~~ GSK2816126 will be permanently discontinued.
- QTcF interval increase from baseline ≥60 msec and maximum ~~QT~~QTcF < 500 msec; GSK2816126~~IP~~ may be restarted ~~at a 33% reduction in dose~~one dose level lower once the QTcF returns to baseline. If QTcF prolongation meeting stopping criteria recurs after re-challenge, GSK2816126 ~~IP~~ must be permanently discontinued.

[1]Based on average QTcF value of triplicate electrocardiograms (ECGs) to include manual over-read. For example, if an ECG demonstrates a prolonged ~~QT~~QTc~~C~~F interval, obtain 2 additional ECGs over a brief period (e.g., within approximately 10 minutes of the abnormal ECG, if possible, and approximately 10 minutes apart from each other), and then use the averaged QTcF values of the 3 ECGs to determine whether the subjects should have study treatment discontinued.

~~The QTc is the QT interval corrected for heart rate according to either Bazett's formula (QTcB), Fridericia's formula (QTcF), or another method, machine or manual over read.~~

- ~~For eligibility and withdrawal, ideally the same QT correction formula will be used for all subjects. However, because this is not always possible, the same QT correction formula *must* be used for *each individual subject* to determine eligibility for and withdrawal from the study.~~

~~For purposes of data analysis, QTcB, QTcF, another QT correction formula, or a composite of available values will be used.~~

Section 3.8.2.1 Management of Infusion ~~Site~~ Reactions

Infusion ~~Site~~ Related Reaction

Rationale for Change: Included text to update monitoring and risk mitigation strategy for infusion reactions in line with updates made through the protocol.

Infusion ~~Site (Histamine)~~ Related Reaction	**Grade 1**: Continue infusion and closely monitor the subject **Grade 2/3**: Temporarily interrupt study medication and: - Administer diphenhydramine ~~50 mg~~ or similar anti-histamine - Provide supportive care per local standard of care (e.g., corticosteroids, oxygen, epinephrine, diuretics, IV fluid) - May resume infusion once resolved to ≤~~</=~~ grade 1* - For grade 3 reactions, corticosteroids may be considered **Grade 4**: - Discontinue infusion. Administer diphenhydramine, corticosteroids and supportive care per local standard of care~~as above~~ - May consider restarting study treatment at a reduced dose or dose level pre-event based on discussion with GSK Medical Monitor

*Recommend following institutional guidelines for re-starting after infusion reactions seen with cytotoxic therapy. A general guideline would be as follows:

- Restart under observation at an infusion rate of 25% of the original rate for the first 30 minutes

- If no reaction, increase infusion rate by 25% of the original rate every half hour until full dose administered

- If Grade 1 reaction, continue at the rate at which the reaction occurs

-If Grade 2 or 3 infusion related reaction consider premedication for all subsequent infusions per local standard of care.

Section 3.8.3 Dose Adjustment for Non-Hematologic Toxicity

REVISED TEXT

Rationale for Change: Dose escalation has been completed, therefore; updated dose adjustments to include reducing by dose level instead of reducing by percentage of received dose were updated in Section 3.4.8.1, Section 3.8.4.2 and Section 3.9.1.

Table 4 Dose Adjustment Guideline for Drug Related Non-Hematologic Toxicity

Worst Grade	Dose Adjustment
G1	No change in dose
G2	Continue dosing with no change OR Consider holding for up to 2 weeks for toxicity to resolve to baseline or ≤ Grade 1, then continue at the same dose OR dose reduce ~~by at least 25%~~to 1 dose level lower per dose escalation scheme if the toxicity is considered a DLT.
G3 and 4	Hold for up to 2 weeks for toxicity to resolve to baseline or ≤Grade 1, then dose reduce ~~by at least 25%.~~to 1 dose level lower per dose escalation scheme If no recovery to ≤Grade 1* or baseline after 14 days, patient should be withdrawn.

If the non-hematologic toxicity or event resolves to baseline or ≤ Grade 1 within 14 days of stopping therapy, treatment with GSK2816126 may be restarted at 1~~with at least 25%~~dose level lower than the current dose ~~reduction~~. For a non-DLT, the treatment with GSK2816126 could restart at a full dose, if deemed appropriate.

If the non-hematologic toxicity does not resolve to ≤Grade 1 or baseline within 14 days, the subject should be withdrawn from the treatment permanently (Section 6.3). However, if the investigator and GSK Medical Monitor agree that further treatment will benefit the subject, treatment can restart ~~with~~ at ~~least 25% dose reduction~~1 dose level lower and under weekly clinical monitoring. If the toxicity resolves to ≤Grade 1 or baseline, the dose may be resumed to the initial dose level.

Section 3.8.4.1 For subjects with lymphoma and multiple myeloma:

REVISED TEXT

When the treatment resumes, the dose may be adjusted based on platelet count, i.e., dose can be reduced by ~~at least 25% increments up to twice~~1 or 2 dose levels when the platelet count ≤25 x 10^9/L (G4 thrombocytopenia) and it is not attributed to the disease. If a subject has persistent G4 thrombocytopenia for 4 weeks not attributed to disease or requires platelet transfusions for bleeding in the absence of the disease, the subject will be withdrawn from the study.

Section 3.8.4.2 For subjects with solid tumors:

REVISED TEXT

- Grade 3 (platelet count between 25,000 to <50,000): After discussion with medical monitor and using sound clinical judgement, continue at same dose or consider dose interruption until~~adjust dose (e.g. consider missing one dose or till~~ count recovery to Grade 2 or less). Monitor platelet count~~CBC~~ at ~~least~~ a minimum of twice ~~a~~ weekly~~, more frequently if necessary~~.

- Grade 4 (platelet count below 25,000): Interrupt study medication and monitor ~~CBC~~ platelet count every 2-3 days. If platelet counts recover to Grade 2, discuss with medical monitor resuming treatment at the same or adjusted dose based on sound clinical judgement. Platelet transfusion is allowed based on institutional guidelines. In case of platelet transfusion, hold drug for at least 7 days from day of transfusion, and if platelet counts recover to Grade 2 consider initiating treatment at a lower dose using sound clinical judgement and after consulting with the GSK medical monitor. Discontinue treatment if drug has to be held for >14 days or greater than 2 dose reductions required.

Section 3.9.1 Dose Modifications

REVISED TEXT

Dose reductions for GSK2816126 will depend on their starting dose. If a subject has a dose reduction for toxicity the dose will be reduced by one dose level ~~by a minimum of 25%~~. Approval from the GSK Medical Monitor is required to restart a dose after 14 days of dose interruption. Following a dose reduction subjects may be re-escalated to a higher dose level with the approval of the GSK Medical Monitor if the toxicity has resolved.

Section 5.1 Number of Subjects

Rationale for Change: updated total number of subjects to be enrolled based on added Part 1 expansion cohorts and revised subject numbers in Part 2.

REVISED TEXT

A maximum of approximately 250~~169~~ subjects will be enrolled. See Section 12.2 for sample size assumptions.

The number of dose levels and the level at which the RP2D (or MTD or MFD) is reached cannot be determined in advance. An adequate number of subjects will be enrolled into the study to establish the recommended dose(s) for further study. It is estimated that approximately 40 subjects will be enrolled into Part 1 dose-escalation of the study. Additionally i~~-~~n Part 1 cohort expansion, approximately 27 GCB-DLBCL subjects and approximately 15 solid tumor subjects containing EZH2 inhibitor sensitizing mutations or subjects with prostate cancer will be enrolled.

Approximately up to ~~129~~ 168 subjects will be enrolled in Part 2 in five expansion cohorts: two GCB-DLBCL cohorts with up to 32~~0~~ subjects from the EZH2 wild-type population, and up to 32~~0~~ subjects from the EZH2 mutation positive population, and two tFL cohorts with up to 32~~16~~ subjects from the EZH2 wild-type population and up to 32~~16~~ subjects from the EZH2 mutation positive population and up to ~~37~~40 subjects in the MM cohort. Additional subjects/cohorts may be enrolled to allow for evaluation of additional dose levels.

Section 5.2.1 Part 1 Inclusion Criteria

Rationale for Change – see rationale for updates to inclusion and exclusion noted under Synopsis.

REVISED TEXT

3. Tumor type criteria

- Relapsed/refractory non-Hodgkin's lymphoma (NHL) that meets ~~one of~~ the following criteria:
    - Germinal Center B cell Diffuse large B cell lymphoma (GCB-DLBCL) ~~or transformed follicular lymphoma~~ relapsed ~~after,~~ or refractory to at least one prior ~~chemotherapy~~ regimen (e.g., rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone [R-CHOP]) AND not a candidate for standard salvage regimens or autologous or allogeneic stem cell transplant. ~~(e.g., due to age, comorbid conditions or failure to respond to salvage chemotherapy).~~ Local confirmation of lymphoma subtype GCB-DLBCL is allowed for enrollment but must be confirmed through central laboratory testing.
    - ~~DLBCL or transformed FL relapsed after or refractory to at least two prior chemotherapy regimens.~~
    - ~~Other NHLs that have failed at least one prior line of therapy and for which there is no standard salvage regimen.~~
- ~~Relapsed and/or refractory MM that have failed prior standard therapy and for which there is no standard salvage regimen.~~

- ~~Solid tumors [RECIST evaluable, with the exception of castrate resistant prostate cancer (CRPC) at least one and not more than three standard of care chemotherapeutic regimens, or tumor for which there is no approved therapy, or for which standard therapy is refused.~~
- Solid tumors that meet the following criteria:
    - Measurable disease by RECIST 1.1 in at least 1 site
        - For Castrate Resistant Prostate Cancer (CRPC) measurable disease can also include PSA level (see below)
    - Disease progression~~evaluable, with the exception of castrate resistant prostate cancer (CRPC)~~ with the last line of therapy and at least one prior standard of care ~~chemotherapeutic~~ regimens, or tumor for which there is no approved therapy, or for which standard therapy is unsuitable or refused.
    - Mutation Status:
        - Solid tumor types, other than prostate, must have one of the following EZH2 inhibitor sensitizing mutations as determined via local testing:
            - An activating mutation in EZH2 (Y641F/C/S/H/N, A677V/G, and/or A687V
            - Loss of a component of the SWI/SNF complex, including, but not limited to, ARID1A, SMARCB1 (aka SNF5/INI1/BAF47), SMARCA4 (aka BRG1), or PBRM1 (aka PB1) as determined by molecular testing (bi-allelic loss or mutation) or immunohistochemistry
            - Loss of BAP1 (ubiquitin carboxy-terminal hydrolase) as determined by molecular testing (bi-allelic loss or mutation) or immunohistochemistry
    - CRPC subjects:
        - Must have measurable disease by either:
            - RECIST1.1 (see Appendix 5) or,
            - A minimum PSA of 5 ng/mL
        - Disease progression on last line of therapy and must have progressed on abiraterone, enzalutamide, or taxane chemotherapy
        - Patients may continue GnRH agonists
        - Small cell prostate cancer is eligible

4. For all subjects: Availability of archival tissue, or willingness to undergo fresh biopsy if archival tissue is not available as described in Section 7.6.1.1,Section 7.6.1.2 and Section 7.6.5.:
5. Must have a pre-existing central venous access such as a port, Hickmann catheter, or a peripherally inserted central catheter (PICC line) or be willing and able to have one inserted.
6. ECOG Performance Status of 0 or 1 (see Appendix 2).
7. Men with a female partner of childbearing potential must have either had a prior bilateral vasectomy with resultant azoospermia, bilateral orchiectomy, or must agree to use one of the contraception methods listed in Section 10.1 from the time of the first dose of study medication until ~~3 months~~at least 2 weeks (14 days) after the last dose of study treatment due to long elimination phase.~~for clearance of any altered sperm~~.
8. **A female subject is eligible to participate if she is of:**~~Women of childbearing potential must have a negative serum pregnancy test within 7 days of first dose of study treatment and agree to use effective contraception, as defined in Section 10.1, during the study and for at least two weeks (14 days) following the last dose of study treatment.~~
   - Non-childbearing potential as defined in Section 10.1.1
   - Child bearing potential as defined in Section 10.1.1 and agree to use effective contraception, as defined in Section 10.1, for an appropriate period of time (as determined by the product label) prior to the start of dosing to sufficiently minimize the risk of pregnancy and for at least 2 weeks (14 days) following the last dose of study treatment. Women of childbearing potential must have a negative serum pregnancy test within 7 days of first dose of study treatment followed by negative urine or serum pregneancy test once every 4 weeks (prior to next dose cycle) thereafter.
9. Adequate organ system function as defined below:

System	LABORATORY VALUES
Hematologic	
ANC	≥1.2 x 10^9/L
Hemoglobin	≥9 g~~/~~/dL
Platelets	≥75x 10^9/L
~~Platelets for Subjects with MM~~	~~≥ 50,000 (transfusion independent)~~
PT/INR and PTT	≤1.5 x ULN
Hepatic	
Albumin	≥2.5 g/dL
Total bilirubin	≤1.5 times ULN
AST and ALT	≤2.5 times ULN without liver metastases ≤5 times ULN if documented liver metastases
Renal	
~~Serum Creatinine~~	~~≤1.5 mg/dL~~ ~~Or~~

System	LABORATORY VALUES
Calculate Creatinine Clearance[a, b] ~~OR~~ ~~24 hr urine Creatinine Clearance~~	≥50 mL/min ~~≥50mL/min~~
~~Reproductive~~/Endocrine for CRPC only	
Testosterone	<50ng/dL (only for subjects with CRPC)
Cardiac	
Left Ventricular Ejection Fraction (LVEF)	≥LLN (minimum of 50% LVEF) by ECHO or MUGA[c]

Abbreviation(s): ANC, absolute neutrophil count; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRPC, castration resistant prostate cancer ECHO, echocardiogram; INR, international normalization ratio, MUGA, multigated (radionuclide) angiogram; PT, prothrombin time, PTT, partial thromboplastin time, ULN, upper limit of normal , LLN, lower limit of normal.

a. Calculated by Cockcroft-Gault formula
b. For MM subjects, adequate renal function is defined as ~~serum creatinine ≤ 2.5 mg/dL OR~~ calculated creatinine clearance ~~(either calculated or obtained via 24 hr urine collection)~~ ≥ 30 mL/min.~~ECHO is the preferred method~~
c. ECHO is the preferred method and should always be used if available

NOTE: Laboratory results obtained during Screening should be used to determine eligibility criteria. In situations where laboratory results are outside the permitted range, the investigator may opt to retest the subject and the subsequent within range screening result may be used to confirm eligibility. ~~Subjects requiring transfusions to meet eligibility criteria are not eligible.~~

Section 5.2.2 Part 2 Inclusion Criteria

REVISED TEXT

1. In addition to inclusion criteria listed for Part 1, Part 2 will enroll GCB-DLBCL, tFL and MM subjects only.
2. Relapsed and/or refractory MM or tFL that have failed prior standard therapy and for which there is no standard salvage regimen

Section 5.2.3 Part 1 and 2 Exclusion Criteria

REVISED TEXT

Subjects meeting any of the following criteria must not be enrolled in the study:

1. ~~Currently r~~Receiving any cancer therapy within 2 weeks of first dose ~~(chemotherapy, radiation therapy, immunotherapy or biologic therapy~~(including surgery, and/or tumor embolization)~~).(permitting corticosteroids Corticosteroids to control systemic or local symptoms, up to a dose of 10 mg prednisone or equivalent daily and stable for at least 7 days prior to enrolment)~~

   Note: the following are allowed:

   - Corticosteroids to control systemic or local symptoms, up to a dose of 10 mg prednisone or equivalent daily and stable for at least 7 days prior to enrollment.

- Subjects with prostate cancer may remain on GnRH agonists. Other hormonal therapies (e.g., bicalutamide, abiraterone and enzlutimide) for prostate cancer must be stopped 4 weeks prior to enrolment.

Note: the following are NOT allowed:

- Chemotherapy regimens with delayed toxicity within the last 3 weeks.
- Nitrogen mustards, Melphalan, Monoclonal antibody or Nitrosourea within the last 6 weeks.
- ~~Hormonal (e.g. anti androgen) therapies for prostate cancer must be stopped 4 to 6 weeks prior to enrolment. Subjects with prostate cancer may remain on luteinizing hormone releasing hormone (LHRH) agonists. Subjects with prostate cancer amy also remain on low dose prednisone or prednisolone (up to 10 mg/day) and still be eligible for this study.~~

2. Any major surgery, radiotherapy or immunotherapy within the 4 weeks prior to first dose of study drug, or palliative radiotherapy to a single symptomatic lesion within the 2 weeks prior to first dose of study drugs.
3. Subjects with prior allogeneic transplant are excluded: however, subjects who have previously received an autologous stem cell transplant are allowed if a minimum of 100 days has elapsed from the time of transplant and the subject has recovered from transplant-associated toxicities prior to the first dose of GSK2816126

- ~~Subjects who have previously received an autologous stem cell transplant are allowed if a minimum of 100 days has elapsed from the time of transplant and the subject has recovered from transplant-associated toxicities prior to the first dose of GSK2816126~~

4. Received an investigational anti-cancer drug within 64 weeks, or within 5 half-lives (whichever is shorter) of the first dose of study drug. At minimum of~~least~~ 14 days must have passed between the last dose of prior investigational agent and the first dose of study drug.
5. Current use of a prohibited medication or expected to require any of these medications during treatment with study drugs (see Section 9).
6. Known HIV, or serological evidence for Hepatitis B (positive HBsAg) or chronic Hepatitis C infection.
   - Subjects who are negative for HBsAg, but HBcAb positive, a HBV DNA (viral load) test will be performed and if ~~positive~~ negative are eligible~~will be excluded~~.
   - Subjects with positive Hepatitis C antibody serology, ~~but~~ with a negative HCV RNA test results are eligible.
7. ~~7.~~ Concurrent use of therapeutic warfin is allowed. However, anticoagulants that do not have reversal agents available are prohibited (see Section 9.2). ~~Current use of~~

~~therapeutic warfarin. Therapeutic dosing of warfarin is defined as resulting in an (International normalization ratio) INR >1.3. Low molecular weight heparin is permitted.~~

~~8. Chemotherapy regimens with delayed toxicity within the 3 weeks prior to first dose of study drug. These include, but are not limited to, monoclonal antibody, immunotherapy, therapy, and nitrogen mustards~~

8. Unresolved toxicity greater than Grade 1 National Cancer Institute – Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4 from previous anti-cancer therapy, with the exception of alopecia and peripheral neuropathy [NCI-CTCAE, 2009].
    - Lymphoma subjects with ≤Grade 3 lymphopenia can be enrolled at the discretion of the investigator
9. Packed red blood cell or platelet transfusion within 7 days of screening laboratory tests.
10. Psychological, familial, sociological or geographical conditions that do not permit compliance with the protocol.
11. Cardiac exclusion criteria:
    - History of acute coronary syndromes (including myocardial infarction and unstable angina), coronary angioplasty, or stenting within the past 6 months prior to first dose of study drug.
    - QTcF interval >450 msec
    - Uncontrolled arrhythmias. Subjects with rate controlled atrial fibrillation for >1 month prior to first dose of study drugs may be eligible.
    - Class II, III or IV heart failure as defined by the New York Heart Association (NYHA) functional classification system.
12. Known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to the study drug or their excipients.
13. Pregnant or lactating female.
14. Unwillingness or inability to follow the procedures outlined in the protocol.
15. Uncontrolled diabetes or other medical condition that may interfere with assessment of toxicity.
16. Central nervous system (CNS) metastases, with the following exception:
    i. Subjects who have previously treated CNS metastases, are asymptomatic, and have no requirement for steroids at least 14 days prior to first dose of study drug.
    ii. Subjects with carcinomatous meningitis are excluded regardless of clinical stability.
17. Invasive malignancy or history of invasive malignancy other than disease under study, except as noted below:

i. Any other invasive malignancy from which the subject has been disease-free for more than 2 years and, in the opinion of the principal investigator and GSK Medical Monitor, will not affect the evaluation of the effects of this clinical trial treatment on currently targeted malignancy, can be included in this clinical trial.
ii. Curatively treated non-melanoma skin cancer and any carcinoma-in-situ.

