TITLE PAGE

Division: Worldwide Development
Information Type: Protocol Amendment

Title:	A phase I open-label, dose escalation study to investigate the safety, pharmacokinetics, pharmacodynamicas and clinical activity of GSK2879552 given orally in subjects with relapsed/refractory small cell lung carcinoma

Compound Number: GSK2879552

Development Phase: I

Effective Date: 22-NOV-2016

Protocol Amendment Number: 04

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Revision Chronology

GlaxoSmithKline Document Number	**Date**	**Version**
2013N173386_01	2013-OCT-09	Original
2013N173386_02	2013-NOV-20	Amendment No.: 01
The starting dose, DLT criteria and safety management criteria are revised according to the regulatory input. One of the eligibility criteria is also modified to allow enrolment of patients without tumor tissues at baseline. Other changes are to clarify one of the exploratory objectives and endpoints, correct the investigational product storage conditions, clarify the definition of subject completion and allow flexibility in the timing of assessments		
2013N173386_03	2015-MAR-06	Amendment No. 2
The protocol is amended to add two new dose strengths that will reduce the pill burden for subjects.		
2013N173386_04	2015-MAY-27	Amendment No. 3
Additional eligibility criteria and safety monitoring measures are put in place to address recent safety findings. Primary end point and futility criteria for Part 2 are modified based on the compound's mechanism of action. Other changes include additional urine and plasma sample collection for metabolite profiling (at the highest dose cohort in Part 1 PK/PD expansion), update in concomitant medications, clarification on the timing for pre- and post-dose optional biopsies, and addressing the inconsistencies in the definition of febrile neutropenia.		
2013N173386_05	2016-NOV-22	Amendment No. 4
Appendix 5 country specific IP label requirements for Korea have been modified. Fetal hemoglobin testing requirement has also been removed for Korea.		

SPONSOR SIGNATORY

PPD

Christopher Carpenter, MD, Ph.D.
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Nov 22 2016
Date

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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

INVESTIGATOR PROTOCOL AGREEMENT PAGE

For protocol number 200858

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)
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
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
AUC(0-τ)	Area under the concentration-time curve over the dosing interval
β-HCG	Beta-Human Chorionic Gonadotropin
BUN	Blood urea nitrogen
Cav	Average concentration
CBC	Complete blood count
CfDNA	Circulating cell free DNA
CKD-EPI equation	The Chronic Kidney Disease Epidemiology Collaboration equation
CL/F	Apparent clearance following oral dosing
Cmax	Maximum observed concentration
Cmin	Minimum observed concentration
Cτ	Pre-dose (trough) concentration at the end of the dosing interval
CO_2	Carbon dioxide
CoREST	CoRepressor for Element-1-Silencing Transcription factor
CPMS	Clinical Pharmacokinetic Modeling and Simulation
CR	Complete response
CRM	Continual Reassessment Method
CT	Computed tomography
CTCs	Circulating tumor cells
CV	Coefficient of variance
DCR	Disease Control Rate
DHEA	Dehydroepiandrosterone
DILI	Drug Induced Liver Injury
DLT	Dose-limiting toxicity
DMPK	Drug Metabolism and Pharmacokinetics
DNA	Deoxyribonucleic acid
EC	Ethics committee
EC_{50}	Half maximal effective concentration
ECG(s)	Electrocardiogram(s)
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EIAC	Enzyme-inducing anticonvulsant
FACTS	Fixed and Adaptive Clinical Trial Simulator
FSH	Follicle Stimulating Hormone

FTIH	First time in humans
GCP	Good Clinical Practice
g/dL	Grams per deciliter
GFR	Glomerular filtration rate
GGT	Gamma glutamyltransferase
GI	Gastrointestinal
GLP	Good Laboratory Practices
GSK	GlaxoSmithKline
H3K4	Histone H3 lysine 4
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HDACs	Histone Deacetylases
Hgb	Hemoglobin
HIV	Human Immunodeficiency Virus
h/hr	Hour(s)
HLA	Human leukocyte antigen
HPLC	High-performance liquid chromatography
HNSTD	Highest Non- Severely Toxic Dose
HRT	Hormone replacement therapy
IB	Investigator's Brochure
ICH	International Conference on Harmonization
IDSL	International Data Standards Library
IgM	Immunoglobulin M
IHC	Immunohistochemistry
IND	Investigational New Drug
INR	International normalization ratio
IP	Investigational Product
IRB	Institutional Review Board
IU	International Unit
IV	Intravenous
Ka	Absorption rate
kg	Kilogram
L	Liter
LFTs	Liver function tests
LLN	Lower limit of normal
ln	Naperian (natural) logarithm
LSD1	Lysine specific demethylase 1
LSLV	Last subject's last visit
LVEF	Left Ventricular Ejection Fraction
uM	Micromole
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligrams
mL	Milliliter

MOCA	Montreal Cognitive Assessment
MPV	Mean platelet volume
MRI	Magnetic resonance imaging
MSDS	Material Safety Data Sheet
msec	Milliseconds
MTD	Maximum tolerated dose
MUGA	Multigated (radionuclide) angiogram
NCI-CTCAE	National Cancer Institute - Common Terminology Criteria for Adverse Events
N-CRM	The Neuenschwander -Continuous Reassessment Method
ng	Nanogram
nM	Nanomole
NOAEL	No observed adverse effect level
NSAIDs	Non-steroidal anti-inflammatory drug
NYHA	New York Heart Association
ORR	Objective Response Rate
PARP	poly ADP ribose polymerase
PCI	Potential clinical importance
PCR	Polymerase chain reaction
PD	Progressive disease or pharmacodynamic
PET	Probability of early termination
PFS	Progression-free survival
PI	Principal Investigator
PK	Pharmacokinetic
PR	Partial response
PRoGRP	Pro Gastrin Releasing Peptide
PT	Prothrombin time
PTS	Platform Technology and Science
PTT	Partial thromboplastin time
QTc	Corrected QT interval duration
QTcB	QT interval corrected for heart rate by Bazett's formula
RAP	Reporting and Analysis Plan
RBC	Red blood cells
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic acid
Ro	Accumulation ratio
RP2D	Recommended Phase 2 Dose
RT-PCR	Reverse transcription-polymerase chain reaction
SAE	Serious adverse event(s)
SCLC	Small Cell Lung Carcinoma
SD	Standard deviation or stable disease
SPM	Study Procedures Manual
STD	Severely Toxic Dose
t	Time of last observed quantifiable concentration
t1/2	Terminal phase half-life
τ	Dosing interval

λz	Apparent terminal phase elimination rate constant
tmax	Time of occurrence of Cmax
ULN	Upper limit of normal
US/USA	United States/United States of America
V/F	Apparent Volume of distribution following oral dosing
WBC	White blood cells
WHO	World Health Organization

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FACTS

PROTOCOL SYNOPSIS

TITLE	A phase I open-label, dose escalation study to investigate the safety, pharmacokinetics, pharmacodynamics and clinical activity of GSK2879552 given orally in subjects with relapsed/refractory small cell lung carcinoma
PROTOCOL NUMBER	200858
CLINICAL PHASE	I
COMPOUND(S)	GSK2879552
STUDY RATIONALE	GSK2879552 is a potent, selective, mechanism-based inactivator of LSD1/CoREST activity. GSK2879552 induces the expression of putative LSD1 target genes and has potent, predominantly cytostatic, anti-proliferative activity in small cell lung carcinoma (SCLC). This FTIH, open-label, dose escalation study will assess the safety, pharmacokinetics (PK), pharmacodynamics (PD), and preliminary clinical activity of GSK2879552 in subjects with relapsed/refractory SCLC.

STUDY OBJECTIVES, ENDPOINTS AND HYPOTHESES

PART 1: Escalation Cohort		
	Objectives	**Endpoints**
Primary	1. To determine the safety, tolerability and Recommended Phase 2 Dose(s) (RP2D) and regimen of GSK2879552 given orally in adult subjects with SCLC.	1. AEs, SAEs, dose limiting toxicities, dose reductions or delays, withdrawals due to toxicities and changes in safety parameters (e.g., laboratory values, vital signs, ECGs, physical examinations).
Secondary	1. To characterize the pharmacokinetics of GSK2879552 after single- and repeat-dose oral administration. 2. To evaluate clinical activity after treatment with GSK2879552. 3. To evaluate the relationship between GSK2879552 exposure and safety/ efficacy/PD parameters	1. GSK2879552 PK parameters following single-(Day 1) and repeat-dose (Day 15) administration of GSK2879552, including AUC, Cmax, tmax, t½ (terminal phase and/or effective half-life), accumulation ratio, and time invariance. 2. Disease Control Rate (DCR) (CR + PR + SD) at week 16 based on Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. 3. Relationship between GSK2879552 exposure markers (e.g. dose, Cmax, Cmin or AUC (0-tau)), and ProGRP, platelet levels in blood, and safety/efficacy parameters.
Exploratory	1. To assess feasibility of a select gene panel for use as a PD assay for GSK2879552 2. To investigate the impact of GSK2879552 on the RNA expression profile in tumor and blood to identify mechanisms of	1. Change from baseline expression in select genes in whole blood and tumor 2. Transcriptomic (RNA) profile of tumor and whole blood pre- and post-treatment with GSK2879552.

	rational combination and potential resistance. 3. To investigate relationship between tumor baseline genomic profile and response or resistance to GSK2879552. 4. To discover circulating response and resistance biomarkers 5. To investigate the impact of GSK2879552 on fetal haemoglobin 6. To characterize the metabolite profile of GSK2879552 after oral single and/or repeat-dosing in some subjects 7. To determine the amount of GSK2879552 excreted in urine after oral single and/or repeat-dosing	3. Tumor DNA, RNA and protein markers at baseline. 4. Circulating biomarkers (e.g. cfDNA, protein and RNA). 5. Pre- and post-treatment fetal haemoglobin levels 6. GSK2879552 metabolites in plasma and/or urine 7. Concentration of GSK2879552 in urine measured with an investigational bio-analytical method and extrapolated to total amount excreted in urine over time
Hypothesis	No formal statistical hypotheses are being tested in Part 1 dose escalation. Analysis of the data obtained from Part 1 will only utilize descriptive methods.	

Part 2: Expansion Cohort		
	Objectives	**Endpoints**
Primary	1. To evaluate clinical activity of GSK2879552 given orally in adult subjects with SCLC.	1. Disease Control Rate (DCR) (CR + PR + SD) at week 16 based on Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.
Secondary	1. To evaluate the safety and tolerability of RP2D of GSK2879552 2. To characterize the population PK of GSK28795522. 3. To evaluate the relationship between GSK2879552 exposure and safety/efficacy/PD parameters. 4. To evaluate duration of response and progression free survival (PFS) 5. To evaluate objective response rate (ORR)	1. AEs, SAEs, dose limiting toxicities, dose reductions or delays, withdrawals due to toxicities and changes in safety assessments (e.g., laboratory parameters, vital signs, physical examinations). 2. Population PK parameters for GSK2879552 such as clearance (CL/F) and volume of distribution (V/F), and relevant covariates which may influence exposure (e.g., age, weight, or disease associated covariates). 3. Relationship between GSK2879552 exposure markers (e.g. dose, Cmin, Cmax or AUC (0-tau)), and ProGRP, platelet levels in blood, and safety/efficacy parameters. 4. Duration of response and PFS 5. % of subjects achieving complete

		response and partial response
Exploratory	1. To assess feasibility of a select gene panel for use as a PD assay for GSK2879552 2. To investigate the impact of GSK2879552 on the RNA expression profile in blood to identify mechanisms of rational combination and potential resistance. 3. To investigate relationship between tumor baseline genomic profile and response or resistance to GSK2879552. 4. To discover circulating response and resistance biomarkers 5. To investigate the impact of GSK2879552 on fetal haemoglobin	1. Change from baseline expression in select genes in whole blood 2. Transcriptomic (RNA) profile of whole blood pre- and post-treatment with GSK2879552. 3. Tumor DNA, RNA and protein markers at baseline. 4. Circulating biomarkers (e.g. cfDNA, protein and RNA). 5. Pre- and post-treatment fetal haemoglobin levels
Hypothesis	Clinical response will be defined as Disease Control Rate (DCR) (CR + PR + SD) at week 16 based on RECIST 1.1. The null hypothesis is: H0: DCR≤15% at week 16 The alternative hypothesis is: HA: DCR≥30% at week 16	

STUDY DESIGN

This is a phase I, open-label, multi-center, non-randomized, 2-part FTIH study.

Part 1 is a dose escalation phase to determine the recommended phase 2 dose (RP2D) for GSK2879552 based on the safety, tolerability, PK, and PD profiles observed after oral administration of GSK2879552. Any dose level(s) may be expanded up to 12 subjects in order to collect additional data on PK and PD.

In Cohort 1, a single subject will receive a dose of GSK2879552 0.25 mg once daily. The subject in Cohort 1 must complete a full 28 days of dosing, and the safety and PK data will be reviewed prior to starting Cohort 2. Starting with Cohort 2 the dose escalation will continue using the Neuenschwander -continuous reassessment method (N-CRM). Built-in safety constraints are in place to prevent exposing subjects to undue risk of toxicity.

Once RP2D is identified, an expansion cohort (Part 2) of up to 30 subjects will be enrolled to further evaluate the clinical activity and tolerability of GSK2879552 in subjects with relapsed/refractory SCLC.

NUMBER OF SUBJECTS	It is estimated that approximately 20 subjects will be enrolled into Part 1 dose-escalation and additional 27 subjects into PK/PD expansion cohorts. Up to 30 subjects will be enrolled in Part 2 (expansion cohort) of the study. A total of approximately 77 subjects will be enrolled in the study. Additional subjects/cohorts may be enrolled to allow for evaluation of additional dose levels.
INCLUSION/ EXCLUSION CRITERIA	Subjects eligible for enrolment 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. Histologically or cytologically confirmed diagnosis of small cell lung carcinoma. Subjects must have measurable disease per RECIST 1.1 (for Part 2 only). 4. Recurrent or refractory disease after receiving at least one prior standard/approved platinum-containing chemotherapy regimen, or where standard therapy is refused. **Part 2 only**: Subjects must have recurrent disease after receiving a maximum of two prior chemotherapy regimen including one platinum containing regimen. Note: Adjuvant/Neoadjuvant chemotherapy is not counted. 5. Eastern Cooperative Oncology Group (ECOG, Appendix 3) performance status of 0 or 1. 6. Tumor tissue requirements: • Availability of archival tissue, or willingness to undergo fresh biopsy at baseline. Patients without baseline tissue may be enrolled with approval from the GSK medical monitor. • Enrollment in PK/PD cohort may be limited to subjects with disease amenable to pre- and post-dose biopsies, and willingness to undergo biopsy 7. All prior treatment-related toxicities must be National Cancer Institute- Common Toxicity Criteria for Adverse Events (NCI-CTCAE), version 4.0 ≤Grade 1 at the time of enrollment (except for alopecia) 8. Adequate baseline organ function defined by

System	Laboratory Values
Hematologic	
Absolute neutrophil count (ANC)	≥ 1.5 X 10^9/L
Hemoglobin	≥ 10 g/dL
Platelets	≥ 125 X 10^9/L
Prothrombin time (PT)/International normalized ratio (INR) and Partial thromboplastin time (PTT)	≤ 1.5 X ULN
Hepatic	
Total bilirubin ALT and AST	≤ 1.25 X ULN[1] ≤2.5 × ULN without liver metastasis ≤5 x ULN if documented liver metastasis
Renal	
Creatinine OR Calculated creatinine clearance by Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (Appendix 2) or measured from 24hr urine	≤1.5 X ULN ≥ 50 mL/min
Cardiac	
Ejection fraction	≥ LLN by Echocardiogram (ECHO)
Metabolic	
TSH, T4 Vitamin B12 BUN Na, K[2], Ca, Cl, CO_2 Glucose (fasting)	WNL ≥ LLN ≤1.5 X ULN WNL ≤1.25 X ULN

1. Isolated bilirubin >1.25 X ULN is acceptable if bilirubin is fractionated and direct bilirubin <35% or subject has a diagnosis of Gilbert's syndrome
2. Replacement of K is allowed if below LLN

1.

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 hematologic eligibility criteria are not eligible.

9. 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 11.1, during the study and for 7 days following the last dose of study treatment.

10. Men with a female partner of childbearing potential must have either had a prior vasectomy or agree to use effective contraception as described in Section 11.1 from the administration of the first dose of study treatment until 3 months after the last dose of study treatment to allow for clearance of any altered sperm.

11. Able to swallow and retain orally administered study treatment and does not have any clinically significant gastrointestinal (GI) abnormalities that may alter absorption such as malabsorption syndrome or major resection of the stomach and/or bowels.

12. **French subjects:** In France, a subject will be eligible for inclusion in this study only if either affiliated to or a beneficiary of a social security category.

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

1. Concurrent malignancy other than SCLC. History of other malignancy is allowed as long as there is no evidence of active disease or need for treatment.
2. Currently receiving anti-cancer therapy (chemotherapy, radiation therapy, immuno- therapy, biologic therapy, hormonal therapy, surgery, and/or tumour embolization)

   Exceptions: Zoledronic acid and denosumab to treat bone metastasis are allowed.
3. Prior treatment with temozolomide, dacarbazine or procarbazine
4. Prior treatment with poly ADP ribose polymerase (PARP) inhibitors (e.g., olaparib, ABT-888)
5. Baseline Montreal Cognitive Assessment (MOCA) score of 22 or lower
6. Received major surgery, radiotherapy, or immunotherapy within 4 weeks of GSK2879552 administration. Chemotherapy regimens with delayed toxicity within the last four weeks (six weeks for prior nitrosourea or mitomycin C). Chemotherapy regimens given continuously or on a weekly basis with limited potential for delayed toxicity or palliative radiation to a limited area (including cranial radiation for brain metastases) within the last two weeks.
7. Administration of an investigational drug within 28 days or 5 half-lives, whichever is ***shorter*** preceding the first dose of study treatment(s) in this study.

   French subjects: The French subject has participated in any study using an investigational study treatment(s) during the previous 28 days.
8. Subjects with current/a history of bleeding disorder or

coagulopathy (e.g., Von Willebrand disease, haemophilia) or who are at particularly high risk for bleeding complications, e.g., prior history of intracranial hemorrhage, clinically significant bleeding episodes in the last 6 months.

9. Requiring anticoagulants at therapeutic doses (e.g., warfarin, direct thrombin inhibitors, etc) or platelet inhibitor (e.g., aspirin, clopidogrel). The following are permitted:

    - Low molecular weight heparin
    - Low dose prophylactic warfarin ≤ 1 mg once daily
    - Low dose aspirin ≤ 100 mg once daily if required for cardiac prophylaxis.

10. Current use of a prohibited medication (Section 10.2) or expected to require any of these medications during treatment with the investigational drug

11. Evidence of severe or uncontrolled systemic diseases (e.g., severe/chronic infection, unstable or uncompensated respiratory, hepatic, renal, or cardiac disease) Any serious and/or unstable pre-existing medical (aside from malignancy exception above), psychiatric disorder, or other conditions that could interfere with subject's safety, obtaining informed consent or compliance to the study procedures, in the opinion of the investigator

12. Known active Human Immunodeficiency Virus (HIV), Hepatitis B Virus (HBV) or Hepatitis C Virus (HCV) infections. Subjects with laboratory evidence of HBV clearance may be enrolled

13. Leptomeningeal metastases or spinal cord compression due to disease.

14. Subjects with previously untreated or uncontrolled brain metastases.

    Note: Subjects previously treated for brain metastases that

    - are asymptomatic and off corticosteroids, OR
    - on stable dose of corticosteroids for at least 1 month prior to study Day 1 are permitted.

    Subject treated with gamma knife can be enrolled 2 weeks post-procedure as long as there are no post-procedure complications and the subject is clinically stable. In addition, subjects treated or currently taking enzyme-inducing anticonvulsant (EIAC) are allowed on study.

15. Cardiac abnormalities as evidenced by any of the following:

    - Clinically significant uncontrolled arrhythmias or uncontrolled hypertension.
    - History or evidence of current ≥Class II congestive heart failure as defined by New York Heart Association (NYHA).

- History of acute coronary syndromes (including unstable angina and myocardial infarction), coronary angioplasty, or stenting within the past 3 months.
- Baseline QTc interval using Bazett's formula ≥450 msec or ≥480 msec in subjects with Bundle Branch Block. QTc value based on single or average of triplicate ECGs obtained over a brief recording period.

16. Have a known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to GSK2879552 or LSD1 inhibitors that contraindicates their participation.
17. Lactating female.
18. Consumption of Seville oranges, grapefruit, grapefruit hybrids or grapefruit juice and/or pommelos, exotic citrus fruits, from 1 day prior to the first dose of study treatment(s) until the last dose of study drug.

STUDY TREATMENT DOSE/ROUTE/ REGIMEN

Product name:	**GSK2879552 Capsule**
Formulation description:	GSK2879552 capsules contain 0.25 mg, 0.5 mg, 2 mg or 5 mg of GSK2879552 as parent.
Dosage form:	Capsule
Unit dose strength(s)	0.25 mg, 0.5 mg, 2 mg and 5 mg
Route/ Regimen	Oral The initial dosing regimen will be continuous oral daily dosing. Subjects should take their doses fasted with approximately 200 mL of water.
Physical description:	0.25 mg GSK2879552: Opaque Size 3 capsule composed of a white body and a white cap with no identifying markings containing a white to slightly coloured powder. 0.5 mg GSK2879552: Opaque Size 1 capsule composed of a light green body and a light green cap with no identifying markings containing a white to slightly coloured powder. 2 mg GSK2879552: Opaque Size 1 capsule composed of a pink body printed with two black lines and a pink cap printed with two black lines, containing a white to slightly coloured powder. 5 mg GSK2879552: Opaque Size 1 capsule composed of a Swedish Orange body and a Swedish Orange cap with no identifying markings containing a white to slightly coloured powder.