Section 6.3 Permanent Discontinuation from Study Treatment

Rationale for Change: Clarify the assessments to occur and timing of the post study treatment Follow Up Visit visit for subjects who discontinue from study treatment.

REVISED TEXT

- Intercurrent illness that prevents further administration of study treatment(s)
- Subject is lost to follow-up
- ~~or~~ Sstudy is closed or terminated
- Female subject who becomes pregnant while on study treatment

Once a subject has permanently discontinued from study treatment, the subject will not be allowed to be retreated.

All subjects who discontinue from study treatment will have safety/disease assessments at the post study treatment Follow Up Visit as specified in the Time and Events Tables.

Section 7.2 Demographic/Medical History and Baseline Assessments

Rationale for Change: Clarified baseline assessments required based on tumor type.

REVISED TEXT

- Disease characteristics for all subjects including:
  - Date of initial diagnosis
  - Initial diagnosis tumor histology
  - ECOG performance status at initial diagnosis
  - ~~LDH level at initial diagnosis~~
  - Tumor location involvement at initial diagnosis
  - Previous cancer treatments (e.g., cytotoxics, radiotherapy, maintenance, surgery)
  - Ongoing toxicities related to previous treatment

  - Best response to previous treatment(s)
  - Date of relapse/refractory diagnosis
  - Tumor histology (if relapse/refractory tumor biopsy completed). For Part 2 subjects, tumor biopsy is mandatory for inclusion. See Section 7.6.5.
  - ~~Ann Arbor stage of relapse/refractory diagnosis for NHL~~
  - ECOG performance score at time of first relapse/refractory diagnosis (as applicable)
  - ~~LDH level at time of first relapse/refractory diagnosis (as applicable)~~

- Diagnostic quality CT imaging with contrast within 28 days of first dose of study treatment identifying nodes, nodal masses, spleen/liver nodules and, if applicable measurable extra nodal disease. Diagnostic quality CT imaging is the preferred method of disease assessment. If PET/CT has been performed within this window, diagnostic CT will not be required. See Section 7.7 for further information.
- If completed and will be utilized for assessment of disease, PET imaging within 28 days of first dose of study treatment. Images may be obtained from standalone PET scanners or via combination PET/CT scanners. Standalone PET does not replace diagnostic CT. See Section 15.4 for further information.
- For NHL, unilateral or bilateral bone marrow biopsy within 35 days prior to commencing study therapy.
- Clinical laboratory tests: hematology, clinical chemistry, coagulation parameters
- Serum beta-human chorionic gonadotropin (β-HCG) pregnancy test for female subjects of childbearing potential only
- 12-lead ECG
- ECHO or MUGA
- Review of concomitant medications
- Baseline assessments for subjects with GCB-DLBCL
  - Ann Arbor stage of initial diagnosis for NHL
  - Ann Arbor stage of relapse/refractory diagnosis for NHL
  - GCB testing confirming status
  - LDH level at initial diagnosis
  - LDH level at time of first relapse/refractory diagnosis (as applicable)

Section 7.3.3 Vital Signs

REVISED TEXT

Vital sign measurements will include systolic and diastolic BP, temperature, respiration rate and pulse rate. Vital signs should be measured after resting for at least 5 minutes in a semi-supine position. Vital signs will be measured more frequently if warranted by clinical condition of the subject. On days where vital signs are measured multiple times (Cycle 1 Day 1), temperature does not need to be repeated unless clinically indicated. Refer to the SPM for details regarding measurement of vital signs.

Section 7.3.4 Safety Electrocardiogram

Rationale for Change: Updated to clarify timing of safety ECGs, review by investigator, and definition of baseline timepoint. Clarified that QTcF would be used for eligibility and stopping criteria decision making. QT corrected by Friedericia's method provides a better assessment of QT interval at the extremes of heart rate. This is a more accepted correction method that is being employed in Oncology studies and the ECG machines centrally provided for GSK studies provides the QTcF values on the reads. This leads to uniform correction of QT and standardization across studies.

REVISED TEXT

Safety t~~T~~welve-lead ECGs will be obtained in triplicate over a brief (e.g., 5-10 minute) recording period at designated time points during the study using an ECG machine that automatically calculates the HR and measures PR, QRS, QT, and QTc intervals. At each assessment, a 12-lead ECG will be performed by qualified personnel at the site after the subject has at least a 5 minute rest and is in a semi-[recumbent or supine] position. Refer to the SPM for details regarding ECG procedures.

Standard 12-lead ECGs (safety ECGs) will be performed as part of the real-time assessment of subjects. ECGs should be reviewed by the investigator on an ongoing basis for safety purposes. The dosing for each new week in the first cycle should not begin until the safety ECG has been reviewed and no significant abnormalities have been detected

The QTc is the QT interval corrected for heart rate according to Fredericia's formula (QTcF).

- For eligibility and withdrawal, QTcF will be used for all subjects
- For purposes of data analysis, QTcF values will be used

Baseline results are defined by the nearest timepoint prior to first dose. For this trial the baseline QTcF value is determined by the mean of the triplicate C1D1 predose QTcF results. If these results are not available, then the mean of QTcF of the screening triplicate ECG results would be used.

Timings for in-house on-drug ECGs on Day 1 only are pre-infusion, post-infusion, before bed (between 9-10pm) and before discharge the next morning. These ECGs are in addition to the Holter monitoring. Subjects will not be discharged from their overnight stay in the Phase I unit after dose 1 until the QTcF is <500 msec.

Section 7.3.5 Holter Monitoring

REVISED TEXT

In addition to the 12-lead safety ECGs performed during the study, continuous 12-lead Holter ECGs (obtained via a Holter monitor) will be acquired for a total of approximately 24 hours beginning an hour before the first infusion. Subjects will be monitored overnight in the CRU. The Holter monitor-derived ECGs will not provide real-time assessment of cardiac rhythm and morphology but will be analyzed retrospectively and included in the DLT and concentration QT analysis.

Refer to Section 3.8.1 for QTc interval withdrawal criteria and additional readings that may be necessary. Refer to the SPM for details regarding Holter monitoring procedures.

Section 7.3.6 Laboratory Assessments

Rationale for Change: Updated to clarify reporting of abnormal laboratory values as Adverse Events. Clarified clinical laboratory tests to be taken (table 8).

REVISED TEXT

All protocol required laboratory assessments~~, as defined in Table 8~~ should be performed according to the Time and Events Table (Section 7.1). Details for the preparation and shipment of samples will be provided in the SPM.

Abnormal laboratory results that are considered by the investigator to be clinically significant should be recorded on the eCRF as AEs. All laboratory tests with values that are significantly abnormal during participation in the study or within 30 days after the last dose of study treatment should be repeated until the values return to normal or baseline. If such values do not return to normal within a period judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

Hematology, clinical chemistry, urinalysis and additional parameters to be tested are listed below and are to be performed at the institutions local laboratory:

Table 8 List of Clinical Laboratory Tests

Hematology			
Platelet Count	*RBC Indices*:	*Automated WBC Differential:*	
RBC Count	MCV	Neutrophils	
WBC Count (absolute)	MCH	Lymphocytes	
Reticulocyte Count	MCHC	Monocytes	
Hemoglobin		Eosinophils	
Hematocrit		Basophils	
Clinical Chemistry			
BUN	Potassium	AST	Total and direct bilirubin
Creatinine	Chloride	ALT	Uric Acid
Sodium	Calcium	Alkaline phosphatase	Total Protein
Magnesium	Glucose	LDH	~~PO4~~
FSH and estradiol (as needed in women of non-child bearing potential and all peri menopausal women~~only~~) Pregnancy test for females (serum B-HCG at screening, Urine or serum B-HCG during Continuation Phase)			

Abbreviation(s): ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; FSH, follicle stimulating hormone; LDH, lactate dehydrogenase; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume~~; PO_4, phosphate~~; RBC, red blood cell; WBC, white blood cell.

Section 7.3.7 Pregnancy Testing and Reporting

REVISED TEXT

Any pregnancy that occurs during study participation must be reported using a clinical trial pregnancy notification and follow –up form. To ensure subject safety, each pregnancy must be reported to GSK within 2 weeks of learning of its occurrence. The pregnancy must be followed up to determine outcome (including premature termination) and status of mother and child. While pregnancy itself is not considered to be an AE or SAE, pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous abortions must be reported as an SAE.

Section 7.4.1 Blood Sample Collection for Pharmacokinetics

Rationale for Change: In Section7.4.1, Section 7.4.2 and Section 7.4.3, clarified the number of subjects and timing of assessments.

REVISED TEXT

~~For at least 4 s~~Subjects participating in the Part 2 ~~Part 1~~ PK/PD expansion cohort, additional blood samples will be collected for metabolite profiling.

Section 7.4.2 Bile Sample Collection for Pharmacokinetics

REVISED TEXT

~~For at least 4 s~~Subjects participating in the Part ~~1~~2 PK/PD expansion cohort, bile samples for analysis of GSK2816126 and its metabolites may~~will~~ be collected via the Entero-Test

[Guiney, 2011] over the time period specified in the Time and Events Table (see Section 7.1).

Section 7.4.3 Urine Sample Collection for Pharmacokinetics

REVISED TEXT

Urine may~~will~~ be collected for metabolic profiling in ~~at least 4~~ subjects in the PK/PD expansion cohort of Part 2~~1~~ at the time points indicated in the Time and Events Schedule (Section 7.1).

Section 7.4.4 Plasma Sample for CYP3A4 Enzyme Activity

REVISED TEXT

Plasma collected in the Part 2 PK/PD expansion cohort may be analyzed for 4β-hydroxycholesterol (as well as cholesterol) as a potential in vivo marker of CYP3A4 enzyme activity and the results will be reported under a separate Mechanistic Safety and Disposition ~~Drug Metabolism and Pharmacokinetics (DMPK)~~ protocol. Samples collected pre-treatment and at steady-state will be compared to evaluate this potential biomarker.

Section 7.4.5 Pharmacokinetic Sample Analysis

REVISED TEXT

Blood sample analysis will be performed under the management of Bioanalysis~~tical~~ Immunogenicity and Biomarker,~~Science and Toxicokinetics~~, In Vitro In Vivo Translation ~~Drug Metabolism and Pharmacokinetics~~, Platform Technology and Science, GSK. Concentrations of GSK2816126 will be determined in blood samples using the most current approved and validated analytical methodology. Blood raw data will be stored in the Good Laboratory Practices (GLP) Archives, GSK. Once the blood has been analyzed for GSK2816126, any remaining blood may be analyzed qualitatively for circulating metabolites and the results reported under a separate DMPK protocol.

If dry blood matrix samples are collected, they will be analyzed under the management of Bioanalysis Immunogenicity and Biomarker, *In Vitro In Vivo* Translation ~~Bioanalytical Science and Toxicokinetics, Drug Metabolism and Pharmacokinetics~~, Platform Technology and Science, GSK. Concentrations of GSK2816126 will be determined in dry blood matrix samples using a validated analytical methodology. Dried blood matrix raw data will be stored in the Good Laboratory Practices (GLP) Archives, GSK.

Urine sample analysis may be performed under the management of ~~Bioanalytical~~ Bioanalysis Immunogenicity and Biomarker, *In Vitro In Vivo* Translation ~~Science and Toxicokinetics, Drug Metabolism and Pharmacokinetics~~, Platform Technology and Science, GSK. Concentrations of GSK2816126 may be determined in urine samples using an investigative analytical methodology. Urine raw data will be stored in the GLP Archives, GSK.

The urine and bile samples may be analyzed for compound-related metabolites and the results will be reported under a separate ~~DMPK~~ protocol.

Plasma analysis for 4β-hydroxycholesterol and cholesterol may be conducted and the results reported under a separate ~~DMPK~~ protocol.

Section 7.6 Translational Research

- **Rationale for Change:** In Section 7.6, provided additional clarity on the biomarker assessments required per protocol.

REVISED TEXT

Translational or biomarker research may be performed on archival tissue, tumor biopsies, blood samples or other surrogate tissue (e.g. skin or hair) collected at various times throughtout the~~on~~ study, to better understand ~~DLBCL, transformed FL, MM,~~ mechanism of action and response to GSK2816126. The successful collection of quality tissue specimens will be critical to furthering our understanding of EZH2 biology and identifying the best way to treat patients with an EZH2 inhibitor.

Section 7.6 Translational Research

REVISED TEXT

Novel candidate biomarkers and subsequently discovered biomarkers of the biological response associated with lymphoma, or other cancers, ~~or medically related conditions~~ and/or the action of GSK2816126 may be identified by application of ~~the following.~~ DNA/gene, RNA and protein analysis of blood and tumor tissue including but not limited to the following analyses:

- Confirmation of GCB-subtype DLBCL status by IHC analysis using the standard methods or tumor GEP signature
- Confirmation of EZH2 WT status by targeted sequencing of EZH2 gene
    - Subject tumors determined to be wild-type for the seven pre-defined EZH2 mutations assessed in the screening assay may~~will~~ be evaluated for the presence of additional, undefined, mutations in the EZH2 gene
- DNA analyses may be performed for somatic mutations in genes of interest (including, but not limited to, EZH2, ~~and~~ UTX, BAP1, ARID1A, SMARCB1, SMARCA4, and PBRM1)~~) by next-generation sequencing or alternative methodology~~. Translocations including, but not limited to, BCL-2, BCL-6 and c-MYC, which have been observed in DLBCL, may also be assessed
- Circulating cell free-DNA (cfDNA) analysis of blood/plasma

- Circulating biomarker (DNA, RNA and/or protein) analysis of plasma
- RNA transcriptome analysis of blood and/or tissue samples.
- Measurement of the levels of a subset of RNA species ~~o~~in blood and/or tissue samples
- Analysis of protein expression by IHC or an alternative method may also be performed for proteins~~genes~~ of interest. ~~including, but not limited to, JARID-2~~

Section 7.6.1 Tumor Biomarker Analysis

REVISED TEXT

To evaluate candidate biomarkers and identify novel predictors of sensitivity and/or resistance to GSK2816126, DNA, RNA or protein measurements will be assessed in archival tumor tissue or fresh biopsies. Specific tests, exploratory analyses and tissue requirements for each tumor type are indicated below and/or Table 6.

~~DLBCL/tFL patients: A requirement for inclusion in this study is availability of archival tissue, or willingness to undergo fresh biopsy for the following:~~

- ~~Confirmation of GCB-subtype DLBCL status by analysis of tumor by IHC using the standard methods (DLBCL subjects)~~
- ~~Confirmation of EZH2 WT status by targeted sequencing of EZH2 gene (DLBCL and tFL subjects)~~
- ~~DNA, RNA or protein measurements to identify predictors of sensitivity or resistance to GSK2816126~~
- ~~All other patients will be asked to submit an archival tumor specimen for retrospective DNA, RNA or protein testing of potential markers of sensitivity and/or resistance; however this will not be an eligibility requirement.~~

Section 7.6.1.1 GCB-DLBCL Subtyping (DLBCL subjects only)

REVISED TEXT

Central confirmation of GCB DLBCL status will be confirmed by an IHC test utilizing the Choi algorithm [Choi, 2009] in part 1 and 2.

Local testing, in advance of central confirmation may be performed to determine GCB status for enrollment using the Choi algorithm or a suitable alternative algorithm.

Section 7.6.1.2 EZH2 Mutation Analysis (required for study entry in Part 2 for GCB-DLBCL and tFL subjects only)

REVISED TEXT

Screening for eligibilityfor Part 2 of the study will be conducted using either an NGS-based gene panel or a custom quantitative real time polymerase chain reaction (RT-PCR)

test based on TaqMan PCR chemistry. Both~~The~~ tests detect~~s~~ 7 known activating mutations in the EZH2 gene: Y641F (c.1937A>T); Y641N (c.1936T>A); Y641S (c.1937A>C); Y641H (c.1936T>C); Y641C (c.1937A>G); A677G (c.2045C>G); and A687V (c.2075C>T) ~~.(Althea[DX], 2014).~~

EZH2 mutation analysis on archival tumor samples or fresh biopsies from subjects enrolled in Part 1 may also be performed, though the presence of an EZH2 mutation is not required for study entry in Part 1.

~~Retention of screen-failure tumor tissue: all or a portion of archival or fresh biopsy tissue from screen-failure subjects, used for central testing of GCB-DLBCL or EZH2 mutation status, will be retained. This tissue may be used in the validation of potential diagnostic assays to detect EZH2 mutations and/or for GCB-DLBCL subtyping.~~

Section 7.6.2 Circulating cell free DNA/RNA Analysis

REVISED TEXT

Plasma samples may~~will~~ be analyzed to investigate mutations, including but not limited to EZH2, in cfDNA.

~~Tumor-specific cfDNA levels detected in plasma or serum have been found to correlate with increasing tumor burden and decline following therapy. Furthermore, cfDNA in cancer subjects can harbor many genetic alterations (mutations, microsatellite alterations, aberrant methylation), which are generally consistent with the tumor. Thus, tumor-specific circulating cfDNA has the potential to be a useful biomarker of therapeutic response as well as offering a less invasive blood based technique for identifying and selecting subjects for certain treatments. Given the promise of cfDNA blood based test for subject selection, this test will be explored to determine whether EZH2 mutations in cfDNA correlate with that in the tumor tissue from which it is derived. This test will also be explored to correlate increasing cfDNA levels with increasing tumor burden.~~ Tumor-specific circulating cell-free deoxyribonucleic acid (cfDNA) levels detected in plasma or serum have been found to correlate with increasing tumor burden and decline following therapy. Furthermore, cfDNA in cancer participants can harbor many genetic alterations (mutations, microsatellite alterations, aberrant methylation), which are generally consistent with the tumor. Additionally exosomes, released from tumors cells into circulation, which contain both DNA and RNA are increasingly being recognized as important source of cancer biomarkers. Thus, tumor-specific circulating cfDNA and exosomes have the potential to be a useful source of biomarkers of therapeutic response as well as offering a less invasive blood based technique for identifying and selecting participants for certain treatment. Methylation status of cfDNA may also be investigated.

Section 7.6.4 RNA Expression Research ~~of a Subset of RNA Species~~

REVISED TEXT

Transcriptional (RNA) analyses may be performed to better understand changes in gene expression profile upon treatment with GSK2816126 in tumor tissue and/or blood..

~~Blood and tissue samples will be collected for RNA expression analyses of a subset of RNA species.~~

RNA expression studies may be conducted using RNA-seq, quantitative RT-PCR, and/or alternative equivalent technologies, which can facilitate the simultaneous measurement of the relative abundances of RNA species resulting in a RNA expression profile for each blood and tumor tissue sample. The RNAs assayed may be those involved in tumor pathogenesis, the absorption, distribution, metabolism, or excretion of GSK2816126, or in the subject's response to GSK2816126. In addition, continuing research may identify other proteins or regulatory RNAs that may be involved in response to GSK2816126 or tumor pathogenesis. The RNAs that code for these proteins and/or regulatory RNAs may also be studied. This will enable the evaluation of changes in RNA expression profiles that may correlate with biological response relating to specific ~~lymphoma, other~~ cancers, and medically related conditions or the action of GSK2816126.

Section 7.6.5 Tumor Tissue collection

REVISED TEXT

Part 1:

- DLBCL subjects: the availability of archived tissue (or willingness to undergo fresh biopsy) is required for determination of EZH2 mutation status, and/or GCB-subtype.

- All other subjects: an archival tumor specimen (or willingness to undergo fresh biopsy) for retrospective DNA, RNA or protein testing of potential markers of sensitivity and/or resistance. ~~however, this will not be an eligibility requirement.~~ Subjects for whom archived tissue is not available and biopsies are not feasible will be eligible for enrolment and participation in the study at the discretion of the GSK medical monitor. Contact GSK medical monitor for confirmation of enrollement and sudy entry if biopsies are not feasible.

- Pre and post treatment biopsies for PD and translational research activities are optional for all subjects.

Part 2:

- DLBCL cohorts: a fresh tumor biopsy is required for all screened subjects to determine EZH2 mutation status and GCB-subtype.

- tFL cohorts: a fresh tumor biopsy is required for all screened subjects to determine EZH2 mutation status.
- MM cohort: an archival tumor specimen or fresh tumor biopsy is required.
- PK/PD cohorts: Pre treatment and post treatment biopsies are required
- Pre and post treatment biopsies for PD and translational research activities are optional for all other subjects.

Retention of screen-failure tumor tissue: all or a portion of archival or fresh biopsy tissue from screen-failure subjects, used for central testing of GCB-DLBCL or EZH2 mutation status, will be retained. This tissue may be used in the validation of potential diagnostic assays to detect EZH2 mutations and/or for GCB-DLBCL subtyping.

~~The availability of archived tissue (or willingness to undergo fresh biopsy) is required for all screened lymphoma subjects for determination of EZH2 mutation status, and/or GCB-subtype of DLBCL subjects.~~

~~A tumor biopsy at progression for biomarker research is recommended for all subjects.~~

~~For Part 1 PK/PD cohorts, pre-treatment and post-treatment tumor biopsies will be initially optional. At MTD, mandatory collection of pre- and post-treatment tumor biopsies will be required for further enrollment of subjects in a PK/PD cohort. Mandatory biopsies may be instituted: at lower dose levels once evidence of target engagement has been demonstrated in surrogate tissue (H3K27me3 from PBMCs in blood); or if sufficient evidence of target engagement (e.g. dose dependence) is not observed in PD assay from surrogate tissue. Optional tumor biopsies may be requested for all or a portion of subjects in Part 2. Subjects for whom biopsies are not feasible will be eligible for enrollment and participation in study at the discretion of the GSK medical monitor. Contact GSK medical monitor for confirmation of enrollment and study entry if biopsies are not feasible.~~

A tumor biopsy at progression for biomarker research is recommended for all subjects.

Further details on sample requirements and collection will be provided in the SPM.

Section 7.6.6 Blood collection

REVISED TEXT

Blood samples will be collected at multiple time points from all subjects on study (Parts 1 and 2) for pharmacodynamic and exploratory biomarker testing (Section 7.1).

A change in frequency of blood biomarker sampling times may be implemented based on emerging data. This would be determined by GSK and documented in formal communication to sites for implementation but would not require a protocol amendment.

Further details on sample requirements and collection will be provided in the SPM.

Section 7.7 Evaluation of Anti-Cancer Activity

Rationale for Change: Clarifiations to the timing of disease assessments and Response Criteria to be used per tumor types. Added response criteria for subjects enrolled with prostate cancer.

REVISED TEXT

Disease assessment may include imaging and physical examination (as indicated for palpable/superficial lesions). Refer to Appendix 4 for more details on response assessment criteria.

- Disease assessment for lymphomas will be completed within 4 weeks of first dose of GSK2816126 and repeated 8 weeks after dosing is initiated, every 12 weeks thereafter, and at the final study visit.

- Disease assessment for solid tumors will be completed within~~at~~ ~~4~~8 weeks of first dose of GSK2816126 and repeated every 8 weeks after dosing is initiated~~thereafter~~, and at the final study visit.

- Disease assessment for MM will be completed within 4 weeks of first dose of GSK2816126, week 4 and repeated every 6weeks thereafter.

Section 7.7 Evaluation of Anti-Cancer Activity

REVISED TEXT

For subjects with NHL, the following B symptoms should be assessed at the time points in the Time and Events Table (Section 7.1):

- night sweats without signs of infection
- unintentional weight loss of ≥10% within the previous 6 months
- recurrent, unexplained fever of greater than 38^{o}C for 2 weeks without signs of infection

If a lymphoma subject had involvement of bone marrow at baseline, and a CR is suspected, a bone marrow biopsy must be obtained~~ as described in Section 7.2.1~~. A repeat bone marrow biopsy will be performed within 8 weeks of the imaging confirmed CR in accordance with the response guidelines. ~~(~~See Appendix 4: Section 15.4 for additional details~~)~~.

Tumor response will be assessed as outlined above and in the Time and Events Schedule by the investigator using:

- Lymphoma Subjects: Revised Response Criteria for Malignant Lymphoma (RRCLM)(Appendix 4)

- Solid Tumor RECIST 1.1 (Appendix 5)

- Multiple Myeloma: International Myeloma Working Group (IMWG) (Appendix 6)

- Prostate: RECIST 1.1 and PSA (Appendix 7)

Section 7.8 Genetic Research

REVISED TEXT

The information regarding genetic research is included in Appendix 8 ~~Appendix 6.~~

Section 8.3.1 Liver Chemistry Stopping Criteria

Rationale for Change: The Liver Events section was reorganized with updated tables and figures. Stopping/monitoring criteria for subjects with baseline ALT ≤2.5xULN have not changed. Stopping/monitoring criteria rules were further clarified for subjects with documented liver metastases/tumor infiltration at baseline and entry criteria ALT>2.5xULN but ≤5xULN. Study treatment restart/rechallange criteria was added. Details moved to Appendix 3.

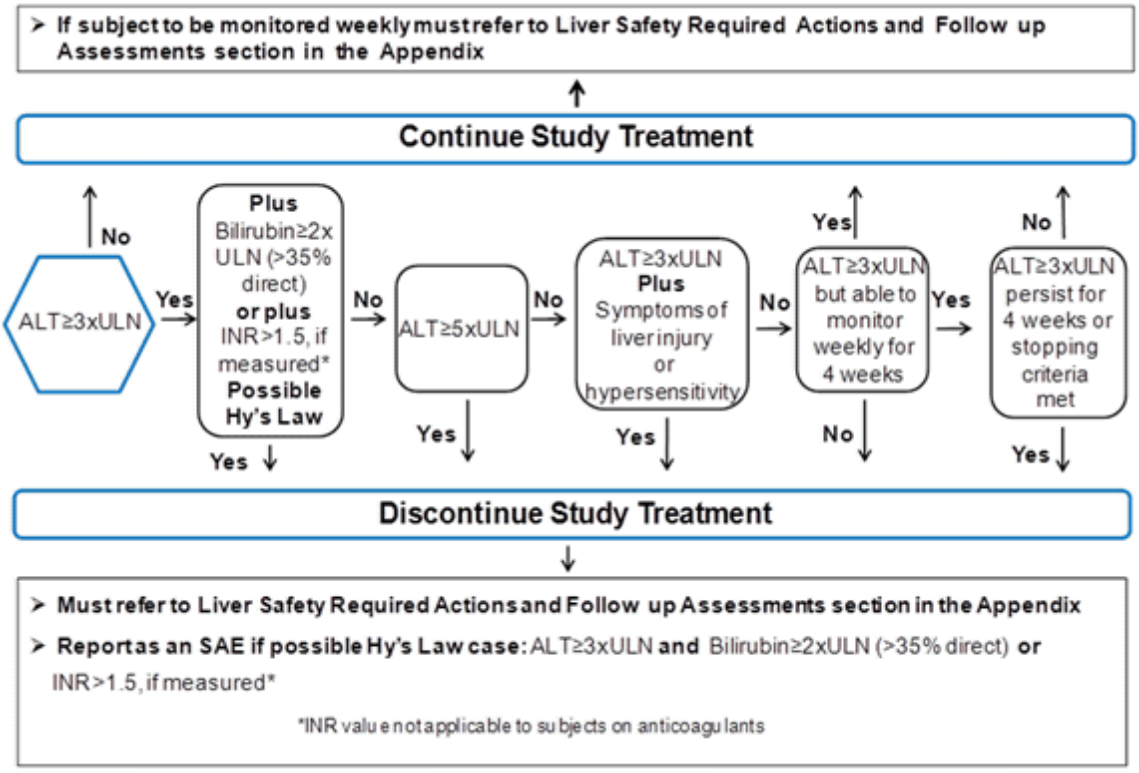
REVISED TEXT

Liver chemistry threshold stopping criteria have been designed to assure subject safety and to evaluate liver event etiology during administration of study treatment(s) and the follow-up period (in alignment with the FDA premarketing clinical liver safety guidance). ~~Study treatment(s) will be stopped if any of the following liver chemistry stopping criteria is/are met:~~

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

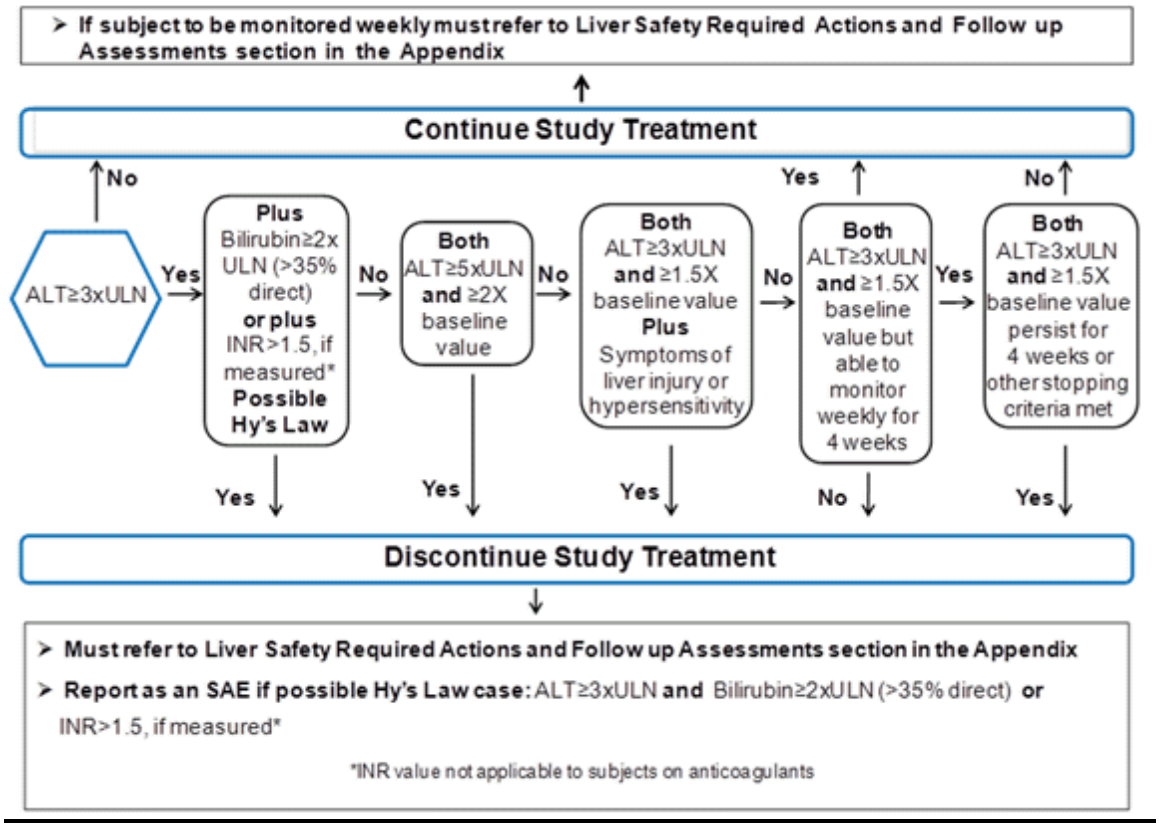
See Figure 1 and Figure 2 for liver stopping criteria for subjects without and with liver metastases, respectively. The algorithms are best read from left to right.

Figure 1 Phase I/II Liver Chemistry Stopping and Increased Monitoring Algorithm for Subjects WITH entry criteria ALT ≤2.5xULN



Liver Safety Required Actions and Follow up Assessments Section can be found in Appendix 3

Figure 2 Phase I/II Liver Chemistry Stopping and Increased Monitoring Algorithm including Subjects WITH documented liver metastases/tumor infiltration at baseline AND entry criteria ALT>2.5xULN but ≤5xULN



Liver Safety Required Actions and Follow up Assessments Section can be found in Appendix 3

Section 8.3.1.1 Study Treatment Restart or Rechallenge

If subject meets liver chemistry stopping criteria do not restart/rechallenge subject with study treatment unless:

- GSK Medical Governance approval is granted
- Ethics and/or Institutional Review Board (IRB) approval is obtained, if required, and
- Separate consent for treatment restart/rechallenge is signed by the subject

Refer to Appendix 3 for full guidance

- ~~ALT ≥3 times ULN and bilirubin ≥2 times ULN (or ALT ≥3 times ULN and INR >1.5)~~

~~**NOTE:** Serum bilirubin fractionation should be performed if testing is available. If fractionation is unavailable, urinary bilirubin is to be measured via dipstick (a measurement of direct bilirubin, which would suggest liver injury).~~

- ~~ALT ≥5 times ULN.~~
- ~~ALT ≥3 times ULN if associated with the appearance or worsening of rash or hepatitis symptoms (fatigue, nausea, vomiting, right upper quadrant pain or tenderness or jaundice) or hypersensitivity (such as fever, rash or eosinophilia).~~
- ~~ALT ≥3 times ULN persists for ≥4 weeks.~~
- ~~ALT ≥3 times ULN and cannot be monitored weekly for 4 weeks.~~

~~Subjects with ALT ≥3 times ULN **and** <5 times ULN **and** bilirubin <2 times ULN, who do not exhibit hepatitis symptoms or rash, can continue study treatment(s) as long as they can be monitored weekly for 4 weeks. See following section for details on weekly follow-up procedures for these subjects.~~

~~Liver Chemistry Follow-up Procedures~~

~~Refer to the diagram in Appendix 3 for a visual presentation of the procedures listed below.~~

~~The procedures listed below are to be followed if a subject meets the liver chemistry stopping criteria defined in Section 8.3.1:~~

~~Immediately and permanently withdraw the subject from study treatment.~~

~~Notify the GSK Medical Monitor within 24 hours of learning of the abnormality to confirm the subject's study treatment(s) cessation and follow-up.~~

~~Complete the "Safety Follow-Up Procedures" listed below.~~

~~Complete the liver event eCRFs. If the event also meets the criteria of a SAE (see Section 8.2) the SAE data collection tool will be completed separately with the relevant details.~~

~~Upon completion of the safety follow-up permanently withdraw the subject from the study and do not rechallenge with study treatment(s).~~

~~Safety Follow-Up Procedures for subjects with ALT ≥3 times ULN:~~

~~Monitor subjects **weekly** until liver chemistries (ALT, AST, alkaline phosphatase [ALP], and bilirubin) resolve, stabilize or return to within baseline values.~~

~~Safety Follow-Up Procedures for subjects with ALT ≥3 times ULN and bilirubin ≥2 times ULN (or ALT ≥3 times ULN and INR >1.5):~~

~~This event is considered an SAE~~ ~~(see Section 8.2). Serum bilirubin fractionation should be performed if testing is available. If fractionation is unavailable, urinary bilirubin is to be measured via dipstick (a measurement of direct bilirubin, which would suggest liver injury).~~

~~Make every reasonable attempt to have subjects return to the clinic within 24 hours~~

for repeat liver chemistries, additional testing, and close monitoring (with specialist or hepatology consultation recommended).

Monitor subjects **twice weekly** until liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) resolve, stabilize or return to within baseline values.