SAFETY ASSESSMENTS

Measurements to evaluate safety will include weight, height, heart rate (HR), blood pressure (BP), temperature, clinical laboratory tests, 12-lead ECG, ECOG performance status, and physical examination.

	AEs and laboratory results will be graded according to the NCI-CTCAE v4.0. Planned time points for all safety assessments are listed in the Time and Events Tables (Section 7.1)
PHARMACOKINETIC/ PHARMACODYNAMIC ASSESSMENT(S)	For all subjects in the dose escalation cohorts in Part 1, serial blood samples for analysis of GSK2879552 concentrations will be collected on Days 1, 8 and 15 at planned time points as listed in the Time and Event Table (Section 7.1). Pre-dose blood sample will be also collected on Days 4 and 22. Thereafter, pre-dose blood sample for analysis of GSK2879552 concentrations will be collected every week for 4 weeks, followed by every 4 weeks. Pre-dose and 24 hour urine sample will be collected on Day 1, and 24 hour urine sample will be collected starting from pre-dose on Day 15 until dosing on Day 16. Pre-dose blood samples for PD, biomarker and translational research will be collected at Screening and on Days 1, 2, 4, 8, 15, 22 and at the end of treatment visit. Pre-dose and post-dose tumor biopsies may be required from a subset of subjects in Part 1, PK/PD expansion cohorts. A minimum of five pairs of evaluable pre- and post-dose biopsies may be collected at selected doses based on emerging PK/PD data. For subjects in the highest dose of Part 1 PK/PD expansion cohort, additional blood samples for GSK2879552 metabolite profiling will be collected on Days 1 and 15 at the same time points as listed in the Time and Event Table (Section 7.1). Additional urine sample will be also collected for GSK2879552 metabolite profiling from the 24 hour urine sample. For all subjects in Part 2 expansion cohorts, limited blood samples for analysis of GSK2879552 concentrations will be collected on Days 1 and 15 at planned time points as listed in the Time and Event Table (Section 7.1). Pre-dose blood sample will be also collected on Days 8, 22, and every 4 week thereafter. Pre-dose blood samples for PD, biomarker and translational research will be collected on Days 1, 8, 15, 22 and at the end of treatment visit. Alterations may be made to the PK/PD sampling schedule based on the results of emerging PK, PD, and safety data.
CLINICAL ACTIVITY ASSESSMENT	Disease assessment will be performed every 8 weeks in all subjects (Parts 1 and 2). Disease assessment may include imaging and physical examination. All post-baseline assessments require imaging of disease sites identified by baseline scans, and they include chest/abdomen/pelvis (if applicable) CT scans with contrast and brain MRI scan, if the disease is present at baseline. Disease progression and response evaluations will be determined according to the definitions established in the RECIST 1.1. Subjects whose disease responds (either complete response [CR] or partial response [PR]) should have a confirmatory disease assessment performed 4 weeks after the date of assessment during which the response was demonstrated. More frequent disease assessments may be performed at the discretion of the investigator. To ensure comparability between the baseline and subsequent assessments, the

	same method of assessment and the same technique will be used when assessing response. The clinical activity will be evaluated by disease control rate at week 16 in Part 2.
TRANSLATIONAL RESEARCH	Comparative examination of pre-treatment, on- treatment and post-treatment markers (which may include DNA, RNA, protein, cell, blood or tissue examination) of subjects may be performed to uncover known or novel candidate biomarkers/profiles which could be used to predict response to treatment with GSK2879552, measure PD and/or response to treatment, or provide new insights into SCLC and medically related conditions.
STATISTICAL METHODS	The total number of subjects to be enrolled in Part 1 will depend on the number of subjects needed to characterize individual dose cohorts. Results of simulations for the dose-escalation phase are shown in Appendix 6. Based on these simulations, the sample size for the dose-escalation portion is expected to be approximately 19-22 subjects. It is anticipated that approximately 57 subjects will be enrolled in Part 1 including PK/PD expansion cohorts. An initial dose escalation will be used to establish the RP2D for GSK2879552. Once the final dose is confirmed, at least 12 and up to 30 subjects will be enrolled at that dose, using decision rules defined in Figure 3. The sample size and stopping rules are based on the methodology of Lee et al. [Lee, 2008]. The assumptions underlying the design are detailed below. H_0: DCR≤15% The alternative hypothesis is: H_A:DCR≥30% Starting with 12 subjects and allowing for a maximum sample size of 30, this design will have a type I error rate (α) of 0.15 and 80% power. 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% 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 design will have a type I error rate of less than 0.15 and a power greater than 80% for a sample size exceeding 30 subjects. 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 disease control rate is 15%, the expected sample size of the design is 24 subjects and probability of early termination (PET) is 75%. Under the alternative hypothesis, if the true disease control rate is 30%, the expected sample size of the design is 29.0 subjects and PET is 10%. **All Subjects Population:** This will consist of all subjects who

received at least one dose of study treatment. Safety and clinical activity data will be evaluated based on this population.

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

The Pharmacodynamic Population: This will consist of those subjects in All Subjects Population and who contribute PD/Biomarker samples.

Additional details of the statistical analysis plan will be provided in the reporting and analysis plan (RAP).

1. INTRODUCTION

1.1. Background – LSD1

LSD1, lysine specific demethylase 1, is a histone H3 lysine 4 mono-methyl (H3K4me1) and di-methyl (H3K4me2) demethylase responsible for controlling the expression of genes that regulate differentiation. LSD1 is frequently found as a component of transcriptional repressive complexes along with other proteins associated with repression such as CoREST (CoRepressor for Element-1-Silencing Transcription factor) and HDACs (Histone Deacetylases) 1 and 2 [You, 2001; Shi, 2003]. These data suggest that LSD1 localization and activity correlates with transcriptional repression and that inhibition of LSD1 will result in increased expression of LSD1 target genes.

LSD1 activity is essential for the maintenance of pluripotency in embryonic stem cells by regulating the balance between H3K4 and H3K27 methylation, thereby keeping differentiation associated genes silenced [Adamo, 2011]. LSD1 also plays a critical role in normal hematopoietic differentiation by mediating repression of a key gene expression program in hematopoietic progenitors [Saleque, 2007].

1.2. Unmet Medical Needs For Small Cell Lung Carcinoma

Small cell lung carcinoma (SCLC) accounts for 15-20% of all lung cancers in the US. Estimated new cases of lung cancer (SCLC and non-small cell lung cancer combined) in the US in 2013 are 228,190 and estimated death are 159,480, accounting for about 27% of all cancer deaths [American Cancer Society, 2013]. Although SCLC is highly responsive to initial chemotherapy, patients with extensive stage SCLC frequently relapse with resistant disease [Hurwitz, 2009]. The response rate to second line treatment is dependent on the time to relapse from first line chemotherapy. For those who have refractory disease (time to relapse < 3 months), response rate to second line treatment is very low (<10%). For those with more sensitive disease, response rate to single-agent second line therapy is approximately 25%. However, the duration of response is short and the overall survival is 5.3 months [Sundstrøm, 2005].

LSD1 is highly expressed in primary small cell lung carcinoma (SCLC). Ninety-eight percent of SCLC tumors represented in a tissue microarray demonstrated very high expression for LSD1 protein. A corresponding tissue microarray containing normal tissue, including lung, was tested and had no positive staining for LSD1.

1.3. GSK2879552

1.3.1. GSK2879552 - Background

An overview of the pre-clinical studies of GSK2879552 is provided below. Detailed information concerning the biology, pharmacology, pharmacokinetics (PK), and safety can be found in the Investigators' Brochure (IB) [GlaxoSmithKline Document Number 2013N168888_01].

GSK2879552 is a potent, selective, mechanism-based inactivator of LSD1/CoREST activity (K_i = 1.7 µM, k_{inact} = 0.1 min^{-1}). While the initial reversible potency (K_i) of GSK2879552 is moderate, complete inhibition of the enzyme is achieved over time due to the irreversible, mechanism-based nature of the inhibition. GSK2879552 induces the expression of putative LSD1 target genes and has potent, predominantly cytostatic, anti-proliferative activity in small cell lung carcinoma (SCLC) with median EC_{50} = 25 nM, range = 2 - 240 nM. In total, 9/28 SCLC lines were found to be sensitive to GSK2879552 treatment while the sensitivity of an additional 7 SCLC lines could not be determined.

1.3.2. Pre-Clinical Pharmacology & Safety of GSK2879552

Pharmacology

GSK2879552 causes an increase in histone 3 lysine 4 di-methylation (H3K4me2) at promoters of putative LSD1 target genes. H3K4 methylation is associated with actively transcribed genes. Consistent with increased promoter H3K4me2, GSK2879552 causes increased expression of a set of genes in sensitive and insensitive SCLC cell lines (average NCI-H526 EC50 = 31 nM) in vitro. The specific genes that are upregulated are unique to each SCLC cell line. Studies are ongoing to assess whether common biological pathways are primarily affected as a result of LSD1 inhibition in SCLC. Additionally, GSK2879552 decreases gene and protein expression of progastrin releasing peptide (ProGRP), a neuroendocrine protein commonly secreted from SCLCs, in both sensitive and insensitive SCLC cell lines.

GSK2879552 activity in SCLC has been further characterized using in vivo subcutaneous xenograft models. GSK2879552 induces the expression of LSD1 target genes in NCI-H526 SCLC subcutaneous xenografts following a single oral dose. Similarly, GSK2879552 induces expression of potential LSD1 target genes in whole blood of immunocompetent mice following a single oral dose. In both SCLC tumors and whole blood, maximal gene activation occurs between 6 and 24 hours after dosing and subsides by 72 hours. Fifty percent of the genes assessed reached > 2-fold expression relative to vehicle treated animals at 1.7 mg/kg (predicted exposure of 234 ng*hr/mL).

GSK2879552 inhibits the growth of NCI-H526 SCLC tumors grown subcutaneously in nude mice (Table 1). Higher doses were tolerated with 4 days on/3 days off dosing with greater tumor growth inhibition.

Table 1 Summary of tumor growth inhibition in NCI-H526 xenografts treated with GSK2879552

Dose	Exposure	NCI-H526			
(mg/Kg)	(ng*hr/mL)[1]	Daily	EOD	2on 2off	4on 3off
45	6300			26%	76%[2]
15	2100	N.T.			
5	700	N.T.	38%	29%	64%[2]
1.5	210	57%[2]	42%		
0.5	70	48%[2]			
0.15	21	36%			
0.05	7	7%			

Dose/schedule combinations shaded in black were not tested. N.T. = not tolerated, EOD = every other day.

1. Exposures are extrapolated from mouse PK study N10194-15
2. $p < 0.05$

Pharmacokinetics The nonclinical pharmacokinetics of GSK2879552 were similar across species. In vitro, GSK2879552 binding to plasma proteins varied between species and was around 64% in mice, 81% in rats, 42% in dogs and 55% in human at a concentration of 0.02 uM (~8 ng/mL). Oral bioavailability was moderate to high (59% in mice, >100% in rats and 85% in dogs). Steady state volume of distribution was moderate to high in all species. GSK2879552 had high clearance in mice and rats and moderate clearance in dogs with a low intrinsic clearance in microsomes and hepatocytes from all species, including humans. GSK2879552 half life was 1 to 3 hours in all species. Systemic exposure to GSK2879552 generally increased dose-proportionally in rats and dogs.

General Toxicology

The systemic toxicity of GSK2879552 administered orally once daily for up to 4 weeks has been evaluated in mice, rats and dogs. Screening genotoxicity studies have also been conducted. Summaries of principal findings following single and repeat dosing of GSK2879552 are presented in Table 2. A comparison of systemic exposures achieved in these studies is presented in Table 3. Details of principal toxicological findings are discussed below.

Morbidity and mortality: In rats given GSK2879552 at doses of up to 100 mg/kg/day for 7 days or up to 0.3 mg/kg/day for 14 days, no morbidity and/or mortality was observed. GSK2879552 administration was associated with hematologic effects at all doses (detailed below), macroscopic and microscopic evidence of multifocal hemorrhage in multiple organs at ≥1 mg/kg/day for 7 days and microscopic evidence of decreased bone marrow cellularity at ≥0.3 mg/kg/day for 14 days.

GSK2879552-related morbidity and/or mortality were observed in rats and dogs given repeat doses of ≥0.4 mg/kg/day or ≥0.1 mg/kg/day, respectively. In rats given a dose of 0.4 mg/kg/day of GSK2879552 for up to 4 weeks, morbidity was observed in 5 of 38 rats between Days 7 and 17. Rats were killed due to deteriorating clinical condition with clinical signs including red nasal discharge, pale extremities, subdued behavior, partial

eye closure, irregular breathing, piloerection and slow movements; these were considered to be associated with a severe reduction in platelet counts. Similar findings occurred in dogs. Following dosing of 1 mg/kg/day GSK2879552 for 7 daily doses or intermittent dosing for 2 cycles of 4 days on-dose and 3 days off-dose, morbidity was observed in 1 of 2 dogs in the daily dosing group at Day 13 and in 1 of 2 dogs in the intermittent dosing group at Day 8. In a 4 week, daily dosing study, morbidity was observed in 1 of 10 dogs at 0.1 mg/kg/day on Day 14 and in 8 of 10 dogs at 0.3 mg/kg/day between Days 13 and 15. Dogs were killed due to adverse clinical observations which included body weight loss (1 mg/kg/day), subdued behavior, decreased activity, reluctance to move, unsteady gait, swaying, slight high stepping and slight stiffening of hind limbs. At necropsy, there were findings in various parts of the digestive tract (red discoloration) and the lymphoid system (red or dark discoloration), correlating microscopically with the lymphoid necrosis and hemorrhage. These effects were secondary to pharmacology-driven severe thrombocytopenia (up to 95% decrease in the affected animals).

Taken together, GSK2879552, even at doses as large as 100 mg/kg/day, lacks serious acute toxicity. However, pharmacology-mediated severe hematologic toxicity, principally thrombocytopenia, leads to secondary morbidity 7 to 14 days following initiation of dosing at doses ≥0.4 mg/kg/day in rats and ≥0.1 mg/kg/day in dogs.

Hematologic Toxicity: The primary effect of GSK2879552 was hematopoietic pancytopenia, principally thrombocytopenia, (in mice, rats and dogs), neutropenia (primarily in rats), and decreased reticulocytes (rats and dogs). In the bone marrow of rats and dogs, there was a shift to immaturity of the megakaryocytic, granulocytic and erythroid lineages. There was an increase in monocyte counts in rats and dogs. In concordance with the critical role played by LSD1 in the maturation of several hematopoietic lineages [Sprussel, 2012], these hematopoietic effects of GSK2879552 represent an on-target pharmacologic effect rather than an off-target, cytotoxic effect or inflammatory response.

In rats, hematopoietic effects of GSK2879552 were characterized primarily by a dose-dependant thrombocytopenia and neutropenia. Dose dependent thrombocytopenia was observed at doses of ≥0.1 mg/kg/day, reaching a maximum 98% reduction at 0.4 mg/kg/day. During treatment, there was increased mean platelet volume (MPV). Following 14 days treatment there was also a decrease in mean collagen-induced platelet aggregation. Following 4 weeks treatment platelet counts recovered in the off-dose period with an initial rebound to approximately 1.5-fold control values 1 week after 4 weeks of dosing at 0.4 mg/kg/day. Neutropenia had a rapid onset (within 7 days) and was dose-dependent at doses ≥0.03 mg/kg/day, reaching a maximum 94% decrease at 1 mg/kg/day. Neutrophil counts began recovery either during the dosing period (0.03 mg/kg/day) or in the off-dose period at ≥0.1 mg/kg/day. During the recovery phase of the 4 week study, neutrophil counts initially increased above control values (~1.4 fold) and were comparable to controls by 14 days. At doses of ≥0.2 mg/kg/day, GSK2879552 also caused a decrease in red blood cell count, an increase in monocytes and an increase in reticulocytes that was of smaller magnitude than its effects on platelets and neutrophils. The levels of RBCs, monocytes and reticulocytes returned to control values by the end of the 4 week recovery period.

In rats, the hematopoietic effect of GSK2879552 (≥0.1 mg/kg/day) was associated with increased megakaryocyte cellularity (with a high proportion of immature cells) in the bone marrow and spleen (spleen weight was increased up to 2-fold at 0.4 mg/kg/day). Megakaryocytes were also present in the liver of rats given ≥0.2 mg/kg/day. Myelofibrosis and hyperostosis of trabecular bone was noted in rats given 0.4 mg/kg/day at the end of the 4 week dosing period that reversed following a 4 week off-dose period. Myeleofibrosis or hyperostosis was not observed in dogs. Following administration of the thrombopoietin agonist romiplostim [Kuter, 2009] for 4 weeks, there was marked thrombocytosis in rats and primates and similar reversible bone marrow myelofibrosis and hyperostosis observed in rats but not in primates.

In dogs, the hematopoietic effect of GSK2879552 was characterized primarily by a time- and dose-dependent thrombocytopenia. In dogs given a single dose of 1 mg/kg, platelet counts began to decline three days after dosing, reached a nadir (60% decrease) on Day 7, began to recover on Day 9, rebounded to a peak of approximately 2-fold pretreatment values on Day 13 and returned to pretreatment values on Day 24. A similar time course for platelet counts was observed in mice that received 5 daily doses of GSK2879552 at 15 or 45 mg/kg/day. In repeat dose studies in dogs, thrombocytopenia occurred at doses ≥0.1 mg/kg/day, reaching a 94% decrease in platelet counts at 1 mg/kg/day, and was associated with an increase in mean platelet volume of the remaining platelets at ≥0.3 mg/kg/day. At 0.3 mg/kg/day in the 4 week study, the nadir in platelet counts was by Day 12 (85% decrease). There was partial, dose-dependent recovery in platelet counts during the dosing period. Following repeat dosing, platelet counts rebounded by up to 3-fold baseline values within 8 days and returned to control values by 4 weeks. At doses of ≥0.1 mg/kg/day, GSK2879552 also affected other hematopoietic lineages, but to a lesser extent than platelets, including decreases in neutrophils (up to 31%) and in red blood cell count (up to 12%); the latter was associated with a regenerative increase in reticulocytes (up to 1.5-fold). Monocytes were increased by up to 5-fold, remained elevated during the dosing period, did not decrease below pretreatment values after cessation of dosing and returned to pretreatment values by 4 weeks after dosing.

The hematopoietic responses to GSK2879552 in dogs were different from that observed in rats in that 1) platelet counts showed no recovery during the dosing period in rats and 2) neutrophil counts were only mildly affected in dogs. The underlying mechanism for these differences is not currently understood.

Lymphoid Organs: In both rats and dogs there were effects noted in lymph nodes and thymus that were reversible during the off-dose period. In rat, this consisted of mild to moderate congestion in the mesenteric and mandibular lymph nodes and lower thymus weight. In dogs, this consisted of red discolouration in the colon, caecum, ileo-colocaecal area, and jejunum. Microscopic findings in dogs were primarily necrosis of the Peyer's patches in the jejunum (minimal) and the ileum (minimal to mild), minimal haemorrhage in the caecum and minimal to mild decreased lymphoid cellularity in the thymus. In both species there were no effects on circulating lymphocyte counts. Although the mechanism underlying these effects on associated lymphoid tissue is currently unknown, the role that LSD1 plays in regulating cytokine expression [Janzer, 2012] and B lymphocyte maturation [Su, 2009] may be involved.

Genotoxicity: In screening studies in vitro, GSK2879552 was not mutagenic in the bacterial mutation assay (Ames) and was not genotoxic in the human lymphocyte micronucleus assay. These results suggest that GSK2879552 does not pose a genotoxic risk.

Reproduction: There were no histologic effects of GSK2879552 on male or female reproductive organs in rats or dogs following 4 weeks dosing. However, based on the expression of LSD1 in reproductive organs and investigations with LSD1 gene disruption [Godmann, 2007; Foster, 2010], GSK2879552 may adversely affect male and female fertility and embryofetal development.

Conclusion: The dose-limiting toxicity in rat and dog oral toxicology studies conducted with GSK2879552 was a dose-dependent, reversible mild to severe thrombocytopenia that was observed after a single high dose (1 mg/kg in dogs) or after repeat doses as low as 0.1 mg/kg/day (rats and dogs). Platelet counts began to decrease on the third day after the initiation of dosing and reached a nadir 7 days following a single dose and by 12 days after lower repeat doses. In repeat dose studies in dogs, a partial, transient recovery of platelet counts occurred during the dosing phase, whereas no recovery in platelet counts occurred in rats during dosing. During the off-dose period, platelet counts rebounded in a dose-dependent manner (the more suppression, the greater the rebound) peaking in approximately 10 days. By 4 weeks after dosing, platelet counts returned to or near pretreatment values in rats and dogs.