In addition, for all subjects with ALT ≥3 times ULN, every attempt must be made to also obtain the following:

- Viral hepatitis serology including:
  - Hepatitis A Immunoglobulin M (IgM) antibody.
  - Hepatitis B surface antigen and Hepatitis B Core Antibody.
  - Hepatitis C RNA.
  - Cytomegalovirus IgM antibody.
  - Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing).
  - Hepatitis E IgM antibody (if subject resides outside the United States (US) or Canada, or has traveled outside US or Canada in past 3 months).
- Blood sample for PK analysis, obtained within 96 hours of last dose. Record the date/time of the PK blood sample draw and the date/time of the last dose of study treatment(s) prior to blood sample draw on the eCRF. If a PK sample cannot be collected in the time period indicated above, **do not obtain a PK sample**. Instructions for sample handling and shipping are included in the SPM.
- Serum creatine phosphokinase and lactate dehydrogenase.
- Fractionate bilirubin, if total bilirubin ≥2 times ULN.
- Obtain complete blood count with differential to assess eosinophilia.
- Record the appearance or worsening of clinical symptoms of hepatitis or hypersensitivity such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash or eosinophilia, on the AE eCRF.
- Record use of concomitant medication(s), acetaminophen, herbal remedies, other over-the-counter medication(s), or putative hepatotoxins on the Concomitant Medications eCRF.
- Record alcohol use on the Liver Events eCRF.
- The following are required for subjects with ALT ≥3 times ULN **and** bilirubin ≥2 times ULN but are optional for other abnormal liver chemistries:
- Anti-nuclear antibody, anti-smooth muscle antibody, and Type 1 anti-liver kidney microsomal antibodies.
- Liver imaging (ultrasound, MRI or CT scan) to evaluate liver disease.
- Liver Imaging and/or Liver Biopsy eCRFs are also to be completed if these tests are performed.

- ~~Serum acetaminophen adduct HPLC assay (quantifies potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week [James, 2009]).~~

~~Only in those with underlying chronic hepatitis B at study entry (identified by positive hepatitis B surface antigen): quantitative hepatitis B DNA and hepatitis delta antibody. **NOTE**: if hepatitis delta antibody assay cannot be performed, it can be replaced with a PCR of hepatitis D RNA virus (where needed) as outlined in: .~~

Rationale for Change: Removal of section as there have been no pre-defined disease-related events.

~~Section 8.4 Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as SAEs~~

~~An event which is part of the natural course of the disease under study (i.e., disease progression or hospitalization due to disease progression) does not need to be reported as a SAE. Death due to disease under study is to be recorded on the Death eCRF. However, if the underlying disease (i.e., progression) is greater than that which would normally be expected for the subject, or if the investigator considers that there was a causal relationship between treatment with study treatment(s) or protocol design or procedures and the disease progression, then this must be reported as a SAE.~~

Section 9.1 Permitted Medications

Rationale for Change; The section was updated to clarify permitted medications for use during the study.

REVISED TEXT

Subjects should receive full supportive care during the study, including transfusions of blood and blood products, and treatment with antibiotics, antiemetics, antidiarrheals, and analgesics, and other care as deemed appropriate and in accordance with their institutional guidelines and considering the list of contra-indicated medicines included in Section 9 of the protocol.

Palliative radation and/or surgical intervention is permitted after discussion with the GSK medical monitor and documenting the treatment in the eCRF.

~~Subjects should not receive other anti-cancer therapy [including chemotherapy, radiation therapy, immunotherapy, biologic therapy, investigational therapy, hormonal therapy (other than leuprolide or other GnRH agonists), surgery or tumor embolization] while on treatment in this study. Other anti-cancer therapy should not be administered unless one of the following occurs: documented disease progression; unacceptable or unmanageable toxicity; subject is withdrawn from the study at the investigator's discretion or consent is withdrawn; or no further clinical benefit is anticipated which requires permanent discontinuation of study drug. Note, palliative radiation and/or surgical intervention may~~

~~be permitted (for example to address pain management) and should be discussed with the GSK medical monitor prior to intervention to determine appropriate dosing and schedule.~~

~~The only caveat is that subjects should not receive those medications listed as prohibited in Section 9.2~~

Questions regarding concomitant medications should be directed to the GSK Medical Monitor for clarification.

Section 9.2 Prohibited and Ceautionary Mmedications

Rationale for Change; Section 9.2, Section 9.3 and Section 9.4 were updated with most recent drug interaction data, including updating the prohibited and cautionary medication tables. Use of therapeutic warfarin was clarified and additional monitoring for bleeding added. Use of anticoagulants that do not have reversal agents available were included as prohibited. Based on review of QTc data from the study with the GSK co-chairs of the QT panel and Global Safety Board, it was agreed that the restriction on the administration of drugs possibly associated with Torsade de Pointes could be relaxed and will be included as medications to be used with caution (Table 14). Additional ECG assessments will be recommended when these medications are initiated after Cycle 1. Exclusion and withdrawal criteria for cardiac monitoring will remain as stated in the protocol (e.g., patients with a QTc > 450 msec are excluded from entry and patients > 500 msec will be withdrawn as dictated by the protocol).

REVISED TEXT

Subjects should not receive those medications listed as prohibited in Section 9.2

Subjects should not receive other anti-cancer therapy, ~~(~~including chemotherapy, radiation therapy, immunotherapy, biologic therapy, investigational therapy,~~and~~ hormone therapy (other than leuprolide or other GnRH angonists for mCRPC), surgery or tumour embolization~~other than for replacement)~~ while on treatment in this study. Other anti-cancer therapy should not be administered unless one of the following occurs: documented disease progression; unacceptable or unmanageable toxicity; subject is withdrawn from the study at the investigator's discretion or consent is withdrawn; or no further clinical benefit is anticipated which requires permanent discontinuation of study drug. ~~Subjects should not receive any other investigational anti-cancer drugs within 28 days or five half-lives, whichever is shorter with a minimum of 14 days, preceding the first dose of GSK2816126.~~

~~Warfarin used for therapeutic doses of anticoagulation is~~ Concurrent use of therapeutic warfarin may be allowed. However, increased monitoring of INR and bleeding with dose titration for warfarin is recommended due to potential increase in warfarin concentration when administered with study treatment GSK2816126. Anticoagulants that do not have reversal agents available are prohibited~~PROHIBITED~~ from 14 days prior to the first dose of study drug through completion of the Final Study Visit~~. Prophylactic warfarin (e.g., to maintain central venous access patency) is permitted.~~

Section 9.2.1 Drugs that may alter the Pharmacokinetics of GSK2816126

It has been demonstrated in vitro that GSK2816126 is metabolized by CYP3A enzymes.~~,~~ ~~h~~Ho~~o~~wever, turnover in human liver microsomes and hepatocytes was low and the relative contribution of this pathway to the elimination of GSK2816126 is presently unknown. GSK2816126 has also been shown to be a substrate of P-gp and BCRP transporters. ~~and may be a substrate for OATP transporters.~~

Therefore, substances that potently inhibit or induce CYP3A, P-gp or BCRP ~~or OATP~~ (Table 9) should be avoided during the course of the study where possible as these drugs could lead to higher/lower exposure in subjects, potentially leading to alterations of the pharmacologic effects of GSK2816126.

The impact of inhibition of P-gp or BCRP on~~by~~ GSK2816126 pharmacokinetics has not been assessed in humans. Drugs that are mild to moderate inhibitors of P-gp and BCRP should be administered with caution because they may alter GSK2816126 levels (Table 10).

Table 9 Prohibited Drugs Potentially Affecting GSK2816126 Pharmacokinetics Resulting in Increased or Decreased GSK2816126 Exposure

PROHIBITED – strong inducers/inhibitors of CYP3A, ~~CYP2C8,~~ Pgp, Bcrp, ~~or OATP~~ since levels of GSK2816126 may be decreased/increased	
Strong CYP~~2C8~~/3A/Pgp/Bcrp Inhibitor/Inducer	**Therapeutic Area**
clarithromycin, telithromycin, rifamycin class agents (e.g. rifampin, rifabutin, rifapentine) troleandomycin	Antibiotics
itraconazole, ketoconazole	Antifungals
Nefazodone	Antidepressants
Amprenavir, atazanivir delaviridine, fosamprenavir indinavir, lopinavir,nelfinavir, ritonavir, saquinavir, tipranivir	Antiretrovirals, Protease Inhibitors
~~*Gemfibrozil*~~	~~Hyperlipidemia~~
carbamazepine, cyclosporine, phenobarbital, amiodarone	Miscellaneous

Table 10 Use with Caution Drugs Potentially Affecting GSK2816126 Pharmacokinetics Resulting in Increased or Decreased GSK2816126 Exposure

USE WITH CAUTION – Potential for Inducers/inhibitors of CYP3A, ~~CYP2C8,~~ Pgp and BCRP~~crp~~ since levels of GSK2816126 may be decreased/increased	
Mild/Moderate CYP3A or Pgp Inhibitor/Inducer	**Therapeutic Area**
~~*erythromycin*~~	~~Antibiotic~~
~~*fluconazole*~~*, voriconazole*	Antifungal
diltiazem, verapamil	Antiarrhythmics
Cortisone (>50 mg), hydrocortisone (>40 mg), prednisone or prednisolone (>10 mg), methylprednisolone or triamcinolone (>8 mg), betamethasone or dexamethasone (>1.5 mg)	Glucocorticoids (oral)
aprepitant, cimetidine, montelukast,	Miscellaneous
2. NOTE: Topical or inhaled steroids are permitted.	

Section 9.3 Drugs that may have their Pharmacokinetics altered by GSK2816126

REVISED TEXT

The potential for pharmacokinetic interactions with drugs likely to be co-administered with GSK2816126 in vivo has not been assessed. In vitro data suggests that GSK2816126 has the potential to inhibit CYP2C8, CYP2C9, CYP2C19, and CYP3A (IC50's <9 μM). GSK2816126 does not appear to be an inhibitor of CYP1A2 or CYP2D6. GSK2816126 is also an in vitro inhibitor of human transporters BCRP, OATP1B1, OATP1B3, OCT2, MATE1 and MATE2-K (IC_{50} values of 21, 13, 34, 2.88, 0.025 and 0.95 μM, respectively) In addition, GSK2816126 was shown to activate human PXR (EC_{50} = 6.3 μM) and, therefore, may have the potential to induce CYP enzymes. A further in vitro study showed induction of CYP3A4 mRNA with a calculated EC_{50} of 4.22-5.43 μM and E_{max} of 3.22-16.5-fold.~~GSK2816126 has also been shown to activate human PXR which is known to induce several drug metabolizing enzymes, primarily CYP3A4.~~

These results suggest that narrow therapeutic index medications that are substrates of CYP2C8, CYP2C9, CYP2C19 and CYP3A4, and/or transporters BCRP, OATP, OCT2, MATE1 and MATE2-K should be prohibited as their levels may be increased, and could lead to adverse effect (Table 11). C~~o~~o-administration of sensitive substrates of these CYPs and/or transporters~~and narrow therapeutic index medications metabolized by CYP2C9~~ should be used with caution~~prohibited~~ as their levels may be increased or decreased (Table 11~~Table 12~~)). Discussion by the PI/staff with the GSK medical monitor(s) must occur before use of these drugs.

~~In addition, narrow therapeutic index medications metabolized by CYP2C8, CYP2C19 and CYP3A4 should also be prohibited as their levels may be increased or decreased (Table 11). However, sensitive medications metabolized by CYP2C8, CYP2C19 and CYP3A4 may be administered with caution (Table 12).~~

Table 11 Prohibited Drugs Potentially Affected by GSK2816126

PROHIBITED – highly sensitive and/or low therapeutic index CYP3A/CYP2C8/CYP2C9/CYP2C19/OCT2/MATE substrates since levels of these drugs may be increased	
CYP3A Substrate	**Therapeutic Area**
alprazolam, diazepam, midazolam, triazolam	Hypnotics and Sedatives
diergotamine, ergotamine, eletriptan	Antimigraine agents
~~*duloxetine,*~~ *pimozide,* ~~*buspirone*~~	Antidepressant, Antipsychotics, Antianxiety agents
cyclosporine, sirolimus, tacrolimus	Immunosuppressive agents
astemizole	Antihistamine
sildenafil, tadalafil, vardenafil	Erectile Dysfunction agents
eplerenone	Selective Aldosterone Blockers
tizanidine	Muscle Relaxant
quinidine	Antiarrhythmics
CYP2C8, CYP2C9 and CYP2C19 Substrate	
Amiodarone	Antiarrhythmics
Paclitaxel	Anticancer
tolbutamide, nateglinide ~~*amitryptyline,*~~	Antidiabetic
~~*amitriptyline, clomipramine, imipramine*~~	~~Antidepressants~~
phenytoin, s-mephenytoin	Anticonvulsants
~~*Warfarin,*~~ *acenocoumarol*	Anticoagulant
Cyclophosphamide	Immunosuppressant
OCT2, MATE1, MATE2-K Substrate	
Cisplatin	Anticancer
Dofetilide, pilsicainide, procainamide	Antiarrhythmics

Table 12 Use with Caution - Drugs Potentially Affected by GSK2816126

USE WITH CAUTION – Monitor for side effects since levels of these drugs may be increased. Consider dose reduction.	
CYP2C8/9/19/3A/OATP1B1/OATP1B3 Substrate	**Therapeutic Area**
felodipine	Calcium Channel Blockers
lovastatin, rosuvastatin, atorvastatin, fluvastatin	HMG-CoA Reductase Inhibitors
oral budesonide	Corticosteroids
fentanyl, alfentanil	Analgesics
Warfarin, cilostazole*	Anticoagulants and Antiplatelets
Rosiglitazone**, repaglinide**	Antidiabetics
OCT2, MATE1, MATE2-K Substrate	
captopril	Anti-Hypertensive
ganciclovir, tenofovir	Antiviral
gabapentin,	Anticonvulsants

USE WITH CAUTION – Monitor for side effects since levels of these drugs may be increased. Consider dose reduction.	
certirizine, ranitidine	H2 Blocker
metformin	Antidiabetics
atecegatran metoxil	Anticoagulants
glycopyrronium	Respiratory, COPD
pindolol, triamterene	Antihypertension
varenicline	Others
USE WITH CAUTION – Monitor for loss of efficacy or substitute another medication	
Substrates of CYP3A4/CYP2B6 that are affected by induction	**Therapeutic Area**
~~ciprofloxacin, levofloxacin, moxifloxacin, gatifloxacin, gemifloxacin~~, doxycycline, chloramphenicol, ~~erythromycin~~	Antibiotics
caspofungin, ~~fluconazole,~~ terbinafine	Antifungals
enalapril, diltiazem, amlodipine, nifedipine, nisoldipine	Antihypertensives
amitriptyline, nortriptyline, desipramine, imipramine, protriptyline, clomipramine, doxepin	Antidepressants
glipizide, glyburide, ~~tolbutamide~~, tolazamide, chlorpropamide	Antidiabetics
zonisamide, valproate, divalproex	Anticonvulsants
buspirone	Antidepressant, Antipsychotics, Antianxiety agents
buprenorphine, naloxone, naltrexone, nalmefene	Opioid agonist/antagonists
aprepitant, clofibrate, ~~disopyramide~~, tramadol, methohexital, estazolam, galantamine, ~~haloperidol,~~ leflunomide, solifenacin, sulfasalazine,	Miscellaneous

*Concurrent use of therapeutic warfarin may be allowed. Increased monitoring of INR and bleeding with dose titration of warfarin is recommended due to potential increase in warfarin concentration when co-administered with GSK2816126. However, anticoagulants that do not have reversal agents available are prohibited

Section 9.4 Drugs and QT prolongation

REVISED TEXT

Co-administration of medications that are known to prolong the QT interval ~~or have a~~and have a ~~possible~~ risk of causing Torsades de Pointes ~~(latest list available on www.crediblemeds.org)~~ are PROHIBITED for 5 half-lives of the drug with a minimum of 14 days prior to the first dose of study drug until discontinuation from the study drug with the exception of amiodarone which is prohibited beginning 6 months prior to Screening through discontinuation from the study. (However, there may be situations when the subject is on study and Advanced Cardiac Life Support requires the use of amiodarone, which should be used as per local clinical guidelines). The medications with a risk of torsade de pointes are provided in Table 13.

Co-administration of medication that are known to prolong the QT interval and have a possible risk of causing Torsades de Pointes "possible-torsadogenic medication"are to be used with Extreme Caution beginning 14 days prior the first dose of study drug until discontinuation from the study. On starting cautionary medications such as in Table 14, additional ECG monitoring should be implemented after cycle 1. Additional ECGs should be taken at the next scheduled study visit following the initiation of the "possible-torsadogenic medication". If there are no abnormalities, regular cardiac safety monitoring can be resumed per Table 6. If there are abnormalities, implement additional cardiotoxcity monitoring as addressed in Section 3.8.1. and contact GSK Medical Monitor.

~~while the medications with a possible risk of torsade de pointes are provided in Table 14 (but are not limited to):~~ Neither list is all inclusive and subject to change based on evolving data. Both tables are taken from the www.crediblemeds.org website available as of 09-Jan-2017. Latest list of medications is available on www.crediblemeds.org website.

Questions regarding concomitant medications whould be directed to the GSK Medical Monitor.