GSK2879552 also caused a dose-dependent decrease in circulating neutrophils, reticulocytes and red blood cells (RBCs). Neutropenia was more severe in rats than dogs. Neutrophil counts rebounded to above pretreatment levels only after cessation of dosing, peaking in 7 to 8 days in rats and in 14 days in dogs. Recovery from suppression of reticulocyte counts, however, differed between rats and dogs. In rats, suppression of reticulocyte counts fully recovered and maximally rebounded during the 4 week dosing period whereas, in dogs, recovery and rebound occurred after dosing, peaking in 20 days. The mild decrease in RBCs was primarily related to internal hemorrhaging secondary to thrombocytopenia, however the reduced reticulocytes may also have contributed to the decrease in RBCs. By 4 weeks after dosing, neutrophil, reticulocyte and red blood cell counts returned to or near pretreatment values in rats and dogs.

GSK2879552 caused a dose-dependent increase in circulating monocytes in rats and dogs. In both species, monocytes remained elevated during the dosing period, did not decrease below pretreatment values after cessation of dosing and returned to pretreatment values by four weeks after dosing.

The decreases in circulating platelets, neutrophils and reticulocytes result from the pharmacologic activity of GSK2879552 on hematopoietic lineages in the bone marrow as evidenced by a shift to immaturity of progenitor cells in the megakaryocytic, granulocytic and erythroid lineages, while the increase in monocytes results from stimulation of monopoiesis. Myelofibrosis and hyperostosis in rat (but not dog) was secondary to the marked regenerative response in the bone marrow in response to the peripheral blood cytopenias and likely represents a rodent specific response. Generally mild to moderate, reversible effects (reduced weight, cellularity or necrosis/hemorrhage) were observed in

lymphoid tissues of rats or dogs without an effect on circulating lymphocytes, of which the relationship to the pharmacology of GSK2879552 is uncertain.

As a result of severe thrombocytopenia, some rats (0.4 mg/kg/day) and dogs (≥0.1 mg/kg/day) on the 4 week toxicology studies were killed due to deteriorating clinical condition which included red nasal discharge, pale extremities, subdued behavior, partial eye closure, irregular breathing, piloerection and slow movements.

Based on the morbidity secondary to thrombocytopenia at 0.4 mg/kg/day, the no observed adverse effect level (NOAEL) in rats was 0.2 mg/kg/day. Gender-averaged systemic exposure on Day 30 at the NOAEL was 367 ng.h/mL (mean AUC_{0-t}) and 81.3 ng/mL (mean C_{max}). In rats, the STD10 was considered to be 0.4 mg/kg/day. Given the morbidity in dogs at 0.3 and 0.1 mg/kg/day, the NOAEL and highest non-severely toxic dose (HNSTD) is 0.03 mg/kg/day [mean $AUC_{(0-t)}$ 22.0 ng.h/mL, mean C_{max} 6.1 ng/mL, (gender averaged based on Day 27 values)].

Table 2 Principal Toxicological Findings in Rats and Dogs Following Oral Administration of GSK2879552 as Single or Repeat Doses for up to 4 Weeks

Finding	Rat		Dog	
	Effect Dose (mg/kg)	No-Effect Dose (mg/kg)	Effect Dose (mg/kg)	No-Effect Dose (mg/kg)
Morbidity/Mortality				
Repeat Dose*	0.4	0.3	0.1	0.03
Hematologic Toxicity				
Platelets – decrease	0.1	0.03	0.1	0.03
Neutrophils – decrease	0.03	NA	0.3	0.1
Reticulocytes - decrease	0.3	0.2	0.3	0.1
Red Blood Cells - decrease	0.2	0.1	0.3	0.1
Monocytes – increase	0.2	0.1	0.1	0.03
Bone marrow - immature phenotype	0.1	0.03	0.03	ND
Myelofibrosis/hyperostosis	0.4	0.3	NO	NA
Lymphoid Organs				
Lymph nodes – congestion	0.1	ND	NO	NA
Lymph nodules – necrosis/hemorrhage	NO	NA	0.03	ND
Thymus – decreased weight	0.2	0.1	NO	NA
Thymus – decreased cellularity	NO	NA	0.03	ND

Key:
* Animals killed due to deteriorating clinical condition with clinical signs including red nasal discharge, pale extremities, subdued behavior, partial eye closure, irregular breathing, piloerection and slow movements. Macroscopic and microscopic evidence of hemorrhage.
NO = not observed; NA = not applicable; ND = not determined

Table 3 Comparative Assessment of Systemic Exposure Following Oral Repeat Dose Administration of GSK2879552 to Rats and Dogs

Species (Duration)	Dose (mg/kg/day)	C_{max} (ng/mL)		AUC (ng.h/mL)	
		Day 1	End of Study	Day 1	End of Study
Rat (7-day)	1	348	335	1890	1770
	10	3640	3880	17700	18400
	100	34600	36600	221000	238000
Rat (14-day)	0.03	3.66	4.90	20.2	36.9
	0.1	14.2	23.3	98.9	139
	0.3	69.6	76.6	375	413
Rat (4 weeks)	0.1	26.1	35.2	120	171
	0.2	**55.4**	**81.3**	**260**	**367**
	0.4	117	151	606	714
Dog (7 to 14-day)	0.3	103	88.7	166	157
	1	299	243	674	549
Dog 14 day	0.03	7.13	10.7	9.50	22.5
	0.1	32.3	37.4	112	176
Dog (4 weeks)	**0.03**	**6.27**	**6.68**	**16.0**	**22.0**
	0.1	25.8	31.7	62.2	81.0
	0.3	107	NA	225	NA

Note: Bold = NOAEL (no observed adverse effect level)
Key:
NA = Not Available (animals terminated prior scheduled end of study)

1.3.3. Pharmacokinetics of GSK2879552 in Humans

GSK2879552 pharmacokinetics have not yet been evaluated in humans. Pharmacokinetics of GSK2879552 in human were predicted using in vitro microsomes and hepatocytes data, as well as in vivo intravenous (IV) pharmacokinetic data from mice, rats, and dogs combined with simple allometric scaling and Dedrick transformation. The human blood clearance is predicted to be around 5.4 mL/min/kg for a 70 kg human. The human blood volume of distribution is predicted to be most likely between 1.0 and 1.5 L/kg leading to a range of terminal half-life of 2.1 to 3.2 hours. Based on the good oral bioavailability in animals and the predicted low human clearance, the oral bioavailability is expected to be around 75% to 100% in humans.

1.4. Benefit:Risk Assessment

Summaries of findings from non-clinical studies conducted with GSK2879552 can be found in the Investigator's Brochure (IB) [GlaxoSmithKline Document Number 2013N168888_01]. Toxicology studies performed in dogs, rats and mice suggest that the primary toxicities of GSK2879552 are hematologic. The following Section outlines the risk assessment and mitigation strategy for this protocol.

Potential Risk of Clinical Significance	**Data/Rationale for Risk**	**Mitigation Strategy**
Lymphoid/hematologic and associated bleeding and infection risks	The primary toxicity with GSK2879552 is a dose-dependent mild-to-severe thrombocytopenia, observed in mice, rats and dogs. A dose-dependent mild-to-severe neutropenia was observed in rats, but not dogs, and was not associated with systemic infections. Mild effects on the erythron were observed in rats and dogs which may reflect both a direct and indirect (i.e., secondary to bleeding/hemorrhage) effect on the erythroid lineage. In general, there was not hypocellularity observed in the bone marrow of these animals.	Informed Consent Form includes the risk of hematologic toxicity. Protocol specifies: - laboratory assessments (complete blood count [CBC]) - Exclusion criteria for subjects with recent history of significant bleeding or elevated bleeding risk - Monitoring for bleeding - Monitoring for infection - Dose stopping/modification criteria - Anticoagulants (e.g., warfarin above 1 mg once daily, direct thrombin inhibitors, etc) at therapeutic doses or platelet inhibitors (e.g., aspirin above 100 mg once daily, clopidogrel) are prohibited from fourteen days prior to the first dose of study drug through completion of the Final Study Visit. - Guideline for platelet transfusion
Mental status change	Two (out of 16) subjects enrolled in 200858 study experienced encephalopathy.	Informed Consent Form is updated to include the risk of mental status change. Protocol eligibility and monitoring criteria are modified: - subjects who have received prior treatment with temozolomide, dacarbazine, procarbazine or PARP inhibitors are excluded - Subjects should have baseline thyroid function, vitamin B12 level and metabolic panel within acceptable limits - Montreal Cognitive Assessment (MOCA) at baseline and weekly for the first 4 weeks and monthly thereafter. - Subjects with baseline MOCA score of ≤ 22 are excluded Protocol stopping criteria is modified: - Dosing will be held and neurology consult will be required if a decrease of 3 points or more from baseline MOCA score or any score of < 22 occurs or in case of any other indication of early encephalopathy as determined by patient history or physical exam

1.4.1. Benefit Assessment

This is an open-label, dose escalation study and the first time in human study of this agent to be conducted in subjects with relapsed/refractory SCLC for which no standard therapies are anticipated to result in a durable remission. GSK2879552 has preclinical activity in SCLC cell lines, however it is unknown whether GSK2879552 will have clinical activity, thus any potential beneficial effect for an individual subject attributable to GSK2879552 is unknown. Data obtained in this study may assist in progressing the knowledge base on SCLC and its treatment, or help identify individuals more likely to benefit or have side-effects from GSK2879552. Study participants may benefit from the medical tests and screening performed during the study.

1.4.2. Overall Benefit:Risk Conclusion

Current data from GSK2879552 preclinical studies indicate a potential to induce the expression of putative LSD1 target genes and to inhibit tumor growth. Taking into account the measures taken to minimize risks to subjects participating in the Phase I clinical trial, the potential risks identified in association with GSK2879552 are justified by the anticipated benefits that may be afforded to subjects with relapsed/refractory SCLC.

2. OBJECTIVES, ENDPOINTS AND HYPOTHESES

2.1. Part 1 Dose Escalation

PART 1: Escalation Cohort		
	Objectives	**Endpoints**
Primary	1. To determine the safety, tolerability and Recommended Phase 2 Dose(s) (RP2D) and regimen of GSK2879552 given orally in adult subjects with small cell lung carcinoma (SCLC).	1. AEs, SAEs, dose limiting toxicities, dose reductions or delays, withdrawals due to toxicities and changes in safety parameters (e.g., laboratory values, vital signs, electrocardiograms [ECGs], physical examinations).
Secondary	1. To characterize the pharmacokinetics (PK) of GSK2879552 after single- and repeat-dose oral administration.	1. GSK2879552 PK parameters following single-(Day 1) and repeat-dose (Day 15) administration of GSK2879552, including AUC, Cmax, time of occurrence of Cmax (tmax), t½ (terminal phase and/or effective half-life), accumulation ratio, and time invariance.
	2. To evaluate clinical activity after treatment with GSK2879552.	2. Disease Control Rate (DCR) (CR + PR + SD) at week 16 based on Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.
	3. To evaluate the relationship between GSK2879552 exposure and	3. Relationship between GSK2879552 exposure markers (e.g. dose, Cmax, Cmin or AUC [0-tau]), and ProGRP, platelet

PART 1: Escalation Cohort		
	Objectives	**Endpoints**
	safety/efficacy/Pharmacodynamic (PD) parameters	levels in blood, and safety/efficacy parameters.
Exploratory	1. To assess feasibility of a select gene panel for use as a PD assay for GSK2879552 2. To investigate the impact of GSK2879552 on the RNA expression profile in tumor and blood to identify mechanisms of rational combination and potential resistance. 3. To investigate relationship between tumor baseline genomic profile and response or resistance to GSK2879552. 4. To discover circulating response and resistance biomarkers 5. To investigate the impact of GSK2879552 on fetal haemoglobin 6. To characterize the metabolite profile of GSK2879552 after oral single and/or repeat-dosing in some subjects 7. To determine the amount of GSK2879552 excreted in urine after oral single and/or repeat-dosing	1. Change from baseline expression in select genes in whole blood and tumor 2. Transcriptomic (RNA) profile of tumor and whole blood pre- and post-treatment with GSK2879552. 3. Tumor DNA, RNA and protein markers at baseline. 4. Circulating biomarkers (e.g. circulating cell free DNA [cfDNA], protein and RNA). 5. Pre- and post-treatment fetal haemoglobin levels 6. GSK2879552 metabolites in plasma and/or urine 7. Concentration of GSK2879552 in urine measured with an investigational bio-analytical method and extrapolated to total amount excreted in urine over time
Hypothesis	No formal statistical hypotheses are being tested in Part 1 dose escalation. Analysis of the data obtained from Part 1 will only utilize descriptive methods.	

2.2. Part 2 Expansion

Part 2: Expansion Cohort		
	Objectives	**Endpoints**
Primary	1. To evaluate clinical activity of GSK2879552 given orally in adult subjects with SCLC.	1. Disease Control Rate (DCR) (CR + PR + SD) at week 16 based on Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.
Secondary	1. To evaluate the safety and tolerability of RP2D of GSK2879552	1. AEs, SAEs, dose limiting toxicities, dose reductions or delays, withdrawals due to toxicities and changes in safety assessments (e.g., laboratory parameters, vital signs, physical examinations).

Part 2: Expansion Cohort		
	Objectives	**Endpoints**
	2. To characterize the population PK of GSK28795522.	2. Population PK parameters for GSK2879552 such as clearance (CL/F) and volume of distribution (V/F), and relevant covariates which may influence exposure (e.g., age, weight, or disease associated covariates).
	3. To evaluate the relationship between GSK2879552 exposure and safety/efficacy/PD parameters.	3. Relationship between GSK2879552 exposure markers (e.g. dose, Cmin, Cmax or AUC [0-tau]), and ProGRP, platelet levels in blood, and safety/efficacy parameters.
	4. To evaluate duration of response and progression free survival (PFS)	4. Duration of response and PFS
	5. To evaluate objective response rate (ORR)	5. % of subjects achieving complete response and partial response
Exploratory	1. To assess feasibility of a select gene panel for use as a PD assay for GSK2879552	1. Change from baseline expression in select genes in whole blood
	2. To investigate the impact of GSK2879552 on the RNA expression profile in blood to identify mechanisms of rational combination and potential resistance.	2. Transcriptomic (RNA) profile of whole blood pre- and post-treatment with GSK2879552.
	3. To investigate relationship between tumor baseline genomic profile and response or resistance to GSK2879552.	3. Tumor DNA, RNA and protein markers at baseline.
	4. To discover circulating response and resistance biomarkers	4. Circulating biomarkers (e.g. cfDNA, protein and RNA).
	5. To investigate the impact of GSK2879552 on fetal haemoglobin	5. Pre- and post-treatment fetal haemoglobin levels
Hypothesis	Clinical response will be defined as Disease Control Rate (DCR) (CR + PR + SD) at week 16 based on Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. The null hypothesis is: H0: DCR ≤15% at week 16 The alternative hypothesis is: HA: DCR ≥30% at week 16	

3. INVESTIGATIONAL PLAN

3.1. Discussion of Study Design

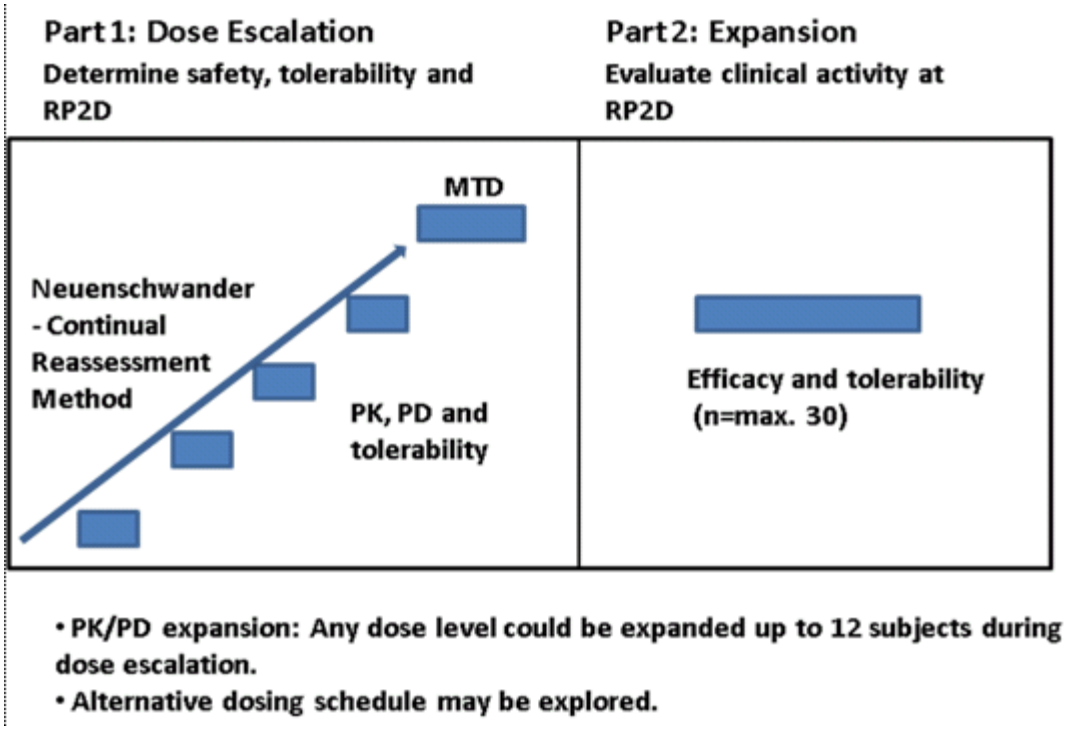
Protocol waivers or exemptions are not allowed. Therefore, adherence to the study design requirements, including those specified in the Time and Events Table (Section 7.1), are essential.

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, multi-center, non-randomized, 2-part first time in human (FTIH) study designed to evaluate the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD) and clinical activity of GSK2879552 given orally (Figure 1).

Figure 1 Study Schema



Part 1 is a dose escalation phase to determine the recommended phase 2 dose (RP2D) for GSK2879552 based on the safety, tolerability, PK, and PD profiles observed after oral administration of GSK2879552. Eligible subjects with relapsed/refractory SCLC will be enrolled in the dose escalation cohorts. Any dose level(s) may be expanded up to 12 subjects in order to collect additional data on PK and PD.

Once RP2D is identified, an expansion cohort (Part 2) of up to 30 subjects will be enrolled to further evaluate the clinical activity and tolerability of GSK2879552 in subjects with relapsed/refractory SCLC.

The proposed treatment schedule of GSK2879552 is continuous daily dosing. The starting dose will be 0.25 mg once daily. Alterations to the dose and schedule may be incorporated based on emerging PK, PD, and tolerability/safety data.

Subjects may continue treatment in the study until disease progression (investigator assessed), unacceptable toxicity, or withdrawal of consent. Subjects enrolled in Part 2 who discontinue study treatment for reasons other than Response Evaluation Criteria in Solid Tumors (RECIST)-defined disease progression will continue to have protocol defined radiological assessments until disease progression per RECIST 1.1, start of new

anti-cancer therapy or withdrawal from study. Every effort should be made to continue radiological assessments until radiological progression per RECIST is observed. The duration of study will depend on recruitment rates and timing of subjects' duration on study.

3.2. Part 1: Dose-Escalation

In Cohort 1, a single subject will receive a dose of GSK2879552 0.25 mg once daily. The subject in Cohort 1 must complete a full 28 days of dosing, and the safety and PK data will be reviewed prior to starting Cohort 2. If the first subject becomes inevaluable for reasons other than toxicity, another subject will be recruited. The dose-escalation decision and rationale will be documented in writing with copies maintained at each study site and in the master study files at GlaxoSmithKline (GSK).

Starting with Cohort 2 the dose escalation will continue using the Neuenschwander - continuous reassessment method (N-CRM) [Neuenschwander, 2008]. A sufficient number of subjects will be enrolled in each cohort to ensure that data from at least one subject that has completed the first 28 days of dosing is available prior to defining a new dose and starting the next cohort. In addition, subjects who fail to take at least 75% of their scheduled doses in the first 28 days for reasons other than toxicity (e.g., dose limiting toxicities) will be replaced.

Maximum Dose Increment

Built-in safety constraints are in place to prevent exposing subjects to undue risk of toxicity. The dose increment will be no more than 100% of the current dose in the absence of any safety signals. The dose increment will be no more than 50% of the current dose after one grade ≥ 2 non-hematologic drug related toxicity (except alopecia, fatigue, asthenia, nausea, vomiting and electrolyte abnormalities as described below), dose limiting toxicity (DLT), Grade 2 thrombocytopenia lasting over 7 days or Grade 3 neutropenia lasting over 7 days is observed. The maximum allowable dose increment will be determined based on the prior dose level data.

Number of Subjects in a Cohort

The dose escalation will continue with 1 subject per cohort until any of the following events are observed, and then each subsequent cohort will consist of a minimum of 2 subjects.

- Dose limiting toxicity
- Grade 2 thrombocytopenia over 7 days
- Grade 3 neutropenia.
- Any Grade 2 or higher non-hematologic adverse event (except alopecia) that is considered related to the study medication with the following exceptions:
- Grade 3 fatigue, asthenia, nausea, and vomiting that respond to standard medical care within 72hrs, electrolyte abnormalities unrelated to underlying malignancy and corrected within 72 hrs

- Any grade adverse event that is 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.

When 2 or more subjects are enrolled in a cohort, dosing start will be staggered by at least 1 week interval between the subjects.

The subsequent cohorts may revert to 1 subject per cohort in either of the following 2 scenarios:

- 2 additional subjects are added at the dose where Grade 2 toxicity is seen in the initial subject and no Grade 2 or higher toxicity is seen in either of the 2 new subjects.
- Subjects treated at next higher dose level do not have a Grade 2 or higher toxicity.

However, the dose escalation may continue with multiple subjects per cohort per the clinical judgment of the Medical Monitor and internal dose-escalation committee in consultation with the investigators. The decision on the number of subjects will be documented in writing together with the dose escalation decision and the rationale.

Completion of Dose Escalation

The dose escalation will complete when RP2D is determined. The RP2D will be the MTD or a lower dose that provides adequate PK exposure and biologic activity with superior tolerability. The identification of MTD may not be necessary if a clear RP2D emerges without reaching the MTD. The final determination of RP2D will be based on the N-CRM suggested dose level, or the biologically active dose (e.g., clinical response), the safety profile, and available PK and 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.

Dose Escalation Committee

An internal dose-escalation committee will be comprised of the following GSK representatives: Medical Monitor, Safety Physician or Scientist, Clinical Scientist, Biostatistician, PK and PD Scientists, and Study Operation Lead. The dose-escalation committee will review available relevant data on demographics, all adverse events including non-DLT toxicities, laboratory assessments, 12-lead ECGs, and dose administration logs, as well as PK and PD data. On the basis of a review of these data and in joint discussions with the participating investigators, a determination will be made as to whether dose escalation should continue as recommended by the N-CRM.

Description of the Continual Reassessment Method

After each cohort, a dosing recommendation for the next cohort will be made using the N-CRM. All available data, including safety, PK and PD data from current and prior cohorts will be reviewed at the dose escalation meeting. Although the N-CRM will be used to recommend the next dosing level, clinical judgment by the Medical Monitor and

internal dose-escalation committee in consultation with the investigators can halt or reduce dose escalation or de-escalate as deemed appropriate at any time during the trial.

The N-CRM design is a type of Bayesian adaptive dose escalation scheme that assumes a two-parameter logistic model for the toxicity rate based on dose. It is a modified version of the original Continual Reassessment Method (CRM) [O'Quigley, 1990]. A CRM-based design uses a statistical model for dose and toxicity, and is expected to locate the MTD efficiently while minimizing the number of subjects exposed to pharmacologically inactive dose levels.

The method is fully adaptive and makes use of all the DLT information available at the time of each dose assignment. In contrast, the 3+3 method only uses information from one dosing cohort at a time.

At the time of each dose escalation decision, the Fixed and Adaptive Clinical Trial Simulator (FACTS, Version 2.3 or higher, Tessella) will be used to obtain, for each potential dose, the posterior probabilities that the DLT rate for that dose lies in each of four toxicity intervals (underdosing, target dose range, excessive toxicity, and unacceptable toxicity). The four DLT toxicity intervals are defined as follows:

- [0%,16%) Underdosing
- [16%, 33%) Target dose range
- [33%, 60%) Excessive toxicity
- [60%, 100%) Unacceptable toxicity

The recommended dose will be the dose with the highest posterior probability of lying in the target dose range with the additional requirement that the sum of the posterior probabilities of the DLT rate lying in the excessive toxicity or unacceptable toxicity range is less than 25%. Selection of the next dose is also subject to the built-in safety constraints of maximum allowed dose increment. An updated estimate of the toxicity curve will be provided at the time of the dose escalation meeting.

Note that de-escalation as well as escalation is possible using this method.

Bayesian Prior

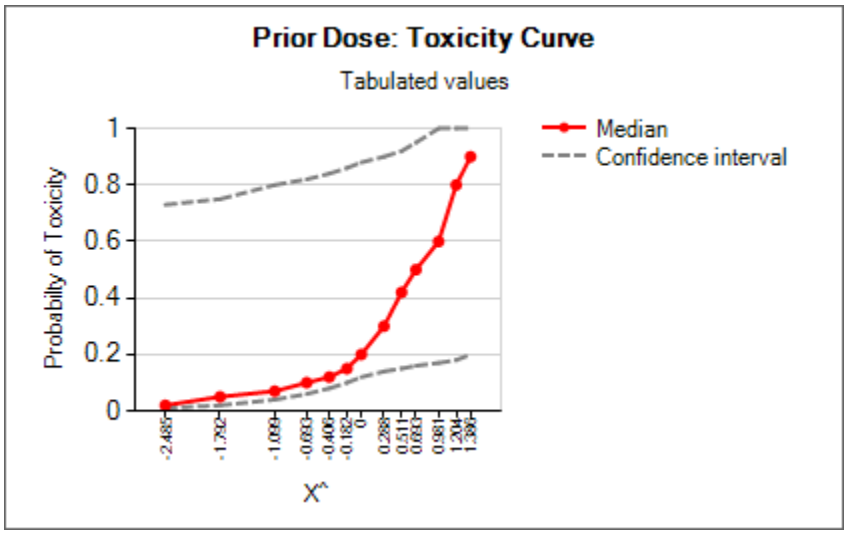
The N-CRM methodology requires that a Bayesian prior for the toxicity curve be pre-specified. The Bayesian prior used for this design was determined using the quantile method. For each dose, an estimate of the median probability of DLT was specified, along with a 95% credible interval. The 95% credible intervals are intentionally wide due to limited information about the toxicity profile of GSK2879552 in humans. Table 4 shows the median prior probability of experiencing a DLT at the given dose along with a 95% credible interval around the median:

Table 4 Specified Prior Probability of DLT

Anticipated Dose (mg)	Median Probability of Toxicity	2.5% Quantile for Probability of Toxicity	97.5% Quantile for Probability of Toxicity
0.25	0.02	0.01	0.73
0.5	0.05	0.02	0.75
1	0.07	0.04	0.8
1.5	0.1	0.06	0.82
2	0.12	0.08	0.84
2.5	0.15	0.1	0.86
3	0.2	0.12	0.88
4	0.3	0.14	0.9
5	0.42	0.15	0.92
6	0.5	0.16	0.95
8	0.6	0.17	1
10	0.8	0.18	1
12	0.9	0.2	1

A graphical presentation of the prior is displayed in the Figure 2. In the figure, the x-axis is natural log (dose/reference dose), where the reference dose is set to 3 mg. Doses are the projected doses. Actual doses used during the conduct of the trial may vary.

Figure 2 Prior Distribution For The Probability of DLT Given Dose



3.3. PK/PD Expansion cohorts

Any dose level(s) in Part 1 may be expanded up to 12 subjects in order to collect adequate data on safety, PK or PD. Pre-dose and post-dose tumor biopsies may be required from a subset of subjects in PK/PD expansion cohorts. A minimum of five pairs

of evaluable pre- and post-dose biopsies may be collected at selected doses based on emerging PK/PD data.

Subjects may be enrolled at previously completed dose levels for the purpose of obtaining additional PK or PD data. A reduced PK schedule may be used in subjects enrolled to obtain additional PD samples. These subjects may have the dose escalated to a higher completed dose level (not exceeding the maximum tolerated dose [MTD]) once the necessary PK/PD procedures have been completed.

3.4. Alternative Dosing and PK/PD Sampling Schedules

Alterations may be made to the dosing schedule and/or PK/PD sampling schedule based on the results of emerging PK, PD, and safety data, and documented in the SPM. These would not require a protocol amendment.

Schedules that incorporate a recovery period may be explored (e.g., 4 days on/3 days off). This approach may be considered if higher exposure is desired for an improved clinical activity (i.e., higher response rate) or therapeutic exposure cannot be achieved without excessive toxicity. If MTD was not exceeded with the initial schedule, the starting dose for the alternate schedule will be the one dose level higher than the highest completed dose level. If MTD was exceeded with the initial schedule, the starting dose for the alternate schedule will be no higher than the highest tested daily dose.

3.5. Dose-Limiting Toxicity

An event will be considered a DLT if it occurs within the first 28 days of treatment, and meets one of the following criteria unless it can be clearly established that the event is unrelated to treatment:

- Recurrent Grade 3 anemia after initial transfusion or Grade 3 anemia lasting > 7 days in subjects who are not transfused.
- Grade 4 neutropenia
- Grade 3 neutropenia > 7 days duration
- Febrile neutropenia as defined by CTCAE v.4.0
- Grade 3 thrombocytopenia requiring dose reduction
- Grade 4 thrombocytopenia lasting > 3 days or of any duration if associated with clinically significant bleeding
- Drug related Grade 3 or 4 non-hematologic toxicity. Fatigue, asthenia, nausea, vomiting or new electrolyte disturbance that respond to standard medical care within 72 hours are exceptions. In addition, electrolyte disturbances associated with underlying malignancy are also excluded.
- Drug related Grade 2 toxicity (at any time during treatment) that in the judgment of the investigator and GSK Medical Monitor is dose-limiting.
- Treatment delay of 14 days or greater due to unresolved drug-related toxicity.

3.6. Maximum Tolerated Dose (MTD) and Recommended Phase 2 Dose (RP2D)

The MTD is defined as the dose with the highest posterior probability of subjects experiencing a DLT in the first 28 days on treatment in the target interval [16%,33%], and for which the probability that the DLT rate lies within the excessive toxicity or the unacceptable toxicity windows is less than 25%. The interval boundaries of 16% and 33% are chosen to be consistent with the traditional 3+3 design toxicity boundary which is 1/6 and 1/3.

The RP2D will be MTD or a lower dose that provides adequate PK exposure and biologic activity with superior tolerability. Up to 12 additional subjects will be enrolled at the dose to further define the safety and tolerability of the dose and schedule.

3.7. Part 2: Expansion Cohort

Once the RP2D has been determined, an expansion cohort of up to 30 subjects will be enrolled in order to better characterize the clinical activity and safety profile of the RP2D.

3.8. 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 DLT, and contingent upon one of the following:

- A higher dose level cohort has been cleared without a DLT
- If a dose level has been cleared and no subjects have been identified for enrolment at the next dose level, and after the subject has competed a minimum of 8 weeks of dosing on that regimen without a DLT, that subject may be escalated to the next higher dose level. In this case, the subject must follow the dosing schedule outlined in the Time and Events Table (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.

3.9. Rationale

3.9.1. Rationale for Population

SCLC is initially responsive to chemotherapy; however, patients ultimately relapse and the response to second line therapy is poor with overall survival of less than 6 months. Additionally, current chemotherapy regimens for SCLC often have substantial and for some patients, intolerable toxicity. Thus, there is a need for new treatments for this disease. Among the cell lines tested, the anti-proliferative activity of GSK2879552 is largely limited to SCLC and acute myeloid leukemia. This may suggest a unique requirement for LSD1 in these tumor types. Both are poorly differentiated tumors and GSK2879552 promotes phenotypic changes associated with differentiation in human AML cells. While the biological mechanisms involved in differentiation of SCLC are not

as well understood, we hypothesize that inhibition of LSD1 may invoke a similar mechanism in SCLC. GSK2879552 induces the expression of putative LSD1 target genes and has potent, predominantly cytostatic, anti-proliferative activity in small cell lung carcinoma (SCLC) cell lines with median EC_{50} = 25 nM. In total, 9/28 SCLC lines were found to be sensitive to GSK2879552 treatment while the sensitivity of an additional 7 SCLC lines could not be determined. GSK2879552 thus may have clinical activity in SCLC, either as a monotherapy or ultimately in combination with standard chemotherapy.

3.9.2. Rationale for Dose

3.9.2.1. Predicted Effective Dose

The potential therapeutic dose for GSK2879552 in human was derived using available preclinical PK, in vitro SCLC cell line data and in vivo PD and efficacy data from SCLC tumor xenograft studies.

In vitro, GSK2879552 showed inhibition of proliferation of small cell lung carcinoma with a median EC50 = 25 nM (range = 2 - 240 nM).

The effect of GSK2879552 was evaluated at daily doses of 0.05 mg/kg up to 15 mg/kg in a mouse NCI-H526 xenograft model. Daily doses of 0.5 mg/kg and 1.5 mg/kg showed significant decreases in tumor growth of 48% and 57% respectively.

The anticipated effective daily doses in humans are around 1.2 mg to 3.5 mg, computed to provide free AUCs similar to the ones predicted for mice receiving 0.5 mg/kg and 1.5 mg/kg, respectively. These predictions have taken into account the 25% difference in plasma protein binding between human and mouse and assume 100% oral bioavailability.

3.9.2.2. Starting Dose

Three approaches have been considered to establish the starting dose for GSK2879552 in subjects with SCLC assuming a 70 kg adult with a surface area of 1.8 m^2.

1. One tenth of the rat severely toxic dose (STD10) as per ICH S9 guidance

The STD10 in the rat was defined as 0.4 mg/kg (free AUC of 137 ng.h/mL and total AUC of 714 ng.h/mL) administered daily for 4 weeks. The main finding was thrombocytopenia leading to morbidity in 5 of 38 rats. One-tenth (1/10) of the rat STD10 is 0.24 mg/m2. This dose would be well tolerated in dogs as it is less than half of the low dose evaluated on the 4 week study (0.03 mg/kg or 0.6 mg/m2) which was the NOAEL and HNSTD. The NOAEL on the 4 week rat study was 0.2 mg/kg (free AUC of 71 ng.h/mL and total AUC of 367 ng.h/mL). A starting dose based on 1/10 of the rat STD10 would translate to a starting dose in man of 0.43 mg using the human equivalent dose calculation.

2. One sixth of the dog highest non severely toxic dose (HNSTD) as per ICH S9 guidance

The HNSTD in the dog was defined as 0.03 mg/kg (free AUC of 12.8 ng.h/mL and total AUC of 22 ng.h/mL) administered daily for 4 weeks. The only finding at this dose was

the observation of immature hematopoietic cells in the bone marrow. It was also the NOAEL. A starting dose based on 1/6 of the dog HNSTD would be 0.1 mg/m2 and translates to a starting dose in man of 0.18 mg using the human equivalent dose calculation.

3. The minimum anticipated biologically effective dose (MABEL)

The principle pharmacologic/toxicologic effect of GSK2879552 in normal animals was hematopoietic maturational arrest leading to peripheral cytopenias. The most sensitive lineage was platelets. In rats, the MABEL was 0.1 mg/kg/day (0.6 mg/m^2; free AUC of 32.8 ng.h/mL and total AUC of 171 ng.h/mL) for causing a mild (26%) reduction in platelet counts and immature hematopoietic cell phenotype in the bone marrow. In dogs, the MABEL was 0.03 mg/kg/day (0.6 mg/m^2; free AUC of 12.8 ng.h/mL and total AUC of 22 ng.h/mL) for causing an immature hematopoietic cell phenotype in the bone marrow, but this dose was not associated with a reduction in circulating platelets. The rat and dog MABEL doses would translate to a dose in man of 1.1 mg using the human equivalent dose calculation. The MABEL dose in humans based on the exposure in rats and dogs is predicted to be 1.6 mg and 0.6 mg, respectively.

The potential therapeutic effect of GSK2879552 was evaluated at daily doses of 0.05 mg/kg up to 15 mg/kg in a mouse NCI-H526 xenograft model. A dose of 0.05 mg/kg provided a no meaningful effect on tumor growth (7% decrease), while a dose of 0.15 mg/kg showed a non-significant decrease in tumor growth of 36% (predicted free AUC of 7.7 ng.h/mL and total AUC of 21 ng.h/mL). The MABEL dose in humans based on the exposure in mice at 0.15 mg/kg is predicted to be 0.4 mg.

Conclusion:

The proposed starting dose of 0.25 mg was selected with the goal of administering a pharmacologically active dose that is reasonably safe to use, in accordance with ICH S9. The selection of this dose also takes into consideration the nature of the dose limiting toxicity seen in GLP studies. In both rodent and non-rodent species, the dose-limiting toxicities were hematologic, principally thrombocytopenia, which resulted from an expected pharmacologic effect of maturational arrest rather than a cytotoxic effect on the bone marrow. Hematologic toxicity is monitorable, manageable with supportive care and dose interruptions as required and is reversible. Eligibility criteria have been designed to mitigate risks associated with the potential for severe cytopenias and close monitoring of hematologic parameters, as well as dose modification and supportive care guidelines are outlined in the protocol. The starting dose of 0.25 mg daily has a predicted total exposure of 11.4 ng.h/mL with a Cmax of 1.4 ng/mL (free AUC of 5.2 ng.h/mL and free Cmax of 0.65 ng/mL)

Refer to the IB [GlaxoSmithKline Document Number 2013N168888_01] for additional information on the preclinical biology and toxicology studies.

3.10. Study Treatment

3.10.1. Treatment Assignment

Subjects will be identified by a unique subject number that will remain consistent for the duration of the study, except for subjects who are allowed intra-subject dose escalation and start the treatment from Day 1 with the new subject numbers allocated to them.

3.10.2. Meals and Dietary Restrictions

Consumption of Seville oranges, grapefruit, grapefruit hybrids, grapefruit juice, pommelos, or exotic citrus fruits is not permitted from 1 day prior to the first dose of study treatment(s) until the last dose of study drug.

Study treatment(s) will be administered under fasting conditions, either 1 hour before or 2 hours after a meal.

On serial PK sampling days, subjects should fast overnight (i.e., at least 8 hours) and should continue fasting until at least 2 hours after administration of the morning dose.

Fasting will consist of avoiding the oral ingestion of calorie-containing products; however, ingestion of water is permitted. Any ongoing, usual concomitant medications may be administered while fasting.

3.10.3. Blinding

This is an open-label study.

3.11. Safety Management Guidelines

3.11.1. 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. Study treatment(s) will be stopped if any of the following liver chemistry stopping criteria is/are met:

1. Alanine aminotransferase (ALT) ≥3 X (times) upper limit of normal (ULN) and bilirubin ≥2 Xs ULN (or ALT ≥3 X ULN and international normalization ratio [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).

2. ALT ≥5 X ULN.
3. ALT ≥3 X 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).

4. ALT ≥3 X ULN persists for ≥4 weeks.
5. ALT ≥3 X ULN and cannot be monitored weekly for 4 weeks.

In subjects with documented liver metastasis at baseline, following liver chemistry stopping criteria is applied:

6. ALT ≥5X ULN and twice the baseline ALT ULN
7. ALT ≥3 X ULN and 1.5 X baseline ALT 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).
8. ALT ≥3 X ULN and 1.5 X baseline ALT ULN persists for ≥4 weeks.
9. ALT ≥3 X ULN and 1.5 X baseline ALT ULN and cannot be monitored weekly for 4 weeks.

Subjects with ALT ≥3 X ULN **and** <5 Xs ULN (for patients with liver metastases at baseline use ALT ≥3 X ULN and 1.5 X baseline ALT ULN **and** ALT <5X ULN and twice the baseline ALT ULN) **and** bilirubin <2 X 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 below for details on weekly follow-up procedures for these subjects.

3.11.1.1. Liver Chemistry Monitoring Criteria

For subjects with ALT ≥3 X ULN **but** <5X ULN **and** bilirubin <2 X ULN, without symptoms indicative of hepatitis or rash, and who can be monitored safety for 4 weeks, the following actions should be taken:

- Notify the GSK Medical Monitor within 24 hours of learning of the abnormality to discuss subject safety.
- Continue administration of study drug(s).
- Evaluate liver chemistries (ALT, AST, alkaline phosphatise, bilirubin) weekly until they resolve, stabilize or return to within baseline levels.
- If at any time the subject meets any of the liver chemistry stopping criteria 1 to 5 (Section 3.11.1), then proceed as described in Section 3.11.1.2).
- If, after 4 weeks of monitoring, ALT <3X ULN and bilirubin <2 X ULN, then monitor subjects twice monthly until liver chemistries normalize or return to within baseline values.

3.11.1.2. Liver Chemistry Follow-up Procedures

Refer to the diagram in Appendix 4 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 3.11.1

- Immediately 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 electronic case report forms (eCRFs). If the event also meets the criteria of a serious adverse event (SAE) (see Section 8.2), the SAE data collection tool will be completed separately with the relevant details.
- Restart or rechallenge of study treatment requires GSK approval as described in Section 9

Safety Follow-Up Procedures for subjects with ALT ≥3 times ULN (for patients with liver metastases at baseline use ALT ≥3 X ULN and 1.5 X baseline ALT ULN)**:**

- Monitor subjects **weekly** until liver chemistries (ALT, aspartate aminotransferase [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 <u>all</u> subjects with ALT ≥3 times ULN (for patients with liver metastases at baseline use ALT ≥3 X ULN and 1.5 X baseline ALT 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 (IgM).
  - Hepatitis C ribonucleic acid (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 48 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 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 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 (>35% direct) **or** ALT ≥3 X ULN and INR >1.5 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, magnetic resonance imaging [MRI] or computed tomography [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 high-performance 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]).
- 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 polymerase chain reaction (PCR) of hepatitis D RNA virus (where needed) – as outlined in: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1153793.

3.11.2. QTc Stopping Criteria

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

- QT interval corrected for heart rate by Bazett's formula (QTcB) >530 msec

[1]Based on average QTc value of triplicate electrocardiograms (ECGs) to include manual over-read. For example, if an ECG demonstrates a prolonged QT 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 QTc values of the 3 ECGs to determine whether the subjects should have study treatment(s) withheld.

QTc will be repeated at least weekly, until the QTc prolongation resolves to Grade 1 or baseline. Once the QTc prolongation resolved, the subject may be re-started on the study treatment(s) if the investigator and GSK Medical Monitor agree that the subject will benefit from further treatment.

For subjects recruited in France, please refer to Appendix 5 for the French specific QTc stopping criteria.