Table 13 Drugs ~~with~~ known to prolong the QT interval and have a Risk of Torsades de Pointes that are ~~not permitted~~PROHIBITED for Co-Administration with GSK2816126

Generic Name	Drug Class	Generic Name	Drug Class
Amiodarone	Anti-arrhythmic	Haloperidol	Anti-psychotic
Anagrelide	Phosphodiesterase 3 inhibitor	Ibogaine(only on non US Market)	Psychedelic
Arsenic trioxide	Anti-cancer	Ibutilide	Anti-arrhythmic
Astemizole (Removed from ~~US~~ Market)	Antihistamine	Levofloxacin	Antibiotic
Azithromycin	Antibiotic	Levomepromazine(Only on Non US Market)	Antipsychotic
Bepridil (Removed from ~~US~~ Market)	Anti-anginal	Levomethadyl acetate (Removed from ~~US~~ Market)	Opiate
Chloroquine	Anti-malarial	Levosulpiride (only on non US Market)	Antipsychotic
Chlorpromazine	Anti-psychotic / Anti-emetic	Mesoridazine (Removed from ~~US~~ Market)	Anti-psychotic
Cilostazol	Phosphodiesterase 3 inhibitor	Methadone	Opiate
Ciprofloxacin	Antibiotic	Moxifloxacin	Antibiotic
Cisapride (Removed from ~~US~~ Market)	GI stimulant	Ondansetron	Anti-emetic

Generic Name	Drug Class	Generic Name	Drug Class
Citalopram	Anti-depressant, SSRI	Oxaliplatin	Antineoplastic Agent
Clarithromycin	Antibiotic	Papaverine HCL (Intra-coronary)	Vasodilator, Coronary
Cocaine	Local anesthetic	Pentamidine	Antibiotic
Disopyramide	Anti-arrhythmic	Pimozide	Anti-psychotic
Dofetilide	Anti-arrhythmic	Probucol (Removed from ~~US~~ Market)	Antilipemic
Domperidone (Only o~~O~~n non US Market)	Anti-nausea	Procainamide ~~(Oral off US mkt)~~	Anti-arrhythmic
Donepezil	Cholinesterase inhibitor	Propofol	Anaesthetic, general
Dronedarone	Anti-arrhythmic	Quinidine	Anti-arrhythmic
Droperidol	Anti-psychotic / Anti-emetic	Roxithromycin (Only on Non US Market)	Antibiotic
Erythromycin	Antibiotic	Sevoflurane	Anesthetic, general
Escitalopram	Anti-depressant, SSRI	Sotalol	Anti-arrhythmic
Flecainide	Anti-arrhythmic	Sparfloxacin (Removed from ~~US~~ Market)	Antibiotic
Fluconazole	Antifungal	Sulpiride (Only non US Market)	Anti-psychotic, atypical
Gatifloxacin (Removed from Market)	Antibiotic	Sulyopride (Only on Non US Market)	Anti-psychotic, atypical
Grepafloxacin (Off market worldwide)	Antibiotic	Terlipressin (Only on non US Market)	Vasoconstrictor
Halofantrine	Anti-malarial	Terfenadine (Removed from US Market)	Antihistamine
		Thioridazine	Anti-psychotic
		Vandetanib	Anti-cancer

Data Source: : www.crediblemeds.org (9 January 2017~~-27 February 2015~~)

Table 14 Drugs Known to prolong the QT interval with a Possible Risk of Torsades de Pointes that ~~are~~ are Permitted for co-administration with Extreme Caution~~Prohibited~~

Generic Name	Drug Class	Generic Name	Drug Class
Alfuzosin	Alpha1-blocker	Mirabegron	Beta3 adrenergic antagonist
Apomorphine	Dopamine agonist	Mirtazapine	Anti-depressant, Tetracyclic
Aripiprazole	Anti-psychotic, atypical	Moexipril/HCTZ	Anti-hypertensive
~~Atazanavir~~	~~Anti-viral~~	Nicardipine	Anti-hypertensive
Artenimol+piperaquine	Antimalarial	Nilotinib	Kinase inhibitor
Asenapine	Anti-psychotic, atypical	Norfloxacin	Antibiotic
Atomoxetine	Norepinephrine reuptake	Nortriptyline	Antibiotic

Generic Name	Drug Class	Generic Name	Drug Class
	inhibitor		
Bedaquiline	Antibiotic	Ofloxacin	Antibiotic
Bendamustine	Alkylating agent	~~Olanzapine~~	~~Anti-psychotic, atypical~~
Bortezomib	Proteasome inhibitor	Osimertinib	Tyrsine kinase inhibitor
Bosutinib	Tyrosine kinase inhibitor	Oxytocin	Oxytocic
Buprenorphine	Opioid receptor modulator	Paliperidone	Anti-psychotic, atypical
Capecitabine	Anticancer	Panobinostat	Histone deacetylase inhibitor
Ceritinib	Kinase inhibitor	Pasireotide	Somatostatin analog
Clomipreamine	Antidepressant, Tricyclic	Pazopanib	Tyrosine kinase inhibitor
Clozapine	Anti-psychotic, atypical	Perflutren lipid microspheres	Imaging contrast agent
Crizotinib	Kinase inhibitor	Perphenazine	Antipsychotic
Cyamemazine (cyamepromazine)(Only on Non US Market)	Antipsychotic	Pipamperone (On non US Market)	Antipsychotic
Dabrafenib	Anti-cancer	Promethazine	Anti-psychotic / Anti-emetic
Dasatinib	Tyrosine kinase inhibitor	~~Quetiapine~~	~~Anti-psychotic, atypical~~
Degarelix	Gonadotropin Releasing Hormone	~~Ranolazine~~	~~Anti-anginal~~
Delamanid (Only on Non US Market)	Antibiotic	Rilpivirine	Anti-viral
Desipramine	Antidepressant, Tricyclic	Risperidone	Anti-psychotic, atypical
Dexmedetomidine	Sedative	~~Roxithromycin (On non US Market)~~	~~Antibiotic~~
~~Dihydroartemisinin+ piperaquine~~	~~Anti-malarial~~	Romidepsin	Histone deacetylase inhibitor
Dolasetron	Anti-emetic~~nausea~~	Saquinavir	Anti-viral
Efavirenz	Antiretroviral	Sertindole (On non US Market)	Anti-psychotic, atypical
Eribulin mesylate	Anti-cancer	Solifenacin	Muscle Relaxant
Ezogabine (Retigabine)	Anticonvulsant	Sorafenib	Tyrosine kinase inhibitor
Famotidine	H2-receptor antagonist	Sunitinib	Anti-cancer
Felbamate	Anti-convulsant	~~Tacrolimus~~	~~Immunosuppressant~~
Fingolimod	Sphingosine phospate receptor modulator	Tamoxifen	Anti-cancer
Flupentixol (Only on Non US Market)	Dopamine 2 and 5HT2a antagonist	Telavancin	Antibiotic
Foscarnet	Anti-viral	Telithromycin	Antibiotic
~~Fosphenytoin~~	~~Anti-convulsant~~	Tetrabenazine ~~(Orphan drug in US)~~	Monoamine Transporter Inhibitor
~~Gatifloxacin (Removed from US Market)~~	~~Antibiotic~~	Tiapride (Only on Non US Market)	Selective D2, D3 dopamine antogonist
Gemifloxacin	Antibiotic	Tizanidine	Muscle relaxant
Granisetron	Anti-emetic~~nausea~~	Tolterodine	Muscle relaxant
Hydrocodone-ER	Analgesic	Toremifene	Estrogen agonist/antagonist

Generic Name	Drug Class	Generic Name	Drug Class
Iloperidone	Anti-psychotic, atypical	Trimipramine	Antidepressant, Tricyclic
Imipramine (melipramine)	Antidepressant, Tricyclic	Tropisetron (only on Non US Market)	Antiemetic
Isradipine	Anti-hypertensive	Vardenafil	Phosphodiesterase inhibitor
Lapatinib	Anti-cancer	Vemurafenib	Kinase Inhibitor
Lenvatinib	Anticancer	Venlafaxine	Anti-depressant, SNRI
Leuprolide	Gonadotropin Receptor Anonist	Vorinostat	~~Anti-Cancer~~Histone deacetylase inhibitor
Lithium	Anti-mania	~~Zipracidone~~	~~Anti-psychotic, atypical~~
Melperone (Only on Non US Market)	Antipsychotic, atypical	Zotepine (Only on Non US Market)	Anti-psychotic, atypical
Mifepristone	Progesterone antagonist		
Data Source: : www.crediblemeds.org (27 February 20159 January 2017)			

If a subject requires medication for hyperemesis, due to the potential of serotonin 5-HT3 receptor antagonists to increase QTcF, palonosetron and ondansetron at a maximum oral dose of 8 mg TID are the only allowed drugs in this class. Intravenous administration of these drugs are not permitted.

Section 10.1.1 Female Subjects

Rationale for Change: Update to reflect current GSK guidance and document standards and to align with Inclusion criteria.

REVISED TEXT

A female of non-childbearing potential is defined as:

- Post menopausal women (including all women 60 years of age or older) with 1 year without menses with an appropriate clinical profile (e.g. age appropriate, >45 years) in the absence of hormone replacement therapy (HRT) or medical suppression of the menstral cycle (e.g. leuprolide treatment). In questionable cases for women <60 years of age, a blood sample with simultaneous follicle stimulating hormone (FSH) and estradiol falling into the central laboratory's post-menopausal reference range is confirmatory [Kronenberg, 2008; Strauss and Barbieri, 2004]. Females under 60 years of age, who are on hormone replacement therapy (HRT) and whose menopausal status is in doubt, will be required to use one of the contraceptive methods listed below if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of post menopausal status prior to study enrollment. For most forms of HRT, at least 2-4 weeks will elapse between the cessation of therapy and the blood draw, this interval depends on the type and dosage of HRT. Following confirmation of their post menopausal status, they can resume use of

HRT during the study without use of a contraceptive method. If laboratory values for FSH and estradiol are drawn and the results do not confirm menopause on a potential subject that otherwise met the specifications for being post menopausal as defined below without question, the subject may still enroll in the study as a female of non-childbearing potential if approved by the medical monitor and the safety physician..

- Females under 60 year of age with a documented bilateral tubal ligation or salpingectomy, hysteroscopic tubal occlusion procedure with follow up confirmation of bilateral tubal occlusion, hysterectomy or bilateral oophorectomy (surgical menopause) and no plans to utilize assisted reproductive techiniques (e.g., in vitro fertilization or donor embryo transfer).

~~(i.e., physiologically incapable of becoming pregnant) is defined as any female who has had a hysterectomy, bilateral oophorectomy (ovariectomy) or bilateral tubal ligation, or is post-menopausal.~~

~~A practical definition accepts menopause after 1 year without menses with an appropriate clinical profile, e.g., age appropriate, >45 years in the absence of hormone replacement therapy (HRT). In questionable cases, the subject must have a follicular stimulating hormone (FSH) value >40 mIU/mL and an estradiol value <40 pg/mL (<140 pmol/L).~~

A female of childbearing potential is defined as any female who does not meet the criteria of non-childbearing potential as described in the previous paragraph and to also include:

- Females with functioning ovaries (i.e. post menarche, premenopausal women with no documented impairment of oviduct or uterine function that would cause sterility).
- Females with oligomenorrhea, females who are peri-menopausal and young females who have begun to menstrusate.

Female subjects of childbearing potential must not become pregnant during the study and so must be sexually inactive by abstinence or use non-hormonal contraceptive methods with a failure rate of <1% per year when used consistently and correctly and , when applicable, in accordance with the product label. These are defined below.

Requirements for Female Subjects of Reproductive Potential: Contraceptive Methods with a Failure Rate of <1% per year:

- GSK2816126 is a potential CYP3A enzyme inducer which may decrease the efficacy of ~~oral~~hormonal contraceptives. Therefore the use of ~~oral~~hormonal contraceptives is excluded ~~except when used with the double barrier method.~~
- ~~Oral contraceptives alone are not adequate in use with this compound.~~
- ~~Contraceptive subdermal implant~~

- ~~Double-barrier method: condom and occlusive cap (diaphragm or cervical/vault caps) plus vaginal spermicidal agent (foam/gel/film/cream/suppository).~~
- ~~Estrogenic vaginal ring if not contraindicated for this subject population or per local practice.~~
- ~~Percutaneous contraceptive patches if not contraindicated for this subject population or per local practice. Implants of levonorgestrel if not contraindicated for this subject population or per local practice. Injectable progesterone if not contraindicated for this subject population or per local practice.~~
- Non-hormonal i~~I~~ntrauterine device (IUD) or intrauterine system (IUS) that meets the <1% failure rate as stated in the product label.
- Male partner sterilization (vasectomy with documentation of azoospermia) prior to the female subject's entry into the study, and this male is the sole partner for that subject. For this definition, "documented" refers to the outcome of the investigator's/designee's medical examination and/or semen analysis of the subj*e*ct or review of the subject's medical history ~~for study eligibility~~or medical history interview provided by the subject or her partner., ~~as obtained via a verbal interview with the subject or from the subject's medical records.~~

These allowed methods of contraception are only effective when used consistently, correctly and in accordance with the product label. The investigator is responsible for ensuring subjects understand how to properly use these methods of contraception.

Section 10.1.2 Male Subjects

Rationale for Change: Update to reflect current GSK guidance and document standards and to align with Inclusion criteria.

REVISED TEXT

To prevent pregnancy in a female partner or to prevent exposure of any partner to the study treatment from a male subject's semen, male subjects must use one of the following contraceptive methods from the time of first dose of study medication until at least 2 weeks (14 days) following last dose of study medication:

- Vasecetomy with documentation of azoospermia or bilateral orchiectomy. The documentation on male sterility can come from the site personnel's; review of subjects medical records, medical examination and/or semen analysis, or medical history interview provided by the subject or his partner.
- Abstinence from penile-vaginal intercourse, defined as sexual inactivity consistent with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

- ~~Complete abstinence from sexual intercourse for 14 days prior to first dose of study treatment, through the dosing period, and for at least one week after the last dose of study treatment.~~
- Male c~~C~~ondom plus partner use of a highly effective contraceptive (< 1% rate of failure per year as stated in the product label) such as intrauterine device or system or hormonal birth control such as contraceptive subdermal implant, combined estrogen and progestogen oral contraceptive, injectable progestogen, contraceptive vaginal ring, or percutaneous contraceptive patches. ~~*(during non-vaginal intercourse with any partner - male or female)* OR~~
- ~~Double-barrier method: condom and occlusive cap (diaphragm or cervical/vault caps) plus spermicidal agent (foam/gel/film/cream/suppository) *(during sexual intercourse with a female)*~~

These allowed methods of contraception are only effective when used consistently, correctly and in accordance with the product label. The investigator is responsible for ensuring subjects understand how to properly use these methods of contraception.

Section 10.4 Sun and UV Exposure Restrictions

Rationale for Change: Clarified the time period subjects should minimize exposure to sunlight.

REVISED TEXT

Prior to starting study drug, subjects should be instructed to follow the below procedures from the time of first dose of study medication until at least 2 weeks (14 days) following last dose of study medication due to long elimination phase of GSK2816126:

- Minimize or avoid prolonged exposure to natural or artificial sunlight (e.g., tanning beds, sunlamps, UVA or UVB treatments)
- Wear loose fitting clothing with long sleeves, sunglasses, and broad rim hat that protect the skin from sun exposure AND use a broad spectrum sunscreen (e.g., UVA and UVB protective with minimum SPF 30) on any uncovered areas of the body if outdoors

Section 12.1.1 Part 1: Dose-Escalation Phase

Rationale for Change: Updated Section 12 to include - GCB-DLBCL cohort expansion added into Part 1 dose escalation phase. The study design was based on predictive probability methodology (Lee, 2008) to allow interim futility/efficacy assessment by comparing the overall responses with the pre-specified futility and efficacy stopping criteria, in order to enabling early decision of opening Part 2 expansion phase or terminating the trial. Due to the improvement of response rates of cancer treatments over time, the study designs in Part 2 expansion phase based on predictive probability method were revised by updating the null and alternative hypothesis, to align with the current typical response rates. The sample size and futility stopping criteria for each cohort (GCB-DLBCL mutant and wild type, tFL mutant and wild type, and MM) are updated

REVISED TEXT

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

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 utilize descriptive methods only.

The cohort expansion of GCB-DLBCL subjects in Part 1 will assess the overall response rate (p) of GCB-DLBCL patients. The null and alternative hypotheses for the overall response rate are detailed below:

The null hypothesis is:

H_0: p≤20%

The alternative hypothesis is:

H_A: p≥40%

For cohort expansion of solid tumor subjects in Part 1, there is no formal statistical hypothesis are being tested. Analysis of the data obtained from solid tumor expansion will utilize descriptive methods only.

Section 12.1.2 Part 2: Expansion Cohorts

REVISED TEXT

The null hypothesis and alternative hypothesis for the four expansion cohorts of GCB-DLBCL and tFL patients in Part 2 are same as those in Part 1. That is, for each cohort:

The null hypothesis is:

H_0: p≤20%

The alternative hypothesis is:

H_A: p≥40%

For MM cohort, the null hypothesis is:

H_0: p≤10%

The alternative hypothesis is:

H_A: p≥25%

~~For Part 2, hypothesized response rates are provided in Section 12.2.2. In this case, a test that the response rate is less than or equal to the null hypothesis rate is being performed using the stopping rules provided in Section 3.4. Descriptive statistics will be used to describe the observed response rates at the RP2D dose used in the expanded cohorts.~~

Section 12.2 Sample Size Determination

REVISED TEXT

The sample size planned for Part 1 arises from the predefined criteria for dose selection and is not driven by statistical considerations.

In addition, Part 1 expansion may include up to 27 GCB-DLBCL subjects at MTD/RP2D twice-weekly for 3 out of 4 weeks followed by 1 week off. This will allow futility/success analysis with type I error rate no more than 0.1and at least 80% of power. Additionally, 15 subjects with solid tumors or prostate cancer may be enrolled for the evaluation of safety, futility and efficacy.

The additional ~~129~~ 168 subjects in Part 2 of the study (which includes ~~approximately 30~~up to 32 subjects each for the EZH2 mutant and EZH2 WT GCB-DLBCL populations, and ~~16 subjects each for the~~ up to 32 subjects each for EZH2 mutant and EZH2 WT tFL populations as well as up to ~~37~~40 MM subjects) will provide additional safety and tolerability information about the treatment and a better precision around the response rate estimate.

Approximately 168 subjects will be enrolled in Part 2 in five expansion cohorts: two GCB-DLBCL cohorts with up to 32 subjects from the EZH2 wild-type population, and up to 32 subjects from the EZH2 mutation positive population, and two tFL cohorts with up to 32 subjects from the EZH2 wild-type population and up to 32 subjects from the EZH2 mutation positive population and up to 40 subjects in the MM cohort. Additional subjects/cohorts may be enrolled to allow for evaluation of additional dose levels.

Section 12.2.1 Part 1: Dose-Escalation Phase

REVISED TEXT

12.2.1.1 Dose Escalation in Part 1

The total number of subjects to be enrolled for dose escalation in Part 1 will depend on the number of subjects needed to characterize individual dose cohorts. The sample size is not driven by statistical considerations. However, it is anticipated that approximately 40 subjects will be enrolled. Given true incidence rates of DLTs, the associated probabilities of escalating to the next dose in a 3+3 scheme are provided for reference below in Table 15.

Table 15 Statistical Basis for Phase I Dose Escalation in a 3+3 Scheme

True incidence of dose-limiting toxicity	10%	20%	30%	40%	50%	60%
Probability of escalating the dose	0.91	0.71	0.49	0.31	0.17	0.08

Section 12.2.1.2 Cohort Expansion in Part 1

For GCB-DLBCL expansion cohort in Part 1, futility and efficacy evaluation of response data will be performed in order to support the early decision of Part 2 expansion. The sample size and stopping rules are based on the predictive probability methodology of Lee & Liu [Lee, 2008]. The predictive probability design is similar to a two-stage design in that it allows for early termination of the trial due to either futility or efficacy. The differences are that the predictive probability design allows for evaluation of stopping rules on an on-going basis, once a minimum number of subjects are evaluable, rather than at only two stages. While the two designs have comparable type I error rates and power, the probability of early termination is greater with the predictive probability design compared with two-stage design.