3.11.3. Mental Status Stopping Criteria

Study treatment will be held and neurology consult obtained if any of the 3 criteria below are met:

- A decrease of 3 points or more from baseline MOCA score
- Any MOCA score of <22
- Any other indication of early encephalopathy as determined by patient history or physical exam

The treatment may resume if one of the following criteria is met:

- A reversible cause other than study treatment is identified and both MOCA score and symptoms return to baseline.

Evaluated by a neurologist and found to have no clear signs/symptoms of encephalopathy or other cognitive dysfunction. This is applicable only in the absence of decrease in MOCA score.All treatment restarts must be approved by GSK medical monitor

The treatment should be permanently discontinued for subjects with documented symptoms with no other cause, even if they return to baseline.

3.12. Guidelines for Events of Special Interest and Dose Modifications

The severity of AEs will be graded utilizing the National Cancer Institute- Common Toxicity Criteria for Adverse Events (NCI-CTCAE), version 4.0. Guidelines for dose modifications and interruptions for management of common toxicities associated with the study treatment(s) are provided in this section.

3.12.1. Dose Adjustment for toxicity

In the event of a DLT or other clinically significant adverse event, treatment will be withheld and supportive therapy administered as clinically indicated. See Table 5 Dose Adjustment Guideline for drug related non-hematologic toxicities based on worst grade.

Table 5 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	Holdfor 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.

1. *Note: Exceptions to ≤ drug-related Grade 1 requirement may be made for rash, alopecia, quickly reversible (<72 hours) laboratory abnormality (example: electrolyte changes).

If the toxicity or event resolves to baseline or ≤ Grade 1 within 14 days of stopping therapy, treatment with GSK2879552 may be restarted with at least **25%** dose reduction. For a non-DLT, the treatment with GSK2879552 could restart at a full dose, if deemed appropriate.

If the 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 once the toxicity resolves to ≤ Grade 1 or baseline.

If >2 consecutive dose reductions are required to resolve the toxicity to ≤ Grade 1 or baseline, the subject will be withdrawn from study.

Following a dose reduction subjects may be re-escalated to a higher dose level if the event is felt to be unlikely to recur and with the approval of the GSK Medical Monitor.

See Section 3.12.2- Section 3.12.4 for dose adjustment guidelines for thrombocytopenia, neutropenia and anemia. For hepatotoxicity, rechallenge guideline in Section 9.1 should be followed.

3.12.2. Management of Thrombocytopenia

In Part 1 Dose Escalation, complete blood count (CBC) will be monitored twice weekly for the first 3 weeks, weekly for the next 5 weeks, and then every 4 weeks. In Part 2 Expansion, CBC will be monitored weekly for the first 3 weeks and thenevery 4 weeks. CBC monitoring frequency will follow planned monitoring frequency described above or

as detailed in Table 6, whichever is more frequent. Platelet monitoring and thrombocytopenia management guideline may change based on emerging data.

Table 6 Thrombocytopenia management guideline

Grade	Platelet count	Monitoring	Dose Adjustment*
G1	<Lower limit of normal (LLN) - 75,000/mm^3	Monitor as per protocol	Continue at the same dose.
G2	<75,000 - 50, 000/mm^3	Weekly for 2 weeks. Then, • if stable, monitor per protocol. • if falling, continue with weekly monitoring until stable	Continue at the same dose.
G3	<50,000 - 25,000/mm^3	Twice weekly for 2 weeks. Then, • if stable, monitor per protocol. • if falling, continue to monitor twice weekly until stable.	• If platelet count is < 50K but > 25K for more than 3 days and **stable**, continue at the same dose. • If platelet count is < 50K but > 25K for more than 3 days and **falling**, interrupt dosing and resume treatment once platelet count >50K ➢ at the same dose if platelet count recovers to > 50K **within** 7 days.** For subjects receiving daily dosing on a continuous schedule, reduce dose by at least 25% if grade 3 thrombocytopenia recurs,. ➢ with reduced dose by at least 25% if platelet count recovers to > 50K **after** 7 days.**.
G3	<50,000 - 25,000/mm^3 and bleeding	As above for G3	Interrupt dosing and resume treatment with reduced dose by at least 25% when bleeding stops and platelet count is >50K.** Administer supportive care including platelet transfusions as indicated.
G4	<25,000 – 10, 000/mm^3	Twice weekly	Interrupt dosing and resume treatment with reduced dose by at least 25% when platelet count is >50K. **
G4	<25,000 – 10, 000/mm^3 and bleeding or <10,000/mm^3;	Twice weekly	Interrupt dosing, initiate platelet transfusions as per guidelines [Slichter, 2007], resume treatment with dose reduced by at least 50% when platelet count is >50K. **

1. * Subjects receiving low dose aspirin should interrupt aspirin when platelet count is < 75,000 mm3.
2. ** When the treatment resume, platelet should be monitored twice weekly for 2 weeks at a minimum.

A prolonged dose interruption over 14 days would meet the treatment discontinuation criteria per Section 6.3.

3.12.3. Management of Neutropenia

For the following, dose should be interrupted and the treatment should resume with dose reduced by at least 25%:

- febrile neutropenia (as defined by CTCAE v.4)
- Grade 4 neutropenia
- Grade 3 neutropenia lasting >7 days

3.12.4. Management of Anemia

Below is the anemia management guideline.

Grade	Dose Adjustment
Grade 1 and 2	Continue at the same dose
Grade 3	Interrupt dosing if Grade 3 anemia > 7 days in duration and/or recurs after transfusion. Resume treatment with reduced dose by at least 25% when hemoglobin (Hgb) ≥ 10 g/dL
Grade 4	Interrupt dosing and provide supportive care (including transfusion). Resume treatment with reduced dose by at least 25% when Hgb ≥ 10 g/dL or discontinue study treatment

3.12.5. Platelet Transfusion Guideline

Prophylactic platelet transfusion in the absence of active bleeding is required when platelet count is < 10,000 /mm^3. Therapeutic platelet transfusion is required for platelets < 25,000 /mm3 accompanied by World Health Organization (WHO) bleeding grade of 2 or higher.

WHO Bleeding grades

- Grade 1, petechiae, ecchymosis, occult blood in body secretions, and mild vaginal spotting
- Grade 2, evidence of gross hemorrhage not requiring red cell transfusions over routine transfusion needs (e.g., epistaxis, hematuria, hematemesis)
- Grade 3, hemorrhage requiring transfusion of 1 or more units of red cells/day
- Grade 4, life-threatening hemorrhage, defined as massive bleeding causing hemodynamic compromise or bleeding into a vital organ (e.g., intracranial, pericardial, or pulmonary hemorrhage)

3.12.6. CBC monitoring and PK sampling Guideline for Dose interruptions/modifications

When the treatment is held due to a hematologic AE, CBC and PK sample should be collected on the first day of dose interruption and 3-4 days after. If the treatment is held

for more than a week, additional PK and CBC sample should be collected at 1 week after the dose interruption.

When the dose resumes at the same or reduced dose, a pre-dose PK sample and CBC should be collected on the day and twice weekly for the first 3 weeks. Once weekly pre-dose and CBC monitoring should continue on weeks 4, 6, and 8 of the resumed dosing. If the dose was reduced, two post-treatment PK samples should be collected at week 2, between 0.5-1 hr and between 4-6 hours from dosing in addition to the pre-dose PK sample.

Less frequent CBC monitoring and PK sample collection may be allowed for individual subjects, if warranted.

4. INVESTIGATIONAL PRODUCT(S)

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

4.1. Description of Investigational Product

Product name:	**GSK2879552 Capsule**
Formulation description:	GSK2879552 capsules contain 0.25 mg, 0.5 mg, 2 mg or 5 mg of GSK2879552 as parent.
Dosage form:	Capsule
Unit dose strength(s)	0.25 mg, 0.5 mg, 2 mg and 5 mg
Route/ Regimen	Oral The initial dosing regimen will be continuous oral daily dosing. Subjects should take their doses fasted with approximately 200 mL of water.
Physical description:	0.25 mg GSK2879552: Opaque Size 3 capsule composed of a white body and a white cap with no identifying markings containing a white to slightly coloured powder. 0.5 mg GSK2879552: Opaque Size 1 capsule composed of a light green body and a light green cap with no identifying markings containing a white to slightly coloured powder. 2 mg GSK2879552: Opaque Size 1 capsule composed of a pink body printed with two black lines and a pink cap printed with two black lines, containing a white to slightly coloured powder. 5 mg GSK2879552: Opaque Size 1 capsule composed of a Swedish Orange body and a Swedish Orange cap with no identifying markings containing a white to slightly coloured powder.

GSK2879552 will be provided to sites by GSK. The contents of the label will be in accordance with all applicable regulatory requirements.

4.2. Handling/Storage of GSK2879552, GSK Investigational Product

Handling

Under normal conditions of handling and administration, investigational product (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.

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

Storage

GSK2879552 must be stored in a secure area under the appropriate physical conditions for the product. Access to and administration of the GSK2879552 will be limited to the investigator and authorized site staff. GSK2879552 must be dispensed or administered only to subjects enrolled in the study and in accordance with the protocol.

GSK2879552 is to be stored at a temperature range of 2-8°C (36-46°F), protected from moisture. 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 investigational product (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 Study Procedures Manual (SPM) for further detailed instructions on product accountability.

4.4. Treatment Compliance

On clinic days, GSK2879552 should be taken in the clinic after safety procedures including blood sampling for CBC and PK/PD samplings, if applicable, are completed. When subjects self-administer study treatment(s) at home, subjects will be instructed to record time and date of dosing in the supplied GSK dosing diary.

Compliance with GSK2879552 will be assessed through querying the subject during the site visits and reviewing the dosing diary, and documented in the source documents and eCRF. A record of the number of GSK2879552 capsules dispensed to and taken by each subject must be maintained and reconciled with study treatment and compliance records.

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 GSK2879552, the investigator should:

- contact the GSK Medical Monitor immediately
- closely monitor the subject for AEs/SAEs and laboratory abnormalities at least 7 days
- 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

The number of dose levels and the level at which the maximum tolerated dose (MTD) or RP2D 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 20 subjects will be enrolled into Part 1 dose-escalation and additional 27 subjects into PK/PD expansion cohorts. Up to 30 subjects will be enrolled in Part 2 (expansion cohort) of the study. A total of approximately 77 subjects will be enrolled in the study. 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 as replacement subjects 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. Inclusion Criteria

Specific information regarding warnings, precautions, contraindications, adverse events (AEs), and other pertinent information on the GSK study treatment that may impact subject eligibility is provided in the Investigator Brochure (IB).

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 enrolment 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. Histologically or cytologically confirmed diagnosis of small cell lung carcinoma. Subjects must have measurable disease per RECIST 1.1 (for Part 2 only).
4. Recurrent or refractory disease after receiving at least one prior standard/approved platinum-containing chemotherapy regimen, or where standard therapy is refused. **Part 2 only**: Subjects must have recurrent disease after receiving a maximum of two prior chemotherapy regimens including at least one platinum containing regimen. **Note**: Adjuvant/Neoadjuvant chemotherapy is not counted.
5. Eastern Cooperative Oncology Group (ECOG, Appendix 3) performance status of 0 or 1.
6. Tumor tissue requirements:
    - Availability of archival tissue, or willingness to undergo fresh biopsy at baseline. Patients without baseline tissue may be enrolled with approval from the GSK medical monitor.
    - Enrollment in PK/PD cohort may be limited to subjects with disease amenable to pre- and post-dose biopsies, and willingness to undergo biopsy.
7. All prior treatment-related toxicities must be National Cancer Institute- Common Toxicity Criteria for Adverse Events (NCI-CTCAE), version 4.0 ≤Grade 1 at the time of enrollment (except for alopecia)
8. Adequate baseline organ function defined by

System	Laboratory Values
Hematologic	
Absolute neutrophil count (ANC)	≥ 1.5 X 10^9/L
Hemoglobin	≥ 10 g/dL
Platelets	≥ 125 X 10^9/L
Prothrombin time (PT)/International normalized ratio (INR) and Partial thromboplastin time (PTT)	≤ 1.5 X ULN
Hepatic	
Total bilirubin ALT and AST	≤ 1.25 X ULN[1] ≤2.5 × ULN without liver metastasis ≤5 x ULN if documented liver metastasis
Renal	
Creatinine OR Calculated creatinine clearance by Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (Appendix 2) or measured from 24hr urine	≤1.5 X ULN ≥ 50 mL/min
Cardiac	
Ejection fraction	≥ LLN by Echocardiogram (ECHO)
Metabolic	
TSH, T4 Vitamin B12 BUN Na, K[2], Ca, Cl, CO_2 Glucose (fasting)	WNL ≥ LLN ≤1.5 X ULN WNL ≤1.25 X ULN

1. Isolated bilirubin >1.5 X ULN is acceptable if bilirubin is fractionated and direct bilirubin <35% or subject has a diagnosis of Gilbert's syndrome
2. Replacement of K is allowed if below LLN

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 hematologic eligibility criteria are not eligible.

9. 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 11.1, during the study and for 7 days following the last dose of study treatment.
10. Men with a female partner of childbearing potential must have either had a prior vasectomy or agree to use effective contraception as described in Section 11.1 from the administration of the first dose of study treatment until 3 months after the last dose of study treatment to allow for clearance of any altered sperm.
11. Able to swallow and retain orally administered study treatment and does not have any clinically significant gastrointestinal (GI) abnormalities that may alter absorption such as malabsorption syndrome or major resection of the stomach and/or bowels.
12. **French subjects:** In France, a subject will be eligible for inclusion in this study only if either affiliated to or a beneficiary of a social security category.

5.2.2. 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. Concurrent malignancy other than SCLC. History of other malignancy is allowed as long as there is no evidence of active disease or need for treatment.
2. Currently receiving anti-cancer therapy (chemotherapy, radiation therapy, immuno-therapy, biologic therapy, hormonal therapy, surgery, and/or tumour embolization)

   Exceptions: Zoledronic acid and denosumab to treat bone metastasis are allowed.
3. Prior treatment with temozolomide, dacarbazine or procarbazine
4. Prior treatment with poly ADP ribose polymerase (PARP) inhibitors (e.g., olaparib, ABT-888)
5. Baseline Montreal Cognitive Assessment (MOCA) score of 22 or lower
6. Received major surgery, radiotherapy, or immunotherapy within 4 weeks of GSK2879552 administration. Chemotherapy regimens with delayed toxicity within the last four weeks (six weeks for prior nitrosourea or mitomycin C). Chemotherapy regimens given continuously or on a weekly basis with limited potential for delayed toxicity or palliative radiation to a limited area (including cranial radiation for brain metastases) within the last two weeks.
7. Administration of an investigational drug within 28 days or 5 half-lives, whichever is ***shorter*** preceding the first dose of study treatment(s) in this study.

   French subjects: The French subject has participated in any study using an investigational study treatment(s) during the previous 28 days.
8. Subjects with current/a history of bleeding disorder or coagulopathy (e.g., Von Willebrand disease, haemophilia) or who are at particularly high risk for bleeding complications, e.g., prior history of intracranial hemorrhage, clinically significant bleeding episodes in the last 6 months.
9. Requiring anticoagulants at therapeutic doses (e.g., warfarin, direct thrombin inhibitors, etc) or platelet inhibitor (e.g., aspirin, clopidogrel). The following are permitted:
   - Low molecular weight heparin
   - Low dose prophylactic warfarin ≤ 1 mg once daily
   - Low dose aspirin ≤ 100 mg once daily if required for cardiac prophylaxis.
10. Current use of a prohibited medication (Section 10.2) or expected to require any of these medications during treatment with the investigational drug
11. Evidence of severe or uncontrolled systemic diseases (e.g., severe/chronic infection, unstable or uncompensated respiratory, hepatic, renal, or cardiac disease) Any serious and/or unstable pre-existing medical (aside from malignancy exception above), psychiatric disorder, or other conditions that could interfere with subject's

safety, obtaining informed consent or compliance to the study procedures, in the opinion of the investigator

12. Known active Human Immunodeficiency Virus (HIV), Hepatitis B Virus (HBV) or Hepatitis C Virus (HCV) infections. Subjects with laboratory evidence of HBV clearance may be enrolled
13. Leptomeningeal metastases or spinal cord compression due to disease.
14. Subjects with previously untreated or uncontrolled brain metastases.

    Note: Subjects previously treated for brain metastases that

    - are asymptomatic and off corticosteroids, OR
    - on stable dose of corticosteroids for at least 1 month prior to study Day 1 are permitted.

    Subject treated with gamma knife can be enrolled 2 weeks post-procedure as long as there are no post-procedure complications and the subject is clinically stable. In addition, subjects treated or currently taking enzyme-inducing anticonvulsant (EIAC) are allowed on study.
15. Cardiac abnormalities as evidenced by any of the following:
    - Clinically significant uncontrolled arrhythmias or uncontrolled hypertension.
    - History or evidence of current ≥Class II congestive heart failure as defined by New York Heart Association (NYHA).
    - History of acute coronary syndromes (including unstable angina and myocardial infarction), coronary angioplasty, or stenting within the past 3 months.
    - Baseline QTc interval using Bazett's formula ≥450 msec or ≥480 msec in subjects with Bundle Branch Block. QTc value based on single or average of triplicate ECGs obtained over a brief recording period.
16. Have a known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to GSK2879552 or LSD1 inhibitors that contraindicates their participation.
17. Lactating female.
18. Consumption of Seville oranges, grapefruit, grapefruit hybrids, grapefruit juice, pommelos, or exotic citrus fruits, from 1 day prior to the first dose of study treatment(s) until the last dose of study drug.

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.

6.2. Subject Completion Criteria

In Part 1, a subject will be considered to have completed the study if they complete screening assessments, at least 28 days of study treatment(s) and the post-treatment follow-up visit.

In Part 2, a subject will be considered to have completed the study if they are followed until disease progression, death or start of new anticancer 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 3.11.1. The investigator may discuss with a GSK Medical Monitor continuing a subject who is receiving benefit but has met the criteria for disease progression according to RECIST, if the following criteria are met: Investigator-determined clinical benefit (e.g. symptomatic improvement), lack of significant toxicity (no drug related grade 3/4 AEs within the last 3 weeks) and no therapeutic alternatives expected to provide durable responses.

In addition, study treatment may be permanently discontinued for any of the following reasons:

- deviation(s) from the protocol
- request of the subject or proxy (withdrawal of consent by subject or proxy)
- investigator's discretion
- Adverse event that is considered by the investigator or a GSK Medical Monitor to warrant permanent discontinuation of study drug.
- A clinically significant adverse event leading to an interruption of treatment for greater than 14 days. If the investigator and GSK Medical Monitor conclude that continued treatment will benefit a subject who has had a > 14 day treatment delay, then the subject may continue therapy with the approval of the GSK Medical Monitor.
- Adverse events requiring >2 dose reductions.
- intercurrent illness that prevents further administration of study treatment(s)
- subject is lost to follow-up study is closed or terminated.

The primary reason study treatment was permanently discontinued must be documented in the subject's medical records and electronic case report form (eCRF).

If the subject voluntarily discontinues from treatment due to toxicity, 'adverse event (AE)' will be recorded as the primary reason for permanently discontinuation on the electronic case report form (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 assessments at the time of discontinuation and during post-study treatment follow-up as specified in Time and Events Table (see Section 7.1)

6.4. Study Completion

A study will be considered completed, having met the study objectives, when all subjects have received treatment for approximately 6 months or have withdrawn from the study, whichever occurs first. At such time, subjects who have not been permanently withdrawn from study treatment and continue to benefit will be offered the opportunity to continue treatment in a separate rollover protocol.

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 ECGs, vital signs, blood draws.

If the blood draw is done first, there should be at least 15 minute interval before the vital signs and 12-lead ECGs measurements are taken.

Detailed procedures for obtaining each assessment are provided in the SPM.

On clinic days, study drug should be taken in the clinic after all the safety procedures (including CBC) and blood sampling for PK/PD, if applicable, are completed.

Visit Window

Baseline disease assessment and ECHO/MUGA should be completed within **35 days** prior to dosing start and pregnancy testing **7 days** prior. All other screening assessments should be completed within **14 days** prior to dosing start.

Visits in the first 3 weeks will be allowed ± **1** day window. The only exceptions are pre- and post -treatment biopsies on Day 1 and 15 where **7 days** and ± **3 days** window will be allowed, respectively.

Visits beyond the first 3 weeks will have **± 3 days** window.

Post-baseline disease assessments will be allowed 7 days window. Subjects who are withdrawn from Part 2 for reasons other than disease progression and continue Q8 week disease assessment will be also allowed **7 days** window.

The End of Treatment visit should be completed within **14 days** from the last dose.

Time Window for PK sampling

0.25, 0.5, 1 and 1.5 hours post dose sampling: ±5 minutes

2, 3, 4 hours post dose sampling: ±10 minutes

6 and 8 hours post dose sampling: ±30 minutes

12 and 24 hours post dose sampling: ±1 hour. The 24 hour sampling should be done before the next dose administration.

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.