The detailed decision rules of the design for Part 1 expansion cohort are listed in Table 16. The decision rules to stop the trial for either futility or efficacy were constructed as follows:

- If Predictive probability of response greater than the null hypothesis$<\theta_L$, then stop the trial and reject the alternative hypothesis (i.e., claim futility); and
- If Predictive probability of response greater than the null hypothesis $>\theta_U$, then stop the trial and reject the null hypothesis (i.e., declare efficacy);
- Otherwise continue enrollment,

Where θ_L and θ_U are prespecified lower and upper limit of probabilities for establishing stopping criteria in terms of futility and efficacy, respectively.

The hypothesis of overall response rate (p) of GCB-DLBCL subjects for the cohort expansion design are detailed below.

The null hypothesis is:

H_0: $p \leq 20\%$

The alternative hypothesis is:

H_A:$p \geq 40\%$

As listed in Table 16, the futility/efficacy evaluation will start with 13 subjects and allow for maximum of 27 subjects (including GCB-DLBCL subjects enrolled at the RP2D in the dose escalation phase.) This design will have a type I error rate (α) of 0.087 and a

power of 0.803. In this particular expansion part, the trial is designed to allow stopping for both futility and efficacy. The trial may be stopped early for futility if the predictive probability of the overall response rate greater than the null hypothesis of 20% is very low, i.e.below 5.0% for this design, and may be stopped early for efficacy if the predictive probability of the overall response rate greater than 20% is very high, i.e. 90.0% or above. The type I error rate, power, and predictive probability of success were derived by explicitly stating null and alternative hypothesis of response rate, the minimum and maximum sample size, futility and efficacy stopping boundaries and the selection of the optimizing criterion as the maximization of power under the alternative hypothesis. The Bayesian prior used in determining the design was Beta (0.15, 0.85), a distribution with a mean response rate of 15%. Under the null hypothesis, that is, if the true response rate is 20%, the expected sample size of the design is 16.48 subjects and probability of early termination (PET) is 96.3%. Under the alternative hypothesis, that is, if the true response rate is at least 40%, the expected sample size of the design is 16.98 subjects and PET is 94.7%.

The input parameters for finding the design shown in Table 16 are:

Nmin	13
Cohort	1
Nmax	27
theta_Lbegin	0.05
theta_Lend	0.05
theta_Lstep	0.001
theta_Upper	0.9
theta_Tbegin	0.9
theta_Tend	0.9
theta_Tstep	0.001
p_0	0.2
p_1	0.4
Prior a0	0.15
Prior b0	0.85
Type I Error	0.1
Power	0.8

Table 16 Stopping Rules for GSK2816126 Part 1 GCB-DLBCL Cohort Expansion

No. of Subjects Evaluated for Response	Stopping Criteria [1]	
	Stop for Futility if No. of Responders (CR+PR) Less Than or Equal To This Number	Declaration of Efficacy if No. of Responders (CR+PR) Greater Than or Equal To This Number
13	2	6
14	2	7
15	2	7
16	3	7
17	3	7
18	3	8
19	4	8
20	4	8
21	5	8
22	5	9
23	5	9
24	6	9
25	6	9
26	7	9
27	8	9

[1]: The specific criteria for stopping the GCB-DLBCL expansion cohort for futility or efficacy. For instance, if there are 20 subjects, then the trial may be stopped for futility if No. of Responders ≤ 4, or Part 2 opened for efficacy if No. of Responders ≥ 8.

Section 12.2.2 Part 2: Expansion Cohort

REVISED TEXT

~~An initial dose escalation will be used to establish the RP2D for GSK2816126. Once the final dose is confirmed, at least 12 and up to 30 subjects in both GCB-DLBCL mutation status cohorts, up to 16 subjects in both tFL mutation status cohorts and up to 37 subjects with MM will be enrolled at that dose, using decision rules defined in in Figure 1, Figure 2 and Figure 3. The sample size and stopping rules are based on the methodology of Lee & Liu [Lee, 2008].~~

Upon completion of cohort expansion in Part 1 and the totality of data supports opening Part 2, GCB-DLBCL and tFL patients in both mutation status, as well as patients with MM will be enrolled at RP2D for Part 2 study. There are 5 cohorts in Part 2, i.e. 2 cohorts for GCB-DLBCL patients (mutant and wild type), 2 cohorts for tFL petients (mutant and wild type), and 1 cohort for MM patients.

For each of GCB-DLBCL and tFL cohorts, at least 10 subjects and up to 32 subjects will be enrolled at the RP2D (including subjects enrolled in the previous stage), using decision rules defined in Table 17. The sample size and stopping rules are based on the methodology of Lee & Liu [Lee, 2008].

The assumptions underlying the design are detailed below for both GCB-DLBCL ~~and tFL~~ cohorts. The null hypothesis is:

H_0: p≤20~~10~~%

The alternative hypothesis is:

H_A:p≥**40**~~10~~%

~~For GCB-DLBCL cohorts, starting with 12 subjects and allowing for a maximum sample size of 30, this design will have a type I error rate (α) of 0.062 and 88.9% power when the true response rate is 30%. The trial is not designed to stop early for efficacy, but is designed to stop early for futility if the predictive probability of success is 5.0% or less. The type I error rate, power, and predictive probability of success to stop early for futility were derived from explicitly stating the minimum and maximum sample size, futility stopping rate and selection of the optimizing criterion as the maximization of power under the alternative hypothesis. The Bayesian prior used in determining the design was Beta (0.15, 0.85), a distribution with a mean response rate of 15%. Under the null hypothesis, if the true response rate is 10%, the expected sample size of the design is 18 subjects per expansion cohort and probability of early termination (PET) is 88.7%. Under the alternative hypothesis, if the true response rate is 30%, the expected sample size of the design is 29 subjects per expansion cohort and PET is 8.8%.~~

~~The assumptions underlying the design are detailed below for both tFL cohorts. The null hypothesis is:~~

~~H_0: p≤5%~~

~~The alternative hypothesis is:~~

~~H_A;p>5%~~

~~For tFL cohorts, starting with 12 subjects and allowing for a maximum sample size of 16, this design will have a type I error rate (α) of 0.043 and 80.1% power when the true response rate is 25%. The trial is not designed to stop early for efficacy, but is designed to stop early for futility if the predictive probability of success is about 1.0% or less. The type I error rate, power, and predictive probability of success to stop early for futility were derived from explicitly stating the minimum and maximum sample size, futility stopping rate and selection of the optimizing criterion as the minimization of the power under the alternative hypothesis. The Bayesian prior used in determining the design was Beta (0.05, 0.95), a distribution with a mean response rate of 5%. Under the null hypothesis, if the true response rate is 5%, the expected sample size of the design is 14 subjects per expansion cohort and probability of early termination (PET) is 83.3%.~~

~~Under the alternative hypothesis, if the true response rate is 30%, the expected sample size of the design is 16 subjects per expansion cohort and PET is 8.5%.~~

As listed in Table 17, the futility/efficacy evaluation will start with 10 subjects and until maximum of 32 subjects. This design allows to stop early for futility only. The design will have a type I error rate (α) of 0.066 and a power of 0.801. The trial may be stopped early for futility if the predictive probability of the overall response rate greater than the null hypothesis of 20% is below 10% for this design. The type I error rate, power, and predictive probability of success were derived by explicitly stating null and alternative hypothesis of response rate, the minimum and maximum sample size, futility and efficacy stopping boundaries and the selection of the optimizing criterion as the maximization of power under the alternative hypothesis. The Bayesian prior used in determining the design was Beta (0.15, 0.85), a distribution with a mean response rate of 15%. Under the null hypothesis, that is, if the true response rate is 20%, the expected sample size of the design is 16.06 subjects and probability of early termination (PET) is 90.8%. Under the alternative hypothesis, that is, if the true response rate is at least 40%, the expected sample size of the design is 29.16 subjects and PET is 18.1%.

The input parameters for the design shown in Table 17 are:

Nmin	10
Cohort	1
Nmax	32
theta_Lbegin	0.1
theta_Lend	0.1
theta_Lstep	0.001
theta_Upper	1
theta_Tbegin	0.9
theta_Tend	0.9
theta_Tstep	0.001
p_0	0.2
p_1	0.4
Prior a0	0.15
Prior b0	0.85
Type I Error	0.1
Power	0.8

Table 17 Stopping Rules for GSK2816126 GCB-DLBCL and tFL Cohort Expansion in Part 2

Number of evaluable subjects	Stop for Futility if No. of Responders (CR+PR) Less Than or Equal To This Number
10	1
11	1
12	2
13	2
14	2
15	3
16	3
17	3
18	3
19	4
20	4
21	4
22	5
23	5
24	5
25	6
26	6
27	6
28	7
29	7
30	8
31	8
32	9

For MM cohort, at least 14 subjects and up to 40 subjects will be enrolled at the RP2D, using decision rules defined in Table 18. The sample size and stopping rules are based on the methodology of Lee & Liu [Lee, 2008]. ~~The assumptions underlying the design are detailed below for MM subjects.~~ The null hypothesis underlying the design is:

H_0: $p \leq 10\sout{5}\%$

The alternative hypothesis is:

H_A; $p \geq 25\sout{5}\%$

The input parameters for the design shown in Table 18 are:

Nmin	14
Cohort	1
Nmax	40
theta_Lbegin	0.1
theta_Lend	0.1
theta_Lstep	0.001
theta_Upper	1
theta_Tbegin	0.9
theta_Tend	0.9
theta_Tstep	0.001
p_0	0.1
p_1	0.25
Prior a0	0.1
Prior b0	0.9
Type I Error	0.1
Power	0.8

Table 18 Stopping Rules for GSK2816126 Cohort Expansion of MM Subjects in Part 2

Number of evaluable subjects	Stop for Futility if No. of Responders (CR+PR) Less Than or Equal To This Number
14	1
15	1
16	1
17	1
18	1
19	1
20	1
21	2
22	2
23	2
24	2
25	2
26	2
27	3
28	3

Number of evaluable subjects	Stop for Futility if No. of Responders (CR+PR) Less Than or Equal To This Number
29	3
30	3
31	3
32	4
33	4
34	4
35	4
36	4
37	5
38	5
39	5
40	6

As listed in Table 18, the futility/efficacy evaluation will start with 14 subjects until maximum of 40 subjects (including MM subjects enrolled at the RP2D in the dose escalation phase, if any). This design allows to stop early for futility only. The design will have a type I error rate (α) of 0.072 and a power of 0.814. The trial may be stopped early for futility if the predictive probability of the overall response rate greater than the null hypothesis of 10% is below 10% for this design. The type I error rate, power, and predictive probability of success were derived by explicitly stating null and alternative hypothesis of response rate, the minimum and maximum sample size, futility and efficacy stopping boundaries and the selection of the optimizing criterion as the maximization of power under the alternative hypothesis. The Bayesian prior used in determining the design was Beta (0.10, 0.90), a distribution with a mean response rate of 10%. Under the null hypothesis, that is, if the true response rate is 10%, the expected sample size of the design is 20.82 subjects and probability of early termination (PET) is 89.0%. Under the alternative hypothesis, that is, if the true response rate is at least 25%, the expected sample size of the design is 36.56 subjects and PET is 16.7%.

~~Starting with 13 subjects and allowing for a maximum sample size of 37, this design will have a type I error rate (α) of 0.032 and about 85% power when the true response rate is 20%. The trial is not designed to stop early for efficacy, but is designed to stop early for futility if the predictive probability of success is about 1.0% or less. The type I error rate, power, and predictive probability of success to stop early for futility were derived from explicitly stating the minimum and maximum sample size, futility stopping rate and selection of the optimizing criterion as the minimization of the power under the alternative hypothesis. The Bayesian prior used in determining the design was Beta (0.20, 0.80), a distribution with a mean response rate of 20%. Under the null hypothesis, if the true response rate is 5%, the expected sample size of the design is 22 subjects and probability of early termination (PET) is 91%. Under the alternative hypothesis, if the~~

~~true response rate is 20%, the expected sample size of the design is 36 subjects per expansion cohort and PET is 10%.~~

Section 12.3.3.1 Primary Comparisons of Interest

REVISED TEXT

All available data, including adverse events, changes in laboratory values and other safety parameters will be evaluated for each dose cohort in Part 1, in addition to futility and success analyses, and for each expansion cohort in Part 2.

Section 12.3.4 Interim Analysis

REVISED TEXT

12.3.4.1 Part 1

~~No formal interim analysis will be performed for Part 1 of the study. Safety, PK, and PD marker data will be examined during Part 1. Prior to determining the GSK2816126 dose for the next cohort, exploratory analyses will be conducted to assess the relationship of GSK2816126 dose levels with safety, PK and PD parameters using all data from available cohorts.~~

Futility and efficacy interim analysis of overall response rate will be performed continuously for GCB-DLBCL expansion cohort in Part 1 of the study, after 13 subjects have been enrolled. In addition, safety, PK, and PD marker data will be examined during Part 1. Prior to determining the GSK2816126 dose for the next cohort, exploratory analyses will be conducted to assess the relationship of GSK2816126 dose levels with safety, PK and PD parameters using all data from available cohorts. If success criteria are reached at an interim analysis for GCB-DLBCL at MTDRP2D twice-weekly every 3 out of 4 weeks followed by 1 week off, and the totality of data support opening Part 2, then Part 2 will begin and Part 1 expansion will close.

Full details of procedures and of the analyses planned at the interim analysis will be provided in the Reporting and Analysis Plan (RAP).

Section 12.3.4 Interim Analysis

REVISED TEXT

Section 12.3.4.2 Part 2

For each expansion cohort, after the initial ~~12~~ 10 subjects have enrolled at the RP2D dose, response data will be reviewed on an ongoing basis and the number of responses observed will be compared with the stopping rules provided in Section ~~3.4~~12.2.2.. In

addition, safety, PK, and PD marker data will be analyzed. Full details of procedures and of the analyses planned at the interim analysis will be provided in the Reporting and Analysis Plan (RAP).

Section 12.4.1.4 Efficacy Analyses

REVISED TEXT

Anti-tumor activity for lymphoma subjects will be assessed based on the Response Criteria listed in Section 15.4. Anti-tumor activity for subjects with solid tumors will be assessed based on the Response Criteria listed in 15.5. Anti-tumor activity for subjects with MM will be assessed based on the Response Criteria listed in 15.6. Anti-tumor activity for subjects with prostate cancer will be assessed based on the Response Criteria listed in 15.7. The response data will be summarized by study part, and cohort within Part 2. Full details will be specified in the RAP.

Section 14 REFERENCES

Rationale for Change: Included new references and reformatted list. Moved references for appendices to the appropriate appendix.
REVISED TEXT

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Section 15.3 Appendix 3: Liver Chemistry Monitoring, Interruption Stopping and Follow-up Criteria

Rationale for Change: The Liver Events section was reorganized with updated tables and figures. Stopping/monitoring criteria for subjects with baseline ALT ≤2.5xULN have not changed. Stopping/monitoring criteria rules were further clarified for subjects with documented liver metastases/tumor infiltration at baseline and entry criteria ALT>2.5xULN but ≤5xULN. Study treatment restart/rechallange criteria was added. Details added to Appendix 3.

REVISED TEXT

Section 15.3.1 Liver Safety Stopping Criteria and Required Action and Follow up Assessments

Phase I/II liver chemistry stopping and increased monitoring criteria have been designed to assure subject safety and evaluate liver event etiology (in alignment with the FDA premarketing clinical liver safety guidance).
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf.

Phase I/II liver chemistry stopping criteria and required follow up assessments

Liver Chemistry Stopping Criteria – Liver Stopping Event **Subject with entry criteria ALT≤ 2.5 x ULN**	
ALT-absolute	ALT ≥ 5xULN
ALT Increase	ALT ≥ 3xULN persists for ≥4 weeks
Bilirubin[1, 2]	ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin)
INR[2]	ALT ≥ 3xULN **and** INR>1.5, if INR measured
Cannot Monitor	ALT ≥ 3xULN **and** cannot be monitored weekly for 4 weeks
Symptomatic[3]	ALT ≥ 3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity
Liver Chemistry Stopping Criteria – Liver Stopping Event **Including subjects with documented liver metastases/tumor infiltration at baseline AND entry criteria ALT>2.5 x ULN but ≤5 x ULN**	
ALT-absolute	**Both** ALT ≥ 5xULN **and** ≥2x baseline value
ALT Increase	**Both** ALT ≥ 3xULN **and ≥** 1.5x baseline value that persists for ≥4 weeks
Bilirubin[1, 2]	ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin)
INR[2]	ALT ≥ 3xULN **and** INR>1.5, if INR measured
Cannot Monitor	**Both** ALT ≥ 3xULN **and ≥** 1.5x baseline value that cannot be monitored for 4 weeks
Symptomatic[3]	**Both** ALT ≥ 3xULN **and ≥** 1.5x baseline value associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity

Required Actions and Follow up Assessments following ANY Liver Stopping Event	
Actions	**Follow Up Assessments**
• **Immediately** discontinue study treatment • Report the event to GSK **within 24 hours** • Complete the liver event eCRF and complete an SAE data collection tool if the event also meets the criteria for an SAE[2]	• Viral hepatitis serology[4] • Blood sample for pharmacokinetic (PK) analysis, obtained approximately 48h after last dose[5] • Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).

- Perform liver event follow up assessments
- Monitor the subject until liver chemistries resolve, stabilize, or return to within baseline (see **MONITORING** below)
- **Do not restart/rechallenge** subject with study treatment unless allowed per protocol and GSK Medical Governance approval **is granted** (refer to Appendix 3)
- If restart/rechallenge is **not granted**, permanently discontinue study treatment and may continue subject in the study for any protocol specified follow up assessments

MONITORING:

For bilirubin or INR criteria:

- Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24 hrs**
- Monitor subjects twice weekly until liver chemistries resolve, stabilize or return to within baseline
- A specialist or hepatology consultation is recommended

For All other criteria:

- Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24-72 hrs**
- Monitor subjects weekly until liver chemistries resolve, stabilize or return to within baseline
- Fractionate bilirubin, if total bilirubin≥2xULN
- Obtain complete blood count with differential to assess eosinophilia
- Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form
- Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications
- Record alcohol use on the liver event alcohol intake case report form

For bilirubin or INR criteria:

- Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG or gamma globulins).
- Serum acetaminophen adduct high pressure liquid chromatography (HPLC) assay (quantifies potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week [James, 2009]).
- Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy eCRF forms.