Time and Events Table: Part 1 – Dose Escalation

	SCR	First Treatment Phase (28 days)									Continuation Phase	EOT
		D 1	D 2	D 4	D 8	D 11	D 15	D 16	D 18	D 22		
Office Visit	X	X	X	X	X	X	X	X	X	X	X	X
Informed consent	X											
Demography	X											
Medical history	X											
Disease characteristics	X											
Study Drug Dosing[14]		< ---------- Daily or per dosing schedule ----------→										
Review subject dosing diary				X	X		X			X	every 4 wks	X
Study Drug Dispensing from Pharmacy		X									every 4 wks	
Complete physical exam	X											X
Montreal Cognitive Assessment	X	X			X		X			X	Wk 4 and every 4 wks	
Brief physical exam		X[11]			X						every 4 wks	
Performace status	X	X[11]			X						every 4 wks	X
Vital Signs	X	X[11]		X	X		X			X	every 4 wks	X
Height and weight[10]	X	X[11]			X						every 4 wks	X
ECHO / MUGA	X											
12-lead ECGs	X	X			X						every 4 wks	X
CBC	X	X[11]		X	X	X	X		X	X	Every week x 4 (wk 4-7), then every 4 wks	X
Chemistry Panel including liver function tests	X				X		X				every 4 wks	X
Vitamin B12, TSH, T4	X											
Coagulation Panel including PT, PTT, INR	X										every 8 wks	X
Fetal hemoglobin		X			X		X			X		

	SCR	First Treatment Phase (28 days)									Continuation Phase	EOT
		D 1	D 2	D 4	D 8	D 11	D 15	D 16	D 18	D 22		
(Hgb F)[18]												
Pregnancy test[8]	X										every 4 wks	X
PK Blood samples		X[1]	X[1]	X[4]	X[2]		X[3]	X[3]		X[4]	Every week x 4 (wk 4-7), then every 4 wks[4]	
Urine for PK		X[12]					X[5]	X[5]				
Blood samples for PD[6] (whole blood)	X	X	X	X	X							
Blood samples for PD[6] (serum)	X	X			X		X			X		
Blood samples for circulating biomarkers[6] (plasma)		X								X		X
Blood samples for translational research[6] (Peripheral blood mononuclear cell)	X		X				X					X
Disease assessment	X										every 8 wks	X[7]
Brain scan	X										As clinically indicated	
Tumor tissue collection or biopsy	X[13]	X[16]					X[16]					X[17]
Adverse Events		continuous										
Con Meds		continuous										
Highest Dose in PK/PD expansion cohort ONLY												
Blood for metabolite evaluation		X[9]	X[9]				X[9]	X[9]				
Urine for metabolite		X[15]	X[15]				X[15]	X[15]				

1. A blood sample will be collected for PK analysis on D1 at following time points: pre-dose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 hrs post dose. Additional samples may be collected at 33 (optional) and 48 hrs post dose in subjects not receiving a dose on Day 2 to better characterize the terminal half-life of GSK2879552, if needed.
2. A blood sample will be collected for PK analysis on D8 at following time points: pre-dose, 0.5, 3 hrs post dose
3. A blood sample will be collected for PK analysis on D15 at following time points: pre-dose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 hrs post dose
4. PK blood sample should be taken pre-dose at the same time as CBC. If the dose has been modified since the last PK sample and an unscheduled CBC sample is taken, a PK sample should be obtained together with the first unscheduled CBC sample. PK sample will not be collected beyond week 48.

5. On D15, 24hr urine will be collected starting from pre-dose on Day 15 and for 24 hours, i.e., until dosing on Day 16. The 24hr urine will be measured and 5 ml aliquot will be taken.
6. Blood samples for PD, circulating biomarkers and translational research should be collected pre-dose.
7. 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.
8. For women of child bearing potential only. Serum pregnancy test is required for screening and f/u visits. Urine pregnancy test is adequate during study visits.
9. Additional samples will be collected for metabolite evaluation in the highest dose cohort in PK/PD expansion cohorts, in at least 6 subjects. The plasma samples will be collected at following time points: pre-dose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 hrs post dose
10. Height will be measured at screening only
11. These procedures do not need to be repeated on Day 1, if the screening visit was within 3 days and they were performed at screening.
12. A urine sample will be collected for PK analysis at pre-dose on D1
13. Baseline tumor tissue collection is mandatory for all subjects. Archival tissue will be acceptable. In the absence of available archival tissue, fresh tissue biopsy will be required.
14. On clinic days, study drug should be taken in the clinic after safety procedures including CBC and PK/PD samplings, if applicable, are completed.
15. On Day 1, pre-dose urine (~100 ml) will be collected for metabolite study. On Days 1 and15, 24hr urine will be collected and measured, and 400 mL urine from at least 6 subjects at the highest dose cohort in PK/PD expansion will be collected for metabolite identification purposes.
16. In a subset of subjects in PK/PD cohorts, fresh pre-treatment and post-treatment biopsies are required. Pre-treatment and post-treatment biopsies are optional for all subjects not enrolled in PK/PD expansion cohorts. Day 1 biopsy (-7 days window) should be collected pre-dose, Day 15 ($\pm$ 3 days window) biopsy can be collected pre- or post- dose. Optional post-treatment biopsy can be collected at a later time point, if desired.
17. Biopsy at the time of progression is optional for all subjects.
18. Korea only: Hgb F not required

Time and Events Table: Part 2 – Expansion Cohort

	SCR	First Treatment Phase (28 days)				Continuation Phase	EOT[11]
		D 1	D 8	D 15	D 22		
Office Visit	X	X	X	X	X	every 4 wks	X
Informed consent	X						
Demography	X						
Medical history	X						
Disease characteristics	X						
Study Drug Dosing[9]		< ---------- Daily or per dosing schedule ----------→					
Review subject dosing diary			X	X	X	every 4 wks	X
Study Drug Dispensing from pharmacy		X				every 4 wks	
Complete physical exam	X						X
Montreal Cognitive Assessment	X	X	X	X	X	Wk 4 and every 4 weeks	
Brief physical exam		X[7]	X			every 4 wks	
ECOG PS	X	X[7]	X			every 4 wks	X
Vital Signs	X	X[7]	X	X	X	every 4 wks	X
Height and weight[6]	X	X[7]	X			every 4 wks	X
ECHO/MUGA	X						
12-lead ECGs	X	X[7]	X			every 4 wks	X
CBC	X	X[7]	X	X	X	every 4 wks	X
Chemistry Panel including LFT	X		X	X		every 4 wks	X
Coagulation Panel including PT, PTT, INR	X					every 8 wks	X
Vitamin B12, TSH, T4	X						
PK Blood samples		X[1]	X[8]	X[2]	X[8]	every 4 wks[8]	
Fetal hemoglobin (Hgb F)[12]		X	X	X	X		

	SCR	First Treatment Phase (28 days)				Continuation Phase	EOT[11]
		D 1	D 8	D 15	D 22		
Pregnancy test[4]	X					every 4 wks	X
Blood samples for PD[3] (serum)	X	X	X	X	X		
Blood samples for circulating biomarkers[3] (plasma)		X			X		X
Blood samples for translational research[3] (CTC)	X			X		Wk 8	X
Disease assessment	X					every 8 wks	X[5]
Brain scan	X					As clinically indicated	
Tumor tissue collection[10]	X	X		X			X
Adverse Events		continuous					
Con Meds		continuous					

1. A serial blood samples will be collected for PK analysis on D1 at pre-dose, 0.5, and 3 hrs post dose,
2. A blood sample will be collected for PK analysis on D15 at pre-dose, between 0.5 to 1 hour, and between 4 and 6 hours
3. Blood samples for PD, circulating biomarkers and translational research should be collected pre-dose.
4. For women of child bearing potential only. Serum pregnancy test is required for screening and f/u visits. Urine pregnancy test is adequate during study visits.
5. 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.
6. Height will be measured at screening only
7. These procedures do not need to be repeated on Day 1, if the screening visit was within 3 days and they were performed at screening.
8. PK blood sample should be taken pre-dose at the same time as CBC.
9. On clinic days, study drug should be taken in the clinic after safety procedures including CBC and PK/PD samplings, if applicable are completed. PK sample will not be collected beyond week 48.
10. Baseline tumor tissue collection is mandatory for all subjects. Archival tissue will be acceptable. In the absence of available archival tissue, fresh tissue biopsy will be required. Fresh biopsies on Day 1, Day 15 and at disease progression are optional for all subjects in Part 2. Day 1 biopsy (-3 days window) should be collected pre-dose, Day 15 ($\pm$ 3 days window) biopsy can be collected pre- or post- dose. Optional post-treatment biopsy can be collected at a later time point, if desired.
11. Subjects enrolled in Part 2 who discontinue study treatment for reasons other than RECIST-defined disease progression will continue to have protocol defined radiological assessments until disease progression per RECIST 1.1, start of new anti-cancer therapy or withdrawal from study.
12. Korea only: Hgb F not required

7.2. Demographic/Medical History and Baseline Assessments

The following demographic parameters will be captured during Screening: year of birth, gender, race and ethnicity.

Medical/medication history will be assessed. Medical, surgical, and treatment history including date of first diagnosis, best response to prior systemic therapy, histology, and current sites of disease will be taken as part of the medical history and disease status.

Details concerning concomitant medication will be recorded starting from screening through post-study follow-up. At a minimum, the drug name, route of administration, dose and frequency of dosing, along with start and stop dates should be recorded.

Fasting will be required for screening clinical laboratory tests.

Baseline (Screening) assessments will include:

- Complete physical examination, including height (in cm) and weight (in kg).
- Vital signs (blood pressure, temperature, respiratory rate, pulse rate)
- Eastern Cooperative Oncology Group (ECOG) performance status
- Clinical laboratory tests: hematology, clinical chemistry, coagulation parameters, vitamin B12, thyroid (TSH, T4)
- Serum beta-human chorionic gonadotropin (β-HCG) pregnancy test for female subjects of childbearing potential only
- 12-lead ECG
- Echocardiogram (ECHO) or multi-gated acquisition (MUGA) scan
- Baseline disease assessment: computed tomography (CT) scan (with IV contrast) of chest, abdomen and pelvis (if applicable)
- Brain magnetic resonance imaging (MRI) with contrast or a CT scan (with/without contrast) if MRI is contraindicated
- Fresh tumor biopsy (preferred) or archival tumor tissue collection
- Montreal Cognitive Assessment

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

Any signs of bleeding, bruising and infection will be monitored closely throughout the study,

Planned time points for all safety assessments are provided in the Time and Events Table (Section 7.1).and will include physical exam, vital signs, clinical laboratory tests including chemistry and hematology, ECGs and ECOG performance status. AEs and toxicities will be assessed throughout the study and will be graded according to NCI-CTCAE v. 4.0.

Additional time points for safety assessment may be added during the course of the study based on emerging pharmacokinetic and safety data to ensure appropriate safety monitoring.

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 Eastern Cooperative Oncology Group (ECOG) scale (Appendix 3) as specified in the Time and Events Table (Section 7.1).

7.3.3. Montreal Cognitive Assessment

Montreal Cognitive Assessment (MOCA) was designed as a rapid screening instrument for mild cognitive dysfunction. It assesses different cognitive domains: attention and concentration, executive functions, memory, language, visuoconstructional skills, conceptual thinking, calculations, and orientation. Time to administer the MOCA is approximately 10 minutes.

The test and administration instructions are freely accessible for clinicians at www.MOCAtest.org. English version 7.1 is shown in Appendix 7.

7.3.4. Vital Signs

Vital sign measurements will include systolic and diastolic blood pressure, temperature, respiration rate and heart 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, temperature does not need to be repeated unless clinically indicated. Refer to the SPM for details regarding measurement of vital signs.

7.3.5. Electrocardiogram

Single 12-lead electrocardiogram (ECGs) will be obtained at designated time points during the study using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and corrected QT (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 Section 3.11.2 for QTc withdrawal criteria. Additional QTc readings may be necessary.

7.3.6. Echocardiogram and/or Multi-gated Acquisition Scans

ECHOs or MUGA scans will be performed at baseline to assess cardiac ejection fraction and cardiac valve morphology for the purpose of study eligibility, as specified in the Time and Events Table (Section 7.1). Additional ECHO assessments may be performed if clinically warranted. The evaluation of the echocardiographer should include an evaluation for left ventricular ejection fraction (LVEF).

7.3.7. Laboratory Assessments

All protocol required laboratory assessments, as defined in Table 7, 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 Study Procedures Manual (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.

All laboratory tests with values that are significantly abnormal during participation in the study or within 28 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, and additional parameters to be tested are listed in Table 7

Table 7 List of Clinical Laboratory Tests

Hematology			
Platelet Count	*RBC Indices*:	*Automated WBC Differential:*	
Red blood cell (RBC) Count	Mean corpuscular volume (MCV)	Neutrophils	
White blood cell (WBC) Count (absolute)	Mean corpuscular hemoglobin (MCH)	Lymphocytes	
Reticulocyte Count	Mean corpuscular hemoglobin concentration (MCHC)	Monocytes	
Hemoglobin		Eosinophils	
Hematocrit		Basophils	
Mean platelet volume (MPV)			
Clinical Chemistry			
Blood urea nitrogen (BUN)	Potassium	Aspartate aminotransferase (AST)	Total and direct bilirubin[1]
Creatinine	Chloride	Alanine aminotransferase (ALT)	Uric Acid
Glucose	Total carbon dioxide (CO_2)	Gamma glutamyl transferase (GGT)	Albumin
Sodium	Calcium	Alkaline phosphatase	Total Protein
Phosphorus	Lactate Dehydrogenase (LDH)	Thyroid Stimulating Hormone	T4
Vitamin B12			
Other tests			
Coagulation Panel including PT, PTT, INR			
Fetal hemoglobin (Hgb F)[2]			
Other screening tests			
Follicle stimulating hormone (FSH) and estradiol (as needed in women of non-child bearing potential only)			

1. Direct bilirubin should be assessed only if total bilirubin is elevated beyond the upper limit of normal (ULN)
2. Korea only: fetal Hgb F not required

7.3.8. 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(s). 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 below during the study until 14 days following the last dose of study treatment(s).

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. Pregnancy complications and elective terminations for medical reasons must be reported as an adverse event (AE) or serious adverse event (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 treatment(s), must be promptly reported to GSK.

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 pharmacokinetic (PK) analysis of GSK2879552 will be collected at the time points indicated in the Time and Events Schedule (Section 7.1). Additional blood samples will be collected for metabolic profiling in one of the PK/PD expansion cohort of Part 1 at the time points indicated in the Time and Events Schedule (Section 7.1)

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 along with the date and time of the prior dose administration. 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.

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

7.4.2. Urine Sample Collection for Pharmacokinetics

Urine samples for pharmacokinetic (PK) analysis of GSK2879552 will be collected at the time points indicated in the Time and Events Schedule (Section 7.1). Additional urine sample will be collected for metabolic profiling in one of the PK/PD expansion cohort of Part 1 (at MTD or RP2D only) at the time points indicated in the Time and Events Schedule (Section 7.1)

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 urine sample collection will be recorded.

7.4.3. Details on PK urine sample collection, processing, storage and shipping procedures are provided in the SPM.Pharmacokinetic Sample Analysis

Plasma sample analysis will be performed under the management of Bioanalytical Science and Toxicokinetics, Drug Metabolism and Pharmacokinetics (DMPK), Platform Technology and Science (PTS), GlaxoSmithKline. Concentrations of GSK2879552 will be determined in plasma samples using the currently approved bioanalytical methodology. Raw data will be stored in the Good Laboratory Practices (GLP) Archives,

GlaxoSmithKline.Once the plasma samples have been analysed for GSK2879552, any remaining plasma may be analysed for other compound-related metabolites and the results reported under a separate GSK PTS-DMPK protocol.

Urine sample analysis may be performed under the management of Bioanalytical Science and Toxicokinetics, Drug Metabolism and Pharmacokinetics, Platform Technology and Science, GlaxoSmithKline. Concentrations of GSK2879552 may be determined in urine samples using an investigative analytical methodology. Urine raw data will be stored in the Good Laboratory Practices (GLP) Archives, GlaxoSmithKline.

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

7.5. Pharmacodynamics

- Changes from baseline in circulating ProGRP levels will be assessed in blood
- Change from baseline in a gene expression panel, including but not limited to GFI1B, KCNJ5, RND2, SERPINE2, ASB4, CACNB3, CD59A, SPARC, and STAB1 will be assessed in whole blood
- Changes in markers including, but not limited to, ProGRP and SCLC-specific LSD1 target genes or proteins in paired baseline and post-treatment tumor tissue will be assessed

7.6. Translational Research

Translational or biomarker research may be performed on archival tissue, fresh tumor biopsies and blood samples collected on study to better understand SCLC and mechanism of action of and response or resistance to GSK2879552.

The results of translational research investigations may be reported separately from the main clinical study report or as an amendment. Endpoints of interest from all comparisons will be descriptively and/or graphically summarized as appropriate to the data. Further details on the translational research analyses will be provided in the RAP.

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 GSK2879552 or provide new insights into SCLC 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 GSK2879552.

All samples maybe retained for a maximum of 15 years after the last subject completes the study.

Novel candidate biomarkers and subsequently discovered biomarkers of the biological response associated with SCLC or medically related conditions and/or the action of GSK2879552 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:

- DNA analyses may be performed for somatic mutations and copy number by next-generation sequencing or alternative methodology. DNA methylation status may be assessed using methylation array technology. These analyses may be performed using DNA from blood or tumor tissue.

- Circulating cell free-DNA analysis of blood/plasma

- Circulating biomarker RNA and protein analysis of blood/plasma

- Analysis of protein or RNA expression by immunohistochemistry (IHC) or alternative method may also be performed for genes of interest including, but not limited to, L-MYC, N-MYC or C-MYC

- RNA transcriptome analysis of blood and tumor tissue samples

- Measurement of the levels of a subset of RNA species on blood and tumor tissue samples

7.6.1. Tumor Biomarker Analysis

In order to further characterize biomarkers related to the activity of GSK2879552, expression of DNA/genes, RNA and proteins will be assessed in archival tissue and tumor biopsies collected on study.

7.6.2. Circulating cell free DNA (cfDNA) Analysis

Tumor-specific circulating nucleic 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 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, cfDNA will be collected to determine whether mutations or other genomic changes in cfDNA correlate with that in the tumor tissue from which it is derived. This test will also be explored to correlate decreasing cfDNA levels with decreasing tumor burden.

7.6.3. Circulating biomarker analysis

Levels of circulating biomarkers may be assessed to determine relationships between biomarker expression and response to GSK2879552, as well as to better understand the expression of circulating biomarkers in SCLC.

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 in cell-free DNA and circulating tumor cells (CTCs) along with burden may be evaluated in plasma and correlated with clinical outcome to treatment with GSK2879552.

7.6.4. RNA Expression Research of a Subset of RNA Species

Blood and tumor tissue samples will be collected for RNA expression analyses of a subset of RNA species.

RNA expression studies may be conducted using quantitative reverse transcription polymerase chain reaction (RT-PCR), and/or alternative equivalent technologies, which can facilitate the simultaneous measurement of the relative abundances of hundreds of RNA species resulting in a RNA expression profile for each blood and tumor tissue sample. The RNAs assayed may be those involved with the pathogenesis of SCLC, the absorption, distribution, metabolism, or excretion of GSK2879552, or in the subject's response to GSK2879552. In addition, continuing research may identify other proteins or regulatory RNAs that may be involved in response to GSK2879552 or the pathogenesis of SCLC. 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 SCLC and medically related conditions or the action of GSK2879552.

7.7. Evaluation of Anti-Cancer Activity

7.7.1. Disease Assessment

Disease assessment may include imaging (e.g., CT, MRI, bone scan, plain radiography) and physical examination (as indicated for palpable/superficial lesions). All post-baseline assessments require imaging of disease sites identified by baseline scans:

- Chest/Abdomen/Pelvis (if applicable) CT scan with contrast
- Brain MRI scan, if disease present at baseline. A CT scan with and without contrast may be performed if a MRI is contraindicated.

Disease assessment will be completed within 5 weeks prior to the first dose of GSK2879552, then every 8 weeks thereafter, and at the final study visit. 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. 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.

Disease progression and response evaluations will be determined according to the definitions established in the RECIST 1.1. Subjects whose disease responds (either complete response [CR] or partial response [PR]) should have a confirmatory disease assessment performed 4 weeks after the date of assessment during which the response

was demonstrated. More frequent disease assessments may be performed at the discretion of the investigator. To ensure comparability between the baseline and subsequent assessments, the same method of assessment and the same technique will be used when assessing response.

GSK requires sites to provide electronic copies (upload digital images or images on CD) of scans for all subjects enrolled in Part 2 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.

7.7.2. Brain MRI and/or CT Scan

A magnetic resonance imaging (MRI) with contrast will be performed at Screening (see Time and Events Table Section 7.1) to rule out any new untreated brain metastases and to verify stability of brain metastases if present. A CT scan with and without contrast may be performed if a MRI is contraindicated.

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 adverse event (AE) or serious adverse event (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 adverse event (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/serious adverse event [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 an SAE

A serious adverse event (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 adverse events (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. Protocol-Specific SAEs:

- All events of possible study treatment-induced liver injury with hyperbilirubinemia defined as alanine aminotransferase (ALT) ≥3 times upper limit of normal (ULN) **and** bilirubin ≥2 times ULN (>35% direct) (or ALT ≥3 times ULN and international normalization ratio (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 patients 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 serious adverse event (SAE). If INR is obtained, include values on the SAE form. INR elevations >1.5 suggest severe liver injury.