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that subject if ALT ≥ 3xULN **and** bilirubin ≥ 2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin) or ALT ≥ 3xULN **and** INR>1.5, if INR measured which may indicate severe liver injury (possible 'Hy's Law'), **must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis)**; INR measurement is not required and the threshold value stated will not apply to subjects receiving anticoagulants
3. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or

eosinophilia)

4. Includes: Hepatitis A IgM antibody; Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM); Hepatitis C RNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody
5. Record the date/time of the PK blood sample draw and the date/time of the last dose of study treatment prior to blood sample draw on the eCRF. If the date or time of the last dose is unclear, provide the subject's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SRM.

Phase I/II Oncology liver chemistry increased monitoring criteria with continued therapy

Liver Chemistry Increased Monitoring Criteria – Liver Monitoring Event	
Criteria	**Actions**
Subject with entry criteria ALT≤2.5x ULN ALT ≥3xULN **but** <5xULN **and** bilirubin <2xULN, **without** symptoms believed to be related to liver injury or hypersensitivity **and** who can be monitored weekly for 4 weeks **Subject with documented liver metastases/tumor infiltration at baseline AND entry criteria ALT>2.5 x ULN but ≤5 x ULN** ALT ≥3x ULN and 1.5x baseline value **but** ALT <5x ULN and 2x baseline value **and** bilirubin <2xULN**, without** symptoms believed to be related to liver injury, or hypersensitivity **and** who can be monitored weekly for 4 weeks	• Notify the GSK medical monitor **within 24 hours** of learning of the abnormality to discuss subject safety. • Subject can continue study treatment • Subject must return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) until they resolve, stabilise or return to within baseline[1] • If at any time subject meets the liver chemistry stopping criteria, proceed as described above **For subjects with entry criteria ALT≤2.5 x ULN** • If, after 4 weeks of monitoring, ALT <3xULN and bilirubin <2xULN, monitor subjects twice monthly until liver chemistries normalize or return to within baseline. **For subjects with documented liver metastases/tumor infiltration at baseline AND entry criteria ALT>2.5 x ULN but ≤5 x ULN** • If, after 4 weeks of monitoring, ALT <3xULN and <1.5x baseline value, and bilirubin <2xULN, monitor subjects twice monthly until liver chemistries normalize or return to within baseline

1. For the purpose of these guidelines "baseline" refers to laboratory assessments performed closest and prior to first dose of study treatment

References

James LP, Letzig L, Simpson PM, Capparelli E, Roberts DW, Hinson JA, Davern TJ, Lee WM. Pharmacokinetics of Acetaminophen-Adduct in Adults with Acetaminophen Overdose and Acute Liver Failure. *Drug Metab Dispos* 2009; 37:1779-1784.

Section 15.3.2 Liver Safety – Study Treatment Restart or Rechallenge Guidelines

If subject meets liver chemistry stopping criteria do not restart/rechallenge subject with study treatment unless:

- GSK Medical Governance approval **is granted** (as described below),
- Ethics and/or IRB approval is obtained, if required, and
- Separate consent for treatment restart/rechallenge is signed by the subject

If GSK Medical Governance approval to restart/rechallenge subject with study treatment **is not granted**, then subject must permanently discontinue study treatment and may continue in the study for protocol-specified follow up assessments

1. Rechallenge Following Liver Stopping Events that are Possibly Related to Study Treatment

Following drug-induced liver injury, **drug rechallenge is associated with a 13% mortality across all drugs in prospective studies** [Andrade, 2009]. Clinical outcomes vary by drug, with nearly 50% fatality with halothane readministered within one month of initial injury. However, some drugs seldom result in recurrent liver injury or fatality.

Risk factors for a fatal drug rechallenge outcome include:

- hypersensitivity with initial liver injury (e.g. fever, rash, eosinophilia) [Andrade, 2009]
- jaundice or bilirubin >2xULN with initial liver injury (direct bilirubin >35% of total)
- subject currently exhibits severe liver injury defined by: ALT ≥3xULN, bilirubin ≥2xULN (direct bilirubin >35% of total), or INR≥1.5
- serious adverse event or fatality has earlier been observed with drug rechallenges [Papay, 2009]
- evidence of drug-related preclinical liability (e.g. reactive metabolites; mitochondrial impairment [Hunt, 2010])

Rechallenge refers to resuming study treatment following drug induced liver injury (DILI). Because of the risks associated with rechallenge after DILI this should only be considered for a subject for whom there is compelling evidence of benefit from a critical

or life-saving medicine, there is no alternative approved medicine available, and a benefit:risk assessment of rechallenge is considered to be favourable.

Approval by GSK for rechallenge with study treatment can be considered where:

- Investigator requests consideration of rechallenge with study treatment for a subject who is receiving compelling benefit with study treatment that exceeds risk, and no effective alternative therapy is available.
- Ethics Committee or Institutional Review Board approval for rechallenge with study treatment must be obtained, as required.
- If the rechallenge is approved by GSK Medical Governance in writing, the subject must be provided with a clear description of the possible benefits and risks of study treatment administration, including the possibility of recurrent, more severe liver injury or death.
- The subject must also provide signed informed consent specifically for the rechallenge with study treatment. Documentation of informed consent must be recorded in the study chart.
- Study treatment must be administered at the dose specified by GSK.
- Subjects approved by GSK Medical Governance for rechallenge with study treatment must return to the clinic twice a week for liver chemistry tests until stable liver chemistries have been demonstrated and then standard laboratory monitoring may resume as per protocol.
- If after study treatment rechallenge, subject meets protocol-defined liver chemistry stopping criteria, study treatment should be permanently discontinued.
- Medical Monitor, and the Ethics Committee or Institutional Review Board as required, must be informed of the subject's outcome following study treatment rechallenge.
- GSK to be notified of any adverse events, as per Section 8 of the protocol..

2. Restart Following Transient Resolving Liver Stopping Events NOT Related to Study Treatment

Restart refers to resuming study treatment following liver stopping events in which there is a clear underlying cause (other than DILI) of the liver event (e.g. biliary obstruction, pancreatic events, hypotension, acute viral hepatitis). Furthermore, there should be no evidence of alcoholic hepatitis or hypersensitivity, and the study treatment should not be associated with HLA markers of liver injury.

Approval by GSK for study treatment restart can be considered where:

- Investigator requests consideration for study treatment restart if liver chemistries have a clear underlying cause (e.g., biliary obstruction, hypotension and liver chemistries have improved to normal or are within 1.5 x baseline and ALT <3xULN).

- Restart risk factors (e.g. fever, rash, eosinophilia, or hypersensitivity, alcoholic hepatitis, possible study treatment-induced liver injury or study treatment has an HLA genetic marker associated with liver injury (e.g. lapatinib, abacavir, amoxicillin/clavulanate) are reviewed and excluded
- Ethics Committee or Institutional Review Board approval of study treatment restart must be obtained, as required.
- If restart of study treatment is approved by GSK Medical Governance in writing, the subject must be provided with a clear description of the possible benefits and risks of study treatment administration, including the possibility of recurrent, more severe liver injury or death.
- The subject must also provide signed informed consent specifically for the study treatment restart. Documentation of informed consent must be recorded in the study chart.
- Study treatment must be administered at the dose specified by GSK.
- Subjects approved by GSK Medical Governance for restarting study treatment must return to the clinic once a week for liver chemistry tests until stable liver chemistries have been demonstrated and then laboratory monitoring may resume as per protocol.
- If after study treatment re-start, subject meets protocol-defined liver chemistry stopping criteria, follow usual stopping criteria instructions.
- Medical Monitor, and the Ethics Committee or Institutional Review Board as required, must be informed of the subject's outcome following study treatment restart.
- GSK, or designee, to be notified of any adverse events, as per Section 8.

References:

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Hunt, CM. Mitochondrial and immunoallergic injury increase risk of positive drug rechallenge after drug-induced liver injury: A systematic review. *Hepatol.* 2010;52:2216-2222.

Papay JI, Clines D, Rafi R, Yuen N, Britt SD, Walsh JS, et al. Drug-induced liver injury following positive drug rechallenge. *Regul Tox Pharm*. 2009;54:84-90.

Section 15.4 Appendix 4 Response Criteria

Rationale for Change; included missing criteria for confirmation scans for assigned PR and CR.

REVISED TEXT

Complete Response

To be assigned a status of complete response, all changes must be confirmed by repeat assessments performed no less than four weeks after the criteria for CR were met.

1. Complete disappearance of all detectable clinical evidence of disease and disease related B-symptoms, if present prior to therapy.

Partial Response

To be assigned a status of complete response, all changes must be confirmed by repeat assessments performed no less than four weeks after the criteria for PR were met.

1. At least a 50% decrease from baseline in the SPD of up six of the largest dominant nodes or nodal masses.
2. No increase in the size of the liver or the spleen. No unequivocal progression in any nonmeasurable or nondominant site.
3. Splenic and hepatic nodules must regress by ≥50% in SPD compared to baseline. If only a single nodule/lesion, it must regress by ≥50% in the greatest transverse diameter compared to baseline.
4. With the exception of splenic and hepatic nodules, involvement of other organs is accessible and no measureable disease should be present.
5. Bone marrow assessment is not relevant for determination of a PR if the sample was positive prior to treatment. However, if positive, the cell type should be specified. Subjects who ~~are~~ achieve CR criteria above, except for persistent morphologic bone marrow involvement will be considered partial responders. When the bone marrow was involved before therapy and a clinical CR was achieved, but no bone marrow assessment after therapy, subjects must be considered partial responders.

Relapsed Disease (after CR)/Progressive Disease (after PR, SD)

Criteria for determining PD for new lesions and target lesions are shown in Table 19~~Table 16~~

Table ~~16~~19 Criteria for determining PD for new lesions and target lesions

Cheson B, Pfister B, Juweid M, Gascoyne RD, Specht L, Horning SJ, et al. Revised response criteria for malignant lymphoma. J Clin Oncol 2007; 25:579-586.

Section 15.5 Appendix 5: RECIST 1.1

Rationale for Change: Clarified that baseline bone scans are to be taken as clinically indicated.

REVISED TEXT

I. Efficacy Assessment

- The following are required at baseline: CT for Chest/Abdomen/Pelvis or MRI for Abdomen/Pelvis and clinical disease assessment for palpable lesions, brain scan and bone scan (bone scan as clinically indicated). At each post baseline assessment, evaluations of the sites of disease identified by these scans are required except for brain scan and bone scans. Brain and Bone scans should be performed as clinically indicated.

A baseline bone scan should be performed as clinically indicated~~is required for all subjects~~. For subjects without bone disease at baseline, subsequent bone scans should only be performed as clinically indicated (e.g. presentation of bone pain). For subjects with bone disease at baseline, a bone scan is required as clinically indicated. In addition, in order to assign a response of CR in a subject with bone disease at baseline, a bone scan must be performed 1 week prior to 4 weeks after.

Section 15.5 Appendix 5: RECIST 1.1

REVISED TEXT

IIIg. Independent Review

Disease progression and response evaluations may~~will~~ be collected centrally during the study and may be reviewed or analyzed by an independent central reviewer. Details will be provided in the SPM.

Chung WH, Hung SL, Chen YT. Genetic predisposition of life-threatening antiepileptic-induced skin reactions. Expert Opin. Drug Saf. 2010; 9: 15-21.

Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D, Verweij J. New response evaluation criteria in solid tumors: Revised RECIST guidelines (version 1.1). European Journal of Cancer. 2009; 45: 228-247.

Section 15.7 Appendix 7: Criteria for Response/Progression: Prostate Cancer

Rationale for Change: Included criteria for response/progression for prostate cancer.

REVISED TEXT

15.7.1 Disease Progression Endpoint

The disease progression endpoint is defined by 1 or more of the following criteria:

- PSA progression according to the PCWG3 criteria
    - Subjects are not required to discontinue treatment on the basis of meeting PSA progression alone.
    - PSA progression [Scher2016] is defined as:
        - *If there has been a decline from baseline*: time from start of therapy to first PSA increase that is ≥25% and ≥2 ng/mL in absolute value from the nadir, and which is confirmed by a second value 3 or more weeks later (i.e., a confirmed rising trend) at least 9 weeks after the start of treatment
        - *If there has NOT been a decline from baseline*: time from start of therapy to first PSA increase that is ≥25% and ≥2 ng/mL in absolute value from the baseline value, determined at least 9 weeks after start of treatment
- Radiographic progression by RECIST 1.1 for subjects with measurable disease. (Appendix 5)
- Bone progression on bone scan according to the PCWG3 criteria
    - Bone progression [Scher, 2016] will be determined as the appearance of ≥2 new lesions on bone scan and at least an additional 2 bone lesions at the next scan (every 8 weeks). The date of progression is the date of the first scan that indicates the change. Subjects should not be discontinued from study treatment(s) due to the occurrence of bone scan changes in the first 12 weeks that do not meet PCWG3 guidelines for progression.

Section 15.7.2 Disease Response Endpoints

- PSA response according to the PCWG3 criteria:
    - Only subjects who have a baseline PSA value and at least one post-baseline assessment will be included in the analysis of PSA response.
    - PSA Response Rate is defined as proportion of subjects with a decrease of ≥50% in the PSA concentration from the baseline PSA value determined at least 9 weeks after start of treatment and confirmed after ≥4 weeks by an additional PSA evaluation.

- Radiographic response By Recist 1.1 for subjects with measurable disease (Appendix 5).

Scher HI, Morris MJ, Stadler WM, Higano C, Basch E, Fizazi K, et al. Trial design and objectives for castration-resistant prostate cancer: updated recommendations from the Prostate Cancer Clinical Trials Working Group 3. *Journal of Clinical Oncology.* 2016; doi: 10.1200/JCO.2015.64.2702.

Section 7.1 Time and Events Table(s)

Rationale for Change: Table 6: Reorganized and added minor clarifications throughout. Added footnote to clarify timing of the post treatment Follow Up Visit. Clarified that assessments in the Continuation Phase that are to be done every 4 weeks should occur at Day 1 of the cycle. Assessments during the continuation phase that occur less frequent (i.e., every 8 weeks) have a ± 7 day window. ECOG assessment added to Continuation Phase and Follow Up Visit. Updated requirement that no need to repeat screening labs (chemistry, hematology, coagulation) if done within 72 hours of first dose. Added clarification for tumor tissue collection for different tumor types. Under PD/PK cohort, added collection of blood for metabolite at Cycle 1 Day 1, urine for metabolite 0-24 hour collection at Cycle 1 day 1 and 0-8 hour collection at Day 15. Simplified disease assessments for prostate cancer. Added clarification to footnotes to support study assessments in table 6.

Removed collection of blood for PD (PBMC) biomarkers and added collection of Whole Blood for biomarkers at Cycle 1 Day1 and Day 18 and C2D1(prior to dosing on all days). Recent preclinical data suggests evaluating histone H3 lysine 27 trimethylation (H3K27me3) in certain blood cell populations may be a better PD biomarker then looking at PBMCs as a whole. To evaluate this, a novel whole blood PD assay was developed which allows classification of blood cell populations and quantitation of H3K27me3. This assay will replace the PBMC PD ELISA used prior to amendment 5 and, as such, PBMC samples will no longer be collected

REVISED TEXT

Table 6 Time and Events~~, Treatment Phase: Screening through Day 28~~ (See also PK sampling table for PK sampling schedule on Day 1 and Day 15)

STUDY PHASE		**SCREEN**	**First Treatment Period Cycle 1**				**Continuation Phase Cycle 2 and beyond**	**Follo w-Up[i]**
VISIT		**Screen**	**Day 1 and 4[a]**	**Day 8 and 11 [a]**	**Day 15 and 18 [a]**	**Day 21**		
VISIT WINDOW (±days)		-14					±7[l]	±7[l]
Assessment (notes)								
Informed consent		X						
Demographic data		X						
~~Register~~ Record subject using IVRS system		X	X					
Height/Weight (Refer to Section 7.3.1)	Measurements in metric scale. Height measured only at screening	X	X				Every 4weeks (Cycle Day 1)	X

STUDY PHASE		**SCREEN**	**First Treatment Period Cycle 1**				**Continuation Phase Cycle 2 and beyond**	**Follow-Up[i]**
VISIT		**Screen**	**Day 1 and 4[a]**	**Day 8 and 11[a]**	**Day 15 and 18[a]**	**Day 21**		
VISIT WINDOW (±days)		-14					±7[l]	±7[l]
~~Serum p~~Pregnancy test	In females of child bearing potential, a serum[j] B-HCG pregnancy test is required within 7 days of first dose of study drug; urine or serum[n] B-HCG test thereafter.	X					Every 4 weeks (Cycle Day 1)	X
Disease characteristics (Refer to Section 7.2)	Record date of diagnosis, primary tumor type, histology, stage, etc.	X						
Prior anti-cancer therapy & radiation	Record date of therapies	X						
Prior surgical procedures		X						
Past and current medical conditions		X						
Alcohol consumption		X						
Past and current tobacco use		X						

STUDY PHASE		**SCREEN**	**First Treatment Period Cycle 1**				**Continuation Phase Cycle 2 and beyond**	**Follow-Up[j]**
VISIT		**Screen**	**Day 1 and 4[a]**	**Day 8 and 11[a]**	**Day 15 and 18[a]**	**Day 21**		
VISIT WINDOW (±days)		-14					±7[l]	±7[l]
Safety Assessments (- 1 Day)								
Physical examination		X	Day 1	Day 8	Day 15	X	Every 4 weeks Cycle Day 1	
ECOG PS	See Appendix 2	X	X	X	X	X	X	X
Vital signs	BP, body temperature, pulse rate, respirations Cycle 1 Day 1 vitals should be taken at same time points as PK draws on PK Table 7	X	X (Day 1 PK Table 7)	X	X	X	Prior to each infusion	X

STUDY PHASE		**SCREEN**	**First Treatment Period Cycle 1**				**Continuation Phase Cycle 2 and beyond**	**Follow-Up[i]**
VISIT		**Screen**	**Day 1 and 4[a]**	**Day 8 and 11[a]**	**Day 15 and 18[a]**	**Day 21**		
VISIT WINDOW (±days)		-14					±7[l]	±7[l]
ECG[b]	Pre-infusion and at the end of infusion except on Day 1 (Section 7.3.4). Two copies of the ECG tracing should be obtained at the time of the ECG, one to be kept in the study file for retrospective collection by the sponsor if necessary. ECG data should be reviewed by qualified personnel with experience in this study population	X	X[b]	X	X		On Day 4 of each cycle	X

STUDY PHASE		**SCREEN**	**First Treatment Period Cycle 1**				**Continuation Phase Cycle 2 and beyond**	**Follow-Up[j]**
VISIT		**Screen**	**Day 1 and 4[a]**	**Day 8 and 11[a]**	**Day 15 and 18[a]**	**Day 21**		
VISIT WINDOW (±days)		-14					±7[l]	±7[l]
Holter Monitoring	Continuous 12-lead Holter ECGs (obtained via a Holter monitor) will be acquired for a total of approximately 24 hours beginning an hour before infusion on **Day 1 only**		X (Day 1)					

STUDY PHASE		**SCREEN**	**First Treatment Period Cycle 1**				**Continuation Phase Cycle 2 and beyond**	**Follow-Up[j]**
VISIT		**Screen**	**Day 1 and 4[a]**	**Day 8 and 11[a]**	**Day 15 and 18[a]**	**Day 21**		
VISIT WINDOW (±days)		-14					±7[l]	±7[l]
ECHO/MUGA	At Screening	X						
Concomitant medications	See Section 9.2 for list of prohibited and cautionary medications	X	X	X	X	X	continuous ~~Every 4 weeks~~	X
Adverse events (Refer to Section 8)	Adverse event assessment should be continuous	X	X	X	X	X	continuous	X

STUDY PHASE		**SCREEN**	**First Treatment Period Cycle 1**				**Continuation Phase Cycle 2 and beyond**	**Follow-Up[j]**
VISIT		**Screen**	**Day 1 and 4[a]**	**Day 8 and 11[a]**	**Day 15 and 18[a]**	**Day 21**		
VISIT WINDOW (±days)		-14					±7[l]	±7[l]
Blood Sampling: on dosing days, collect blood samples prior to dosing unless otherwise noted								
Chemistry	No need to repeat at pre-dose Day 1 if screening assessments were performed within 72 hours~~14 days~~ of first dose (- 1 day visit window after screening)	X	X	X	X	X	Prior to every infusion	X
Hematology	No need to repeat at pre-dose Day 1 if screening assessments were performed within 72 hours~~14 days~~ of first dose (- 1 day visit window after screening)	X	X	X	X	X	Prior to every infusion	X

STUDY PHASE		**SCREEN**	**First Treatment Period Cycle 1**				**Continuation Phase Cycle 2 and beyond**	**Follow-Up[i]**
VISIT		**Screen**	**Day 1 and 4[a]**	**Day 8 and 11[a]**	**Day 15 and 18[a]**	**Day 21**		
VISIT WINDOW (±days)		-14					±7[l]	±7[l]
Coagulation	PT/PTT/INR. No need to repeat at pre-dose Day 1 if screening assessments were performed within 72 hours~~14 days~~ of first dose (- 1 day visit window after screening)	X						
Blood sample for circulating biomarkers	A blood sample for circulating biomarkers should be obtained on Day 1 (prior to treatment), Day 21 (~~and at the time of disease progression~~)		X			X		X (at progression)

STUDY PHASE		**SCREEN**	**First Treatment Period Cycle 1**				**Continuation Phase Cycle 2 and beyond**	**Follow-Up[j]**
VISIT		**Screen**	**Day 1 and 4[a]**	**Day 8 and 11[a]**	**Day 15 and 18[a]**	**Day 21**		
VISIT WINDOW (±days)		-14					±7[l]	±7[l]
Blood sample for Genetic research	A 6mL blood sample should be collected after screening (preferably on day 1) if informed consent has been obtained for Genetic research		X					

STUDY PHASE		**SCREEN**	**First Treatment Period Cycle 1**				**Continuation Phase Cycle 2 and beyond**	**Follow-Up[i]**
VISIT		**Screen**	**Day 1 and 4[a]**	**Day 8 and 11[a]**	**Day 15 and 18[a]**	**Day 21**		
VISIT WINDOW (±days)		-14					±7[l]	±7[l]
~~Blood for PD biomarkers~~	~~Blood samples for PD biomarkers should be obtained prior to dosing on D1 (baseline), 2 hours after the end of the infusion on day 1, 4, 8, 11, 15, and 18 and at day 21 and 28 visits (± 1-2 days).~~		~~X~~	~~X~~	~~X~~	~~X~~		
Whole Blood for Biomarkers[g]	Whole blood should be obtained prior to dosing on day 1,day 18 and C2D1 (sample taken prior to dosing)		X (Day 1)		X (Day 18)		X (C2W1D1 pre dose only)	

STUDY PHASE		**SCREEN**	**First Treatment Period** **Cycle 1**				**Continuation Phase** **Cycle 2 and beyond**	**Follow-Up[i]**
VISIT		**Screen**	**Day 1 and 4[a]**	**Day 8 and 11[a]**	**Day 15 and 18[a]**	**Day 21**		
VISIT WINDOW (±days)		-14					±7[l]	±7[l]
PK sampling for Part 1	For details, see Table 7		Day 1 (Table 7) Day 4 pre-dose and end of infusion	Soon after ECG ~~and PD biomarker~~ collection	Day 15 (Table 7)	At time of ~~PD~~ circulating biomarker collection	Cycle 2, 4, 6 and 12 – pre-dose and within 5 min prior to end of infusion on Day 4	

STUDY PHASE		**SCREEN**	**First Treatment Period** **Cycle 1**				**Continuation Phase** **Cycle 2 and beyond**	**Follow-Up[i]**
VISIT		**Screen**	**Day 1 and 4[a]**	**Day 8 and 11[a]**	**Day 15 and 18[a]**	**Day 21**		
VISIT WINDOW (±days)		-14					±7[l]	±7[l]
PK sampling for Part 2	Three samples to be collected on Day 1 and Day 11: Predose within 60 minutes prior to start of infusion, single draw between 0.5 and 1.9 h from start of infusion, single draw between 3-6h following end of infusion.		Day 1 and pre-dose on Day 4	X (after 4th dose, Day 11)	pre-dose on Day 15		Cycle 2, 4, 6 and 12 – pre-dose and within 5 min prior to end of infusion on Day 4	

STUDY PHASE		**SCREEN**	**First Treatment Period Cycle 1**				**Continuation Phase Cycle 2 and beyond**	**Follo w-Up[j]**
VISIT		**Screen**	**Day 1 and 4[a]**	**Day 8 and 11[a]**	**Day 15 and 18[a]**	**Day 21**		
VISIT WINDOW (±days)		-14					±7[l]	±7[l]
Translational Research								
Tumor Tissue for EZH2 mutation and GCB confirmation testing (required: for all GCB DLBCL and tFL subjects)[c]~~Archival Tissue for mutation testing (Required: All DLBCL and tFL subjects Parts 1 and 2)~~	Availability of archival tissue (or fresh biopsy) is required for central testing of GCB-subtype (DLBCL only) and EZH2 mutation status	X						
Tumor tissue for solid tumors (including prostate subjects)[c]	Availability of archival tissue (or fresh biopsy)	X						

STUDY PHASE		**SCREEN**	**First Treatment Period** **Cycle 1**				**Continuation Phase** **Cycle 2 and beyond**	**Follow-Up[i]**
VISIT		**Screen**	**Day 1 and 4[a]**	**Day 8 and 11[a]**	**Day 15 and 18[a]**	**Day 21**		
VISIT WINDOW (±days)		-14					±7[l]	±7[l]
Tumor biopsy for PD optional for Part 1 and Part 2. Required for ~~Part 1 and~~ PK/PD cohort at MTD	A tumor biopsy should be obtained at D1 (up to -14 days) and after 6th dose Day 18(+3 day window)		X		X (After 6th dose, Day 18)[h]			
Tumor biopsy for biomarker research	Recommended for all subjects ~~in Part 2~~							X (at pro-gression)

STUDY PHASE	**SCREEN**	**First Treatment Period Cycle 1**				**Continuation Phase Cycle 2 and beyond**	**Follow-Up[j]**
VISIT	**Screen**	**Day 1 and 4[a]**	**Day 8 and 11[a]**	**Day 15 and 18[a]**	**Day 21**		
VISIT WINDOW (±days)	-14					±7[l]	±7[l]
Additional Assessments for PD/PK Cohort[m]							
Blood for metabolite evaluation (Part 2~~1~~ PK/PD expansion cohort only~~— at least 4 subjects~~)		Day 1 (Table 7)		Day 15 (Table 7)			
Urine for ~~PK~~ Metabolite (Part ~~1~~2 PK/PD expansion cohort only) ~~at least 4 subjects)~~	On Day 15, urine samples should be collected while subject is in the office	~~X~~ Day 1 prior to first dose and from 0 to 24h		Day 15 from 0 to ~~24~~ 8 h			

STUDY PHASE		**SCREEN**	**First Treatment Period Cycle 1**				**Continuation Phase Cycle 2 and beyond**	**Follow-Up[j]**
VISIT		**Screen**	**Day 1 and 4[a]**	**Day 8 and 11[a]**	**Day 15 and 18[a]**	**Day 21**		
VISIT WINDOW (±days)		-14					±7[l]	±7[l]
Bile for metabolite ~~PK~~ (Part ~~1~~2 PK/PD expansion cohort only) – at least 4 subjects)			~~X (prior to first dose~~		Day 15			
Plasma for 4β-hydroxycholesterol and cholesterol assay (Part ~~1~~2 PK/PD expansion cohort only)			X (Day 1 p~~P~~rior to First Dose)			X (~~Day 21 only)~~		

STUDY PHASE		**SCREEN**	**First Treatment Period Cycle 1**				**Continuation Phase Cycle 2 and beyond**	**Follow-Up[j]**
VISIT		**Screen**	**Day 1 and 4[a]**	**Day 8 and 11[a]**	**Day 15 and 18[a]**	**Day 21**		
VISIT WINDOW (±days)		-14					±7[l]	±7[l]
~~Surrogate Tissue for PD and Translational Research~~	~~A surrogate tissue biopsy should be obtained at D1 (up to -14 days) and after 6th dose Day 18 (+3 day window)~~		~~X~~		~~X~~			
Disease Assessments for Lymphoma Subjects: *Baseline disease assessments at screening and repeated 8 weeks after dosing is initiated and every 12 weeks thereafter*								
CT[k]	Must be completed within 4 weeks of first dose of GSK2816126 and repeated 8 weeks after dosing is initiated. Every 12 weeks thereafter	X					X	X[d]

STUDY PHASE		**SCREEN**	**First Treatment Period Cycle 1**				**Continuation Phase Cycle 2 and beyond**	**Follow-Up[i]**
VISIT		**Screen**	**Day 1 and 4[a]**	**Day 8 and 11[a]**	**Day 15 and 18[a]**	**Day 21**		
VISIT WINDOW (±days)		-14					±7[l]	±7[l]
Positron emission tomography (PET)	The use of standalone PET or PET in combination with CT scan is optional. Standalone PET doesse not replace CT	X[e]					X[d,e]	X[d,e]
Bone Marrow biopsy ~~(See Section 3.8.4)~~	See Section 7.7	X					X[f]	X[f]
B symptoms	See Section 7.7	X	X	X	X	X	X	
~~Disease assessment~~	~~Baseline disease assessments at screening and repeated every 8 weeks~~	~~X~~					~~X~~	~~X[d]~~

STUDY PHASE		**SCREEN**	**First Treatment Period Cycle 1**				**Continuation Phase Cycle 2 and beyond**	**Follow-Up[j]**
VISIT		**Screen**	**Day 1 and 4[a]**	**Day 8 and 11[a]**	**Day 15 and 18[a]**	**Day 21**		
VISIT WINDOW (±days)		-14					±7[l]	±7[l]
Disease Assessments for Multiple Myeloma (MM) subjects: Baseline disease assessments at screening, week 4 and then every 6 weeks there after unless otherwise noted								
Disease Characteristics	Every 6 weeks after Wk4, Including cytogenetics as appropriate	X						
Total Protein, CRP, β2 microglobulin	Every 6 weeks after Wk4	X						
Response Assessment	Every 6 weeks after Wk4; Response criteria in Appendix 6							
SPEP, FLC assay, quantitative immunoglobulins (IgG, IgA, IgM)	Not required for subjects with non-secretory MM	X						
UPEP	Only required if paraprotein is present in urine	X						

STUDY PHASE		**SCREEN**	**First Treatment Period Cycle 1**				**Continuation Phase Cycle 2 and beyond**	**Follow-Up[j]**
VISIT		**Screen**	**Day 1 and 4[a]**	**Day 8 and 11[a]**	**Day 15 and 18[a]**	**Day 21**		
VISIT WINDOW (±days)		-14					±7[l]	±7[l]
Extramedullary Disease Assessment	Only required for MM with extramedullary disease	X						
BM aspirate and biopsy	Required for non-secretory MM, or as appropriate for other subjects	X			Day 18		Week 10, Day 1	
Disease Assessments for Solid Tumors: Baseline disease assessments at screening and repeated every 8 weeks after dosing is initiated								
CT/MRI[k]	Must be completed within 4 weeks of first dose of GSK2816126 and~~Must be~~ repeated every 8 weeks	X					X[d]	X[d]

STUDY PHASE		**SCREEN**	**First Treatment Period Cycle 1**				**Continuation Phase Cycle 2 and beyond**	**Follow-Up[i]**
VISIT		**Screen**	**Day 1 and 4[a]**	**Day 8 and 11[a]**	**Day 15 and 18[a]**	**Day 21**		
VISIT WINDOW (±days)		-14					±7[l]	±7[l]
Positron emission tomography (PET)	The use of standalone PET or PET in combination with CT scan is optional. Standalone PET does not replace CT	X[e]					X[e]	X[d,e]
Disease Assessments for Prostate Cancer: (in addition to those assessments for all solid tumor subjects): Baseline disease assessments at screening and repeated as noted below after dosing is initiated								
~~Vitamin D_3 and PTH~~		~~X~~					~~X~~	~~X[d]~~
~~Urinalysis~~ ~~Urine microscopy~~ ~~UPC~~		~~X~~					~~X[e]~~	~~X[d,e]~~
~~Urine electrolytes~~		~~X~~						
PSA	Wk 9 and every ~~4~~8 weeks thereafter	X					Every 4 weeks (Cycle Day 1)	X
~~ECOG Performance status~~	~~See Appendix 2~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~		

STUDY PHASE	**SCREEN**	**First Treatment Period Cycle 1**				**Continuation Phase Cycle 2 and beyond**	**Follow-Up[j]**
VISIT	**Screen**	**Day 1 and 4[a]**	**Day 8 and 11[a]**	**Day 15 and 18[a]**	**Day 21**		
VISIT WINDOW (±days)	-14					±7[l]	±7[l]
Study Medication							
GSK2816126 Dosing	Dosed 2x weekly with at least 2-3 non-dosing days apart (3 weeks on/1 week off)						

a. A subject is to receive two doses per week which should be given with at least 2 non-dosing days in between on the same day of the week during Cycle 1. ~~3 days apart.~~ If there is a need to change scheduling after Cycle 1, the scheduled days of the week can change as long as there are 2-3-~~4~~ non-dosing days between dos~~es~~ing days.

b. Timings for triplicate in-house on-drug ECGs are pre-infusion, at the end of infusion, before bed, and before discharge the next morning for Day 1 of cycle 1 only. Other protocol-mandated ECGs should be performed in triplicate pre-infusion and at the end of infusion (Section 7.3.4). Two copies of the ECG tracing should be obtained at the time of the ECG, one to be kept in the study file for retrospective collection by the sponsor if necessary. ECG data should be reviewed by qualified personnel with experience in this study population

c. Retention of screen-failure tumor tissue: all or a portion of archival or fresh biopsy tissue from screen-failure subjects, used for central testing of GCB-DLBCL or EZH2 mutation status, will be retained. This tissue may be used in the validation of potential diagnostic assays to detect EZH2 mutations and/or for GCB-DLBCL subtyping.

d. If the Follow-up visit ≥ 8~~12~~weeks from the previous response scan time point, scans should be obtained to confirm/ evaluate response.

e. Standalone PET dose not replace CT. Diagnostic CT is the preferred method of disease assessment. PET/CT may be used as an alternative at the investigator's discretion.

f. Only if initially and/or previously positive & required for CR or as clinically indicated.

g. Whole Blood for Biomarker sample at Cycle 2 day 1 must be taken prior to start of dosing.

h. If tissue sample not able to be taken at C1D18, site should discuss with GSK regarding having the sample taken at the next Cycle visit

i. Serum beta-human chorionic gonadotropin (B-HCG) pregnancy test

j. Follow up visit should be performed 30 days from last dose of study medication

k. Baseline brain scans are required for all subjects. Thereafter brain scans should be conducted as clinically indicated. Bone scans are to be conducted as clinically indicated at baseline and subsequent follow up timepoints. Subjects undergoing baseline full body CT/PET will not require this additional scans, unless clinically indicated.

l. After Cycle 1, assessments that are conducted at less frequent intervals (i.e., every 8 weeks) will have a visit window of ± 7 days after Cycle 1

m. Part 2 subjects enrolled into the PK/PD cohort will have these assessments performed in addition to all other study assessments included in the Time and Events table

Table 7 Time and Events, PK Sampling Table for Part 1, Day 1 and Day 15

	Duration of Infusion in hours		
	2	**3**	**4**
From start of infusion - 60 mins	Predose	Predose	Predose
± 5 mins	0.5 hr	0.5 hr	0.5 hr
± 5 mins	1 hr	1 hr	1 hr
- 5 mins	2 hr (prior to end of infusion)	2 hr	2 hr
- 5 mins		3 hr (prior to end of infusion)	4 hr (prior to end of infusion)
From end of infusion ± 5 mins	0.5 h	0.5 h	0.5 h
± 5 mins	1 hr	1 hr	1 hr
± 5 mins	2 hr	2 hr	2 hr
± 15 mins	4 hr	4 hr	4 hr
± 15 mins	6 hr	6 hr	6 hr
From start of infusion ± 1hour	12 hr (Day 1 only)	12 hr (Day 1 only)	12 hr (Day 1 only)
± 1 hour	18 hr (Day 1 only)	18 hr (Day 1 only)	18 hr (Day 1 only)
± 1 hour	24 hr	24 hr	24 hr
± 2 hour	**72 or 96 hr	72 or 96 hr	72 or 96 hr

**72 hour sample corresponds to Cycle 1 Day 4 pre infusion sample. EOI sample should also be taken at C1D4.

15.10. Appendix 10: Country Specific Requirements

No country-specific requirements exist.