- Any new primary cancers

8.2.1. Sentinel Events

A Sentinel Event is a GSK-defined SAE that is not necessarily drug-related but has been associated historically with adverse reactions for other drugs and is therefore worthy of heightened pharmacovigilance. The GSK Medical Monitor is accountable for reviewing all SAEs for possible Sentinel Events which is mandated at GSK. The GSK medical monitor may request additional clinical information on an urgent basis if a possible Sentinel Event is identified on SAE review. The current GSK-defined Sentinel Events are listed below:

- Acquired Long QT Syndrome
- Agranulocytosis/Severe Neutropenia
- Anaphylaxis & Anaphylactoid Reactions
- Hepatotoxicity
- Acute Renal Failure
- Seizure
- Stevens Johnson syndrome/Toxic epidermal necrosis

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., electrocardiogram [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 adverse event (AE) or serious adverse event (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. Cardiovascular (CV) 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. 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 serious adverse event (SAE). Death due to disease under study is to be recorded on the Death electronic case report form (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.

8.5. 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 adverse event (AE) or serious adverse event (SAE).

AEs will be collected from the time the first dose of study treatment is administered until 28 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 8.2.

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 28 days, the investigator may report any AE that they believe possibly related to study treatment.

8.5.1. 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?”

“Have you had any (other) medical problems since your last visit/contact?”

“Have you taken any new medicines, other than those provided in this study, since your last visit/contact?”

8.5.2. Prompt Reporting of SAEs and Other Events to GSK

Serious adverse events (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:				
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 adverse events (AEs) and serious adverse events (SAEs) are provided in the Study Procedures Manual (SPM).

8.5.3. 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. STUDY TREATMENT RESTART OR RECHALLENGE

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

1) GSK Medical Governance approval **is granted** (as described below),
2) Ethics and/or IRB approval is obtained, if required, and
3) 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.

9.1. Rechallenge Following Liver Event That Are Possibly Related To Study Treatment

Following drug-induced liver injury, drug rechallenge is associated with 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; Hunt, 2010]
- evidence of drug-related preclinical liability (e.g. reactive metabolites; mitochondrial impairment[3])

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 rechallange with study treatment can be considered where:

- Principal Investigator (PI) 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 laboratory monitoring may resume as per protocol.
- If subject exhibits protocol-defined liver chemistry elevations, study treatment should be permanently discontinued as protocol specified.
- GSK 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 8.3-and Section 8.5.

9.2. Restart Following Transient, Resolving Liver Events Not Related to Study Treatment

Restart refers to resuming study treatment following liver events meeting stopping criteria 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 human leukocyte antigen (HLA) markers of liver injury.

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

- Principal Investigator (PI) 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 protocol defined stopping criteria for liver chemistry elevations are met, study treatment must be stopped.
- GSK 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 to be notified of any adverse events, as per Section 8.3 and Section 8.5.

10. 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 electronic case report form (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.

10.1. Permitted Medication(s)

Subjects should receive full supportive care during the study, including transfusion of blood and blood products, and treatment with antibiotics, antiemetics, antidiarrheals, and analgesics, as appropriate.

Low molecular weight heparin, low dose prophylactic warfarin ≤1 mg once daily, or low dose aspirin ≤ 100 mg once daily (if required for cardiac prophylaxis) is permitted.

Zoledronic acid and denosumab to treat bone metastasis are permitted.

The use of G-CSF is not recommended while the patient is taking the study medication. However, it can be administered during dose interruptions to speed recovery from neutropenia at the investigator's discretion.

10.2. Prohibited and Cautionary Medication(s)

Subjects should not receive other anti-cancer therapy (chemotherapy, radiation therapy, immunotherapy, biologic therapy, and hormone therapy other than for replacement) while on treatment in this study. 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 GSK2879552.

Anticoagulants at therapeutic doses (e.g., warfarin, direct thrombin inhibitors, etc) or platelet inhibitor (e.g., clopidogrel) are prohibited from 14 days prior to the first dose of study drug through completion of the Final Study Visit.

10.2.1. Drugs that may alter the Pharmacokinetics of GSK2879552

All co-meds should be used with caution since little is known about the mechanism of clearance of GSK2879552. In vitro data in human microsomes and hepatocytes suggest that GSK2879552 has a negligible turnover.

10.2.2. Drugs that may have their PKs altered by GSK2879552

The potential for pharmacokinetic interactions with drugs likely to be co-administered with GSK2879552 in vivo has not been assessed. In vitro data suggests that GSK2879552 has very low potential to inhibit CYP enzymes. GSK2879552 has also been shown to not activate human PXR which is known to induce several drug metabolizing enzymes.

GSK2879552 is not an inhibitor of human efflux transporters P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) and uptake transporters organic anion transporting polypeptide 1B1 (OATP1B1) and OATP1B3.

Co-administration of sensitive and narrow therapeutic index medications affected by strong inhibitors of OCT and MATE should be avoided when possible or monitored carefully. Examples of such drugs are dofetillide, pilsicainide and procainamide.

10.2.3. 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 GSK2879552 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 (DHEA), yohimbe, saw palmetto, and ginseng

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

11. LIFESTYLE AND/OR DIETARY RESTRICTIONS

11.1. Contraception

11.1.1. Female Subjects

A female of non-childbearing potential (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 < 40pg/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.

Female subjects of childbearing potential must not become pregnant during the study and so must be sexually inactive by abstinence or use contraceptive methods with a failure rate of <1%.

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 7days prior to first dose of study treatment, through the dosing period, and for at least 7 days after the last dose of study treatment.

Contraceptive Methods with a Failure Rate of <1%

- Oral contraceptives (either combined or progesterone only) if not contraindicated for this subject population or per local practice.
- 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.
- Intrauterine device or intrauterine system 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 of the subject or review of the subject's medical history for study eligibility, as obtained via a verbal interview with the subject or from the subject's medical records.
- Double-barrier method: condom and occlusive cap (diaphragm or cervical/vault caps) plus vaginal spermicidal agent (foam/gel/film/cream/suppository)

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.

11.1.2. 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:

- Abstinence, 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 from the first dose, through the dosing period, and for 3 months after the last dose of study treatment.

- Condom *(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)*

11.2. Caffeine, Alcohol, Food, 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 serial PK sampling day (e.g., Part 1, Days 1 and 15).

Subjects should abstain from consumption of Seville oranges, grapefruit, grapefruit hybrids or grapefruit juice and/or pommelos, exotic citrus fruits, from 1 day prior to the first dose of study treatment until the last dose of study drug.

12. DATA MANAGEMENT

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

Management of clinical data will be performed in accordance with applicable GSK standards and data cleaning procedures to ensure the integrity of the data, e.g. removing errors and inconsistencies in the data. AEs and concomitant medications terms will be coded using Medical Dictionary for Regulatory Activities (MedDRA) and an internal validated medication dictionary, GSK Drug. Electronic CRFs (eCRFs), including queries and audit trails, will be retained by GSK, and copies will be sent to the investigator to maintain as the investigator copy.

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

13. DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

13.1. Hypothesis(es)

13.1.1. Part 1: Dose-Escalation Phase

No formal statistical hypotheses are being tested. Analysis of the data obtained from this study will be focused on comparison between dose cohorts and only descriptive methods will be used in analysis of the data obtained from this study.

13.1.2. Part 2: Expansion Cohort

The sample size and stopping rules are based on the methodology of Lee et al. [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.

Clinical response will be defined as disease control rate (DCR) (CR + PR + SD) based on RECIST 1.1 at week 16. Biologic activity of cytostatic agents is characterized by the stabilization of the disease rather than the shrinkage of tumor lesions. As they slow or stop the growth of tumors and the developmentof metastases, DCR may be a more appropriate end point in the evaluation of cytostatic agents [Francart, 2006; Lara, 2008] such as GSK2879552.

The null hypothesis is:

H0: DCR ≤15%

The alternative hypothesis is:

HA:DCR ≥30%

After 12 subjects have been enrolled to examine safety and efficacy, the observed unconfirmed disease control rate at 16 weeks will guide further enrolment according to the rules summarized in Figure 3. In order to stop for futility as quickly as possible if there is no sign of efficacy, confirmation of responses is not required. A maximum of **30** subjects will be enrolled in the Part 2 expansion cohort. All available data will be considered in making enrollment decisions.

Figure 3 Stopping Rules for Cohort Expansion: GSK2879552

	Number of Subjects Responding (i.e., controlled disease) at 16 weeks					
Number of Subjects	0	1	2	3	4	≥5
12						
13						
14						
15						
16						
17						
18						
19						
20						
21						
22						
23						
24						
25						
26						
27						
28						
29						
30						

1. The shaded regions are the specific regions for stopping the study for futility. For instance, if there is no response in fourteen subjects, then the predictive probability for success will be 5.0% or less (the futility criterion) and consideration should be given to stop enrolment.

13.2. Sample Size Determination

13.2.1. 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. Results of simulations for the dose-escalation phase are shown in Appendix 6. Based on these simulations, the sample size for the dose-escalation portion is expected to be approximately 19-22 subjects. However, it is anticipated that approximately 57 subjects will be enrolled including PK/PD expansion cohorts.

13.2.2. Part 2: Expansion Cohort

An initial dose escalation will be used to establish the RP2D for GSK2879552. Once the final dose is confirmed, at least 12 and up to 30 subjects will be enrolled at that dose, using decision rules based on the disease control rate (DCR) as defined in Figure 3. The

sample size and stopping rules are based on the methodology of Lee et al. [Lee, 2008]. The assumptions underlying the design are detailed below.

H_0: DCR ≤15%

The alternative hypothesis is:

H_A:DCR ≥30%

Starting with 12 subjects and allowing for a maximum sample size of 30, this design will have a type I error rate (α) of 0.15 and 80% power. 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% 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 design will have a type I error rate of less than 0.15 and a power greater than 80% for a sample size exceeding 30 subjects. 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 DCR at 16 weeks is 15%, the expected sample size of the design is 24 subjects and probability of early termination (PET) is 75%. Under the alternative hypothesis, if the true DCR at 16 weeks is 30%, the expected sample size of the design is 29 subjects and PET is 10%.

13.3. Sample Size Sensitivity

No sample size sensitivity was performed.

13.3.1. Sample Size Re-estimation

Sample size re-estimation is not planned for this study.

13.4. Data Analysis Considerations

13.4.1. Analysis Populations

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

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

The Pharmacodynamic Population: This will consist of those subjects in All Subjects Population and who contribute PD/Biomarker samples.

13.5. Interim Analysis

13.5.1. Part 1: Dose-Escalation

No formal interim analysis will be performed for Part 1 of the study. Safety, PK, PD/biomarker data will be examined during Part 1. Prior to determining GSK2879552 dose for the next cohort, exploratory analysis will be conducted to assess the relationship of GSK2879552 dose levels with safety, PK and PD parameters using all data from available cohorts.

13.5.2. Part 2: Expansion Cohort

After the initial 12 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 13.1.2.

13.6. Key Elements of Analysis Plan

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.

As it is anticipated that accrual will be spread thinly across centers and summaries of data by center would be unlikely to be information, data from all participating centers will be pooled prior to analysis.

All data up to the time of study completion/withdrawal from study will be included in the analysis, regardless of duration of treatment.

As the duration of treatment for a given subject will depend on efficacy and tolerability, the duration of follow-up will vary between subjects. Consequently there will be no imputation for missing data.

Demographic and baseline characteristics will be summarized.

13.6.1. Anti-Cancer Activity Analyses

For Part 1, anti-tumor activities will be evaluated based on clinical evidence and response criteria. If the data warrant, the response data will be summarized by dose level.

Clinical response will be defined as disease control rate (DCR) (CR + PR + SD) based on RECIST 1.1 at week 16. The primary aim of Part 2 is to detect a clinically meaningful disease control rate of 30% relative to a 15% disease control rate suggesting no activity.

13.6.2. Safety Analyses

The All Treated Population will be used for the analysis of safety data. All serially collected safety endpoints (e.g. laboratory tests, vital signs, electrocardiogram [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.

For Part 1, DLTs will be listed for each subject and summarized according to GSK International Data Standards Library (IDSL) standards. All other relevant safety data will be listed and summarized according to the GSK IDSL standards as well. Complete details of the safety analyses will be provided in the RAP.

13.6.2.1. Extent of Exposure

Extent of exposure of GSK2879552 will depend on tolerability of the subjects to the doses administered and the course of their disease. The number of subjects exposed to GSK2879552 will be summarized for each dose level administered.

13.6.2.2. Adverse Events

AEs will be coded using the standard MedDRA and grouped by system organ class. Adverse events (AEs) will be graded by the investigator according to the NCI-CTCAE, (version 4.0).

Events will be summarized by frequency and proportion of total subjects, by system organ class and preferred term. Separate summaries will be given for all AEs, treatment-related AEs, SAEs and AEs leading to discontinuation of study treatment. AEs, if listed in the NCI-CTCAE (version 4.0), will be summarized by the maximum grade. Otherwise, the AEs will be summarized by maximum intensity.

Characteristics (e.g. number of occurrences, action taken, grade, etc) of the following AE of special interest will be summarized separately: thrombocytopenia

The incidence of deaths and the primary cause of death will be summarized and listed.

13.6.2.3. Clinical Laboratory Evaluations

Hematology and clinical chemistry data will be summarized using frequencies and proportions according to NCI-CTCAE (version 4.0). Laboratory test results outside the reference ranges that do not have associated NCI-CTCAE criteria will be summarized using proportions. Further details will be provided in the RAP.

13.6.2.4. Other Safety Measures

Data for vital signs, ECGs, and ECHOs will be summarized based on predetermined criteria identified to be of potential clinical importance (PCI). Further details will be provided in the RAP.

13.6.3. Pharmacokinetic Analyses

13.6.3.1. Pharmacokinetic Parameters

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

Non-compartmental Pharmacokinetic Analyses

Pharmacokinetic analysis of GSK2879552 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[0-t] and/or AUC[0-∞]) after single dose and AUC(0-t) and AUC(0-τ) after repeated administration
- apparent terminal phase elimination rate constant (λz)
- apparent terminal phase half-life (t½)

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

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

Metabolic Profiling

In a subset of subjects, plasma samples will be pooled and analyzed qualitatively for circulating metabolites; 0-24 hour urine samples will also be analyzed for GSK2879552 and compound related metabolites. These results will be performed under a separate DMPK protocol and reported separately.

Population Pharmacokinetics

Plasma concentration-time data from Part 2 (Expansion Cohort) 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 PK parameters (absorption rate, Ka, apparent clearance, CL/F and volume of distribution, V/F) and summary exposure measures (Cmax, AUC and Cav = AUC/τ) and identify relevant covariates (e.g., age, weight, or disease related covariates).

13.6.3.2. Statistical Analysis of PK Data

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

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

Cmax and AUC (AUC[0-∞], single dose, and AUC[0-τ], steady state) will be plotted as a function of the dose administered. If more than 2 dose cohorts are evaluated, dose proportionality of AUC and Cmax for GSK2879552 will be assessed using the power model (details will be provided in the RAP).

13.6.4. Pharmacokinetic/Pharmacodynamic Analyses

Observed or predicted concentrations will be combined with safety, efficacy, and/or pharmacodynamic measures of interest to examine potential exposure response relationships.

Quantitative safety parameters and biomarkers of interest will be plotted graphically against summary exposure measures (eg; Cmax, Ctrough, and Cav). Where evidence of a signal is seen, linear and non-linear mixed effect models will be fitted to the data to estimate PK/PD parameters of interest; e.g. slope, baseline (E0), or exposure producing 50% of the maximum effect (EC50), and maximum effect (Emax).

Overall efficacy data and overall tumor burden may be described using categorical model and/or continuous models with summary exposure parameters (eg; Cmax, Ctrough, and Cav) as covariates derived from the population PK analysis.

13.6.4.1. Translational Research Analyses

Exploratory analysis may be performed to examine potential relationships between anticancer activity and changes in markers of LSD 1 target inhibition or tumor biology or between anticancer activity and potential markers of sensitivity or resistance.

The results of translational research investigations may be reported separately from the main clinical study report or as an amendment. Endpoints of interest from all comparisons will be descriptively and/or graphically summarized as appropriate to the data. Further details on the translational research analyses will be provided in the RAP.

13.6.4.2. Novel Biomarker(s) Analyses

The results of these biomarker investigations may be reported separately from the main clinical study report. All endpoints of interest from all comparisons will be descriptively and/or graphically summarized as appropriate to the data.

Additional exploratory analyses may be performed to further characterize the novel biomarker.

14. STUDY CONDUCT CONSIDERATIONS

14.1. Posting of Information on Clinicaltrials.gov

Study information from this protocol will be posted on publicly available clinical trial registers before enrolment of subjects begins.

14.2. 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 Conference 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.

14.3. 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.

14.4. 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.

14.5. 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.

14.6. 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.

14.7. 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.

14.8. 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 eight 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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APPENDICES

Appendix 1: NYHA Functional Classification System

The **New York Heart Association (NYHA) Functional Classification: Class I, II, III or IV Heart Failure** [NYHA, 1994] provides a simple way of classifying the extent of heart failure. It places subjects in one of 4 categories based on the level of limitation experienced during physical activity:

Class	Symptoms
Class I (Mild)	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation or dyspnea (shortness of breath).
Class II (Mild)	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation or dyspnea.
Class III (Moderate)	Marked limitation of physical activity. Comfortable at rest, but less than ordinary physical activity results in fatigue, palpitation or dyspnea.
Class IV (Severe)	Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.

Reference:

The Criteria Committee of the New York Heart Association (NYHA). Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th Ed. Boston, Mass: Little, Brown & Co.; 1994:253-256.

Appendix 2: CKD-EPI EQUATION

The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation is a new equation, published in 2009 (Levey, 2009), to estimate glomerular filtration rate (GFR) from serum creatinine, age, sex, and race for adults age ≥ 18 years.

The equation is given below for creatinine in mg/dL:

Race	Sex	Serum Creatinine, S_{cr} (mg/dL)	Equation (age in years for ≥ 18)
Black	Female	≤ 0.7	$GFR = 166 \times (S_{cr}/0.7)^{-0.329} \times (0.993)^{Age}$
Black	Female	> 0.7	$GFR = 166 \times (S_{cr}/0.7)^{-1.209} \times (0.993)^{Age}$
Black	Male	≤ 0.9	$GFR = 163 \times (S_{cr}/0.9)^{-0.411} \times (0.993)^{Age}$
Black	Male	> 0.9	$GFR = 163 \times (S_{cr}/0.9)^{-1.209} \times (0.993)^{Age}$
White or other	Female	≤ 0.7	$GFR = 144 \times (S_{cr}/0.7)^{-0.329} \times (0.993)^{Age}$
White or other	Female	> 0.7	$GFR = 144 \times (S_{cr}/0.7)^{-1.209} \times (0.993)^{Age}$
White or other	Male	≤ 0.9	$GFR = 141 \times (S_{cr}/0.9)^{-0.411} \times (0.993)^{Age}$
White or other	Male	> 0.9	$GFR = 141 \times (S_{cr}/0.9)^{-1.209} \times (0.993)^{Age}$

CKD-EPI equation expressed as a single equation:

$GFR = 141 \times \min(S_{cr}/\kappa, 1)^{\alpha} \times \max(S_{cr}/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018$ [if female] × 1.159 [if black] where S_{cr} is serum creatinine in mg/dL, κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of S_{cr}/κ or 1, and max indicates the maximum of
S_{cr}/κ or 1.

The equation is given below for creatinine in µmol/L:

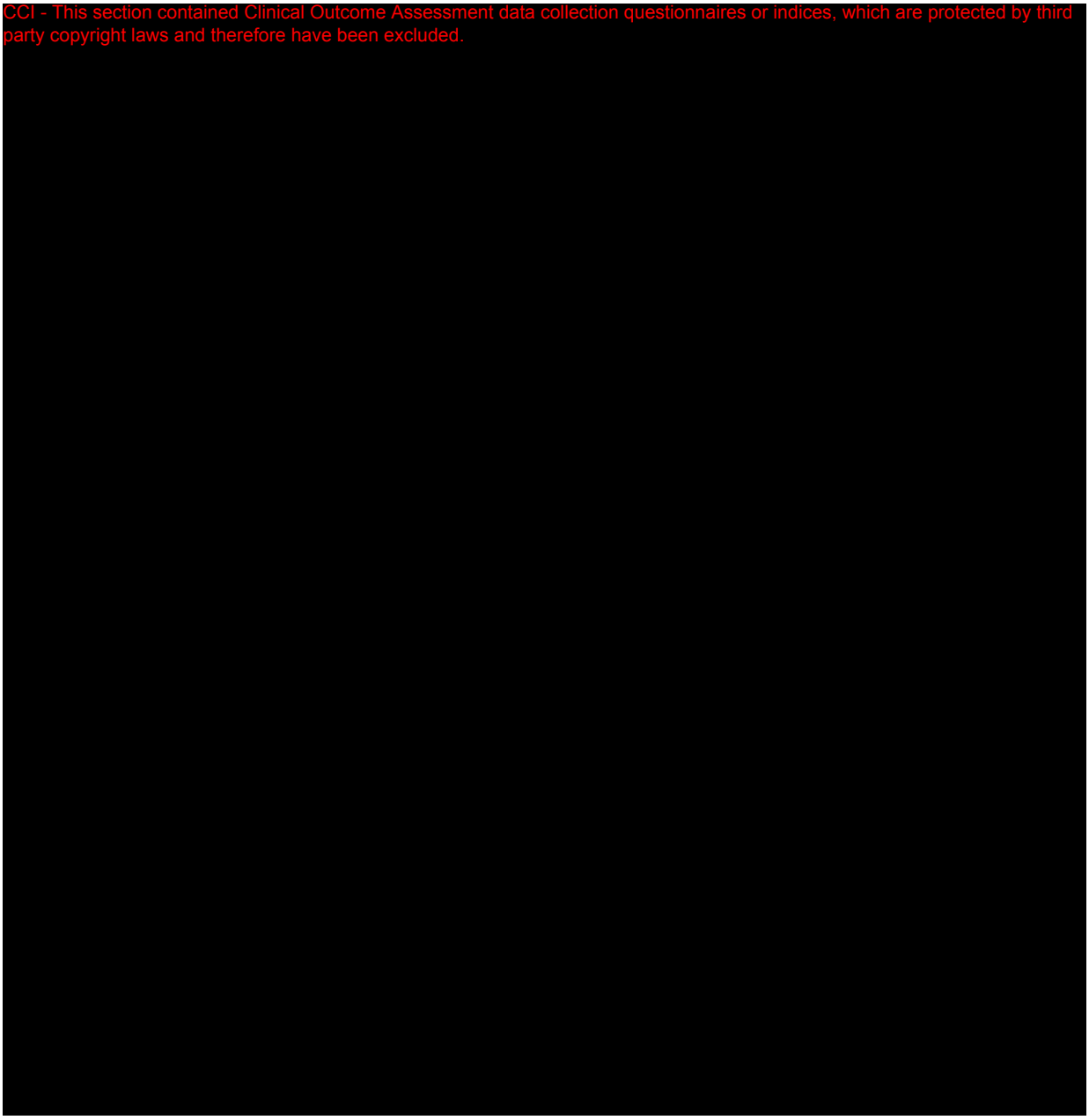
Race	Sex	Serum Creatinine, S_{cr} (µmol/L)	Equation (age in years for ≥ 18)
Black	Female	≤ 61.9	$GFR = 166 \times (S_{cr}/61.9)^{-0.329} \times (0.993)^{Age}$
Black	Female	> 61.9	$GFR = 166 \times (S_{cr}/61.9)^{-1.209} \times (0.993)^{Age}$
Black	Male	≤ 79.6	$GFR = 163 \times (S_{cr}/79.6)^{-0.411} \times (0.993)^{Age}$
Black	Male	> 79.6	$GFR = 163 \times (S_{cr}/79.6)^{-1.209} \times (0.993)^{Age}$
White or other	Female	≤ 61.9	$GFR = 144 \times (S_{cr}/61.9)^{-0.329} \times (0.993)^{Age}$
White or other	Female	> 61.9	$GFR = 144 \times (S_{cr}/61.9)^{-1.209} \times (0.993)^{Age}$
White or other	Male	≤ 79.6	$GFR = 141 \times (S_{cr}/79.6)^{-0.411} \times (0.993)^{Age}$
White or other	Male	> 79.6	$GFR = 141 \times (S_{cr}/79.6)^{-1.209} \times (0.993)^{Age}$

$GFR = 141 \times \min(S_{cr}/\kappa, 1)\kappa \times \max(S_{cr}/\kappa, 1)\text{-}1.209 \times 0.993Age \times 1.018$ [if female] × 1.159 [if black] where S_{cr} is serum creatinine in µmol/L, κ is 61.9 for females and 79.6 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of S_{cr}/κ or 1, and max indicates the maximum of S_{cr}/κ or 1.

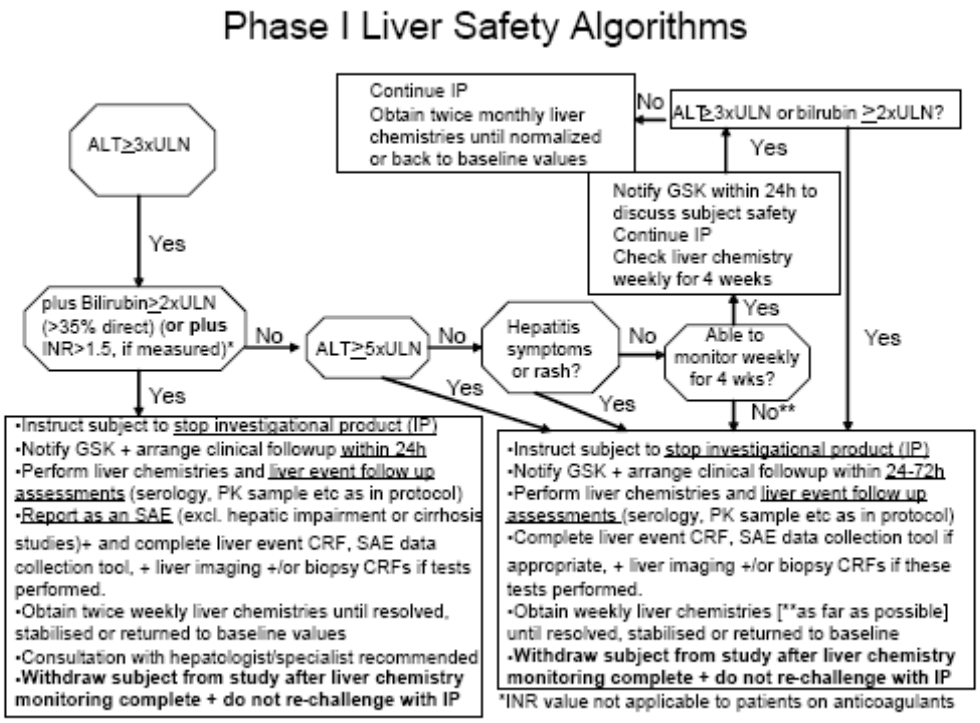
Reference:

Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, 3rd, Feldman HI, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150(9):604-12.

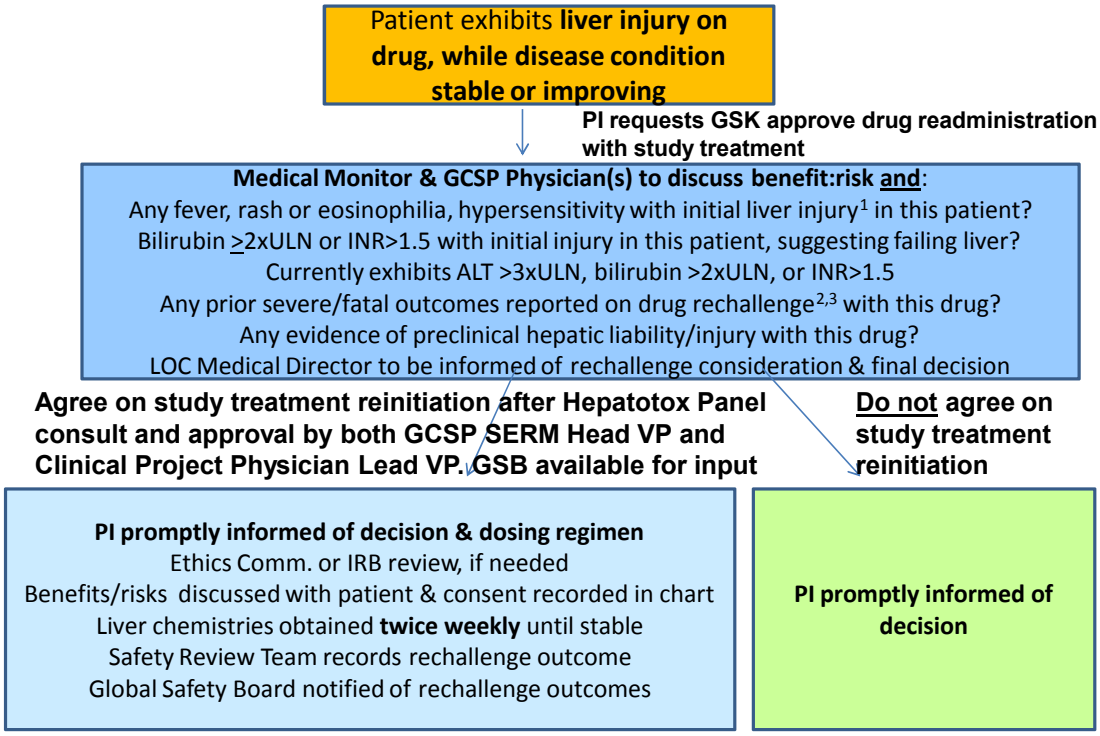
Appendix 3: ECOG Performance Status1



Appendix 4: Liver Safety Guidelines



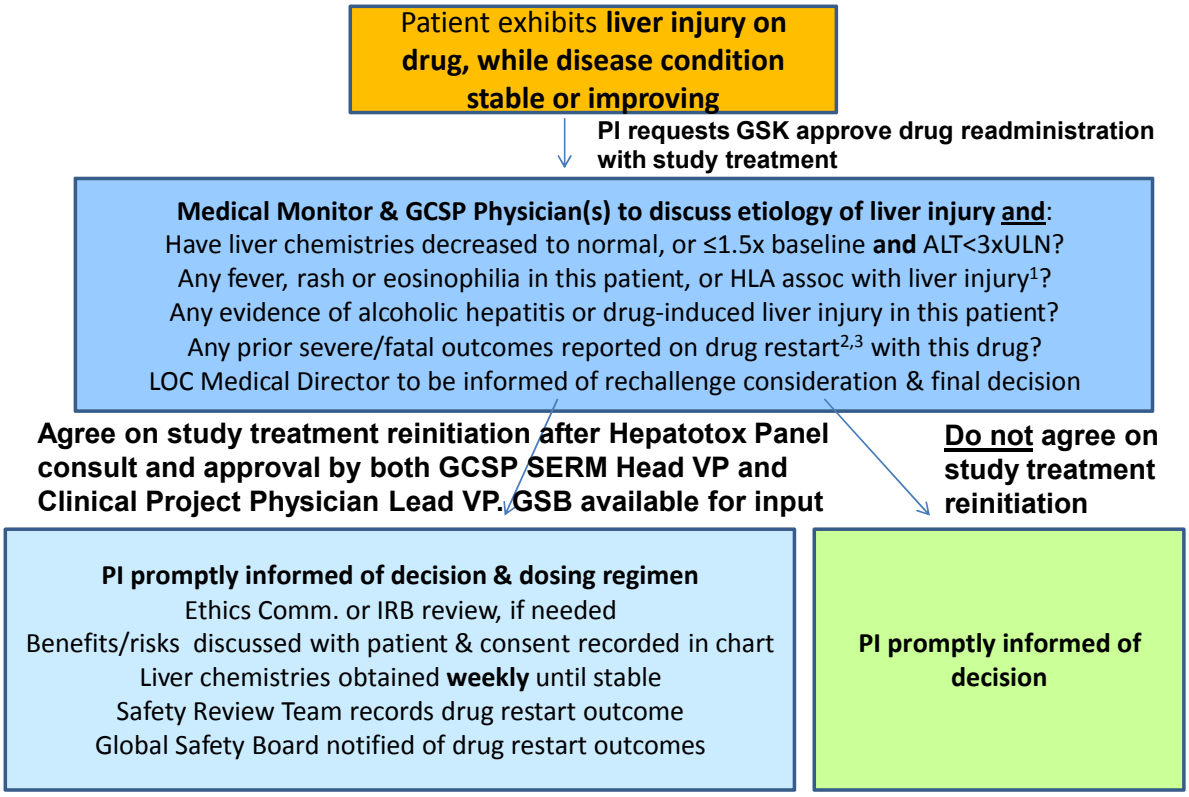
GSK process for drug rechallenge approvals



[1]Andrade RJ. Expert Opin Drug Saf 2009;8:709-714.
[2]Papay JI. Regul Tox Pharm 2009;54:84-90.
[3]Hunt CM. Hepatol 2010;52:2216-2222.

1

GSK process for drug restart approvals



[1]Andrade RJ. Expert Opin Drug Saf 2009;8:709-714.
[2]Papay JI. Regul Tox Pharm 2009;54:84-90.
[3]Hunt CM. Hepatol 2010;52:2216-2222.

2

Appendix 5: Country Specific Requirements

France:

French Specific QTc Stopping Criteria:

In line with local requirements, **a French subject** that meets the criteria QTc[1] below will have study treatment withheld:

QTcB > 500 msec

[1]Based on average corrected QT (QTc) interval value of triplicate electrocardiograms (ECGs) to include manual over-read. For example, if an ECG demonstrates a prolonged QT interval, obtain 2 more ECGs over a brief period, and then use the averaged QTc values of the 3 ECGs to determine whether the subjects should have study treatment withheld.

If the QTc prolongation resolves to Grade 1 or baseline, the subject may be re-started on the study treatment if the investigator and GSK Medical Monitor agree that the subject will benefit from further treatment.

No other known country specific requirements are currently required.

Korea:

Investigational Product Label: subject identification number and visit number will not be included in the IP label. However, it will be tracked at site pharmacy when the IP is dispensed to each subject. (Note: This is an open label study, thus treatment number is not applicable)

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PPD

Appendix 6 Simulation Results of N-CRM in Dose Escalation Phase

Simulations were conducted to determine the average sample size and percentage of times each dose was selected under three different scenarios. For each scenario, 1000 clinical trials were simulated. Details are provided in Table 8.Doses are the projected doses.

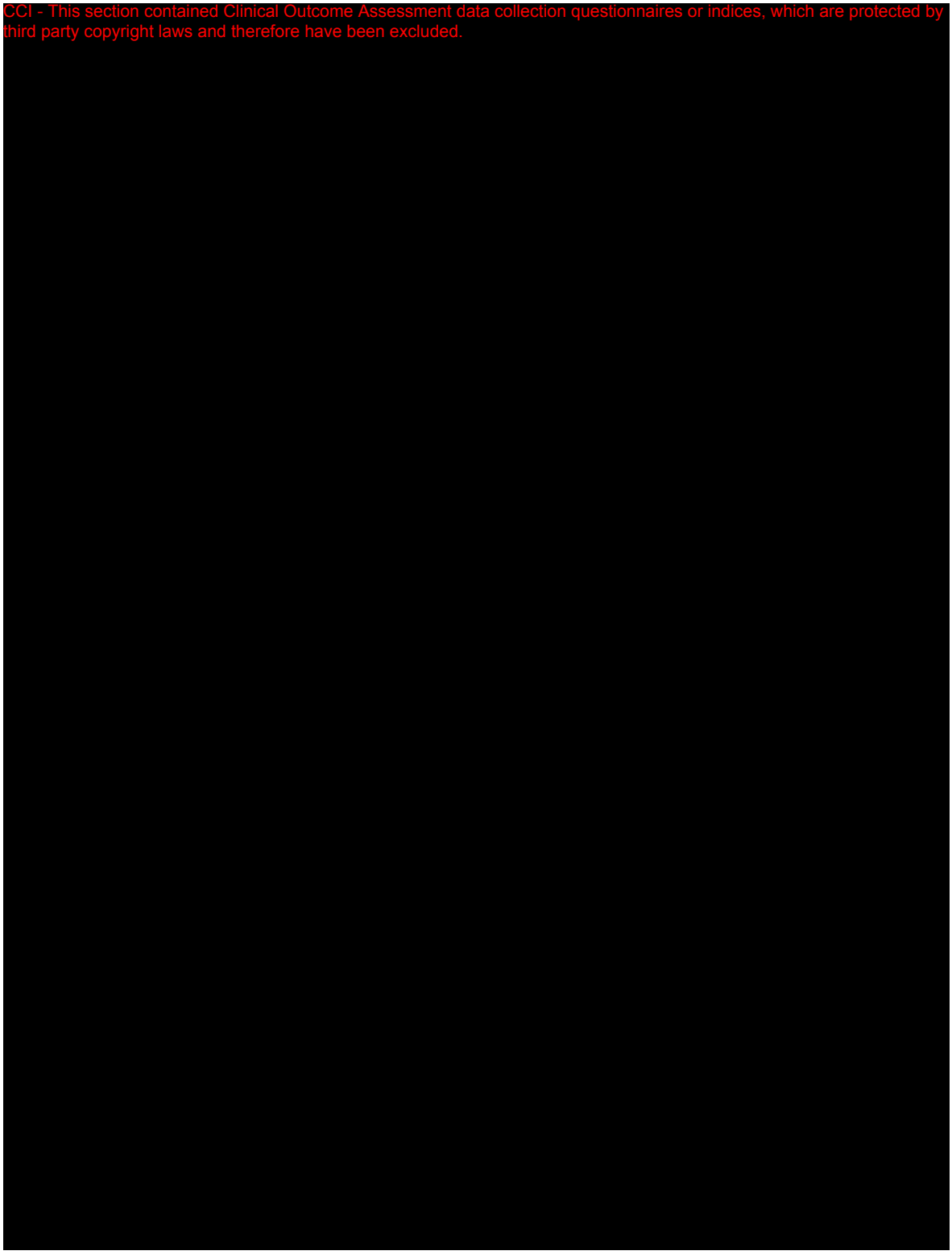
The specified prior probabilities discussed in Section 3.3 were used to determine an explicit equation for the prior distribution using the FACTS software. The parameters (s.d.) of the explicit distribution are α= -0.9917 (1.382), ln(β)=0.3615 (0.8838), and ρ=-0.6808 where α and ln(β) are distributed as bivariate normal with correlation ρ.

Table 8 Simulation Results Under Various Scenarios

Dose (mg)	Scenario 1: Steep Dose-Toxicity Curve		Scenario 2: Moderate Dose-Toxicity Curve		Scenario 3: Shallow Dose-Toxicity Curve	
	True DLT Rate	Percent of Trials Selecting Dose as MTD (%)	True DLT Rate	Percent of Trials Selecting Dose as MTD (%)	True DLT Rate	Percent of Trials Selecting Dose as MTD (%)
0.25	0.03	1	0.03	1.1	0.01	0.1
0.5	0.05	1.9	0.05	1.3	0.02	0.3
1	0.07	3.4	0.07	2.8	0.04	0.9
1.5	0.12	9.5	0.1	6.1	0.06	1.2
2	0.16	13.4	0.15	9.3	0.08	1.7
2.5	0.23	17.8	0.17	13.1	0.1	6
3	0.25	46	0.2	41.5	0.12	37.3
4	0.35	6.9	0.24	14.5	0.14	14.9
5	0.6	0.1	0.25	6.1	0.17	11.7
6	0.8	0	0.28	3.8	0.19	15.3
8	0.9	0	0.38	0.2	0.21	6.1
10	0.92	0	0.5	0.2	0.27	2.8
12	0.95	0	0.6	0	0.4	1.7

The average sample size over the 1000 clinical trials simulated under Scenarios 1-3 was 18.6, 19.3, and 21 respectively.

Appendix 7: Montreal Cognitive Assessment



Appendix 8: Protocol Amendment Changes

AMENDMENT 4

Where the Amendment Applies

Protocol Amendment 4 applies to Korea only

Summary of Amendment

Appendix 5 country specific IP label requirements for Korea have been modified. Fetal hemoglobin testing requirement has also been removed for Korea.

PREVIOUS TEXT

Appendix 5: Country Specific Requirements

France:

French Specific QTc Stopping Criteria:

In line with local requirements, **a French subject** that meets the criteria QTc[1] below will have study treatment withheld:

QTcB > 500 msec

[1]Based on average corrected QT (QTc) interval value of triplicate electrocardiograms (ECGs) to include manual over-read. For example, if an ECG demonstrates a prolonged QT interval, obtain 2 more ECGs over a brief period, and then use the averaged QTc values of the 3 ECGs to determine whether the subjects should have study treatment withheld.

If the QTc prolongation resolves to Grade 1 or baseline, the subject may be re-started on the study treatment if the investigator and GSK Medical Monitor agree that the subject will benefit from further treatment.

No other known country specific requirements are currently required.

REVISED TEXT

Appendix 5: Country Specific Requirements

France:

French Specific QTc Stopping Criteria:

In line with local requirements, **a French subject** that meets the criteria QTc[1] below will have study treatment withheld:

QTcB > 500 msec

[1]Based on average corrected QT (QTc) interval value of triplicate electrocardiograms (ECGs) to include manual over-read. For example, if an ECG demonstrates a prolonged QT interval, obtain 2 more ECGs over a brief period, and then use the averaged QTc values of the 3 ECGs to determine whether the subjects should have study treatment withheld.

If the QTc prolongation resolves to Grade 1 or baseline, the subject may be re-started on the study treatment if the investigator and GSK Medical Monitor agree that the subject will benefit from further treatment.

~~No other known country specific requirements are currently required.~~

Korea:

Investigational Product Label: subject identification number and visit number will not be included in the IP label. However, it will be tracked at site pharmacy when the IP is dispensed to each subject. (Note: This is an open label study, thus treatment number is not applicable)

GSK2879552

PPD

PREVIOUS TEXT

Time and Events Table: Part 1 – Dose Escalation

	SCR	First Treatment Phase (28 days)									Continuation Phase	EOT
		D 1	D 2	D 4	D 8	D 11	D 15	D 16	D 18	D 22		
Fetal hemoglobin (Hgb F)		X			X		X			X		

REVISED TEXT

Time and Events Table: Part 1 – Dose Escalation

	SCR	First Treatment Phase (28 days)									Continuation Phase	EOT
		D 1	D 2	D 4	D 8	D 11	D 15	D 16	D 18	D 22		
Fetal hemoglobin (Hgb F)[18]		X			X		X			X		

(Footnote added)

18. Korea only: Hgb F not required

PREVIOUS TEXT

Time and Events Table: Part 2 – Expansion Cohort

	SCR	First Treatment Phase (28 days)				Continuation Phase	EOT[11]
		D 1	D 8	D 15	D 22		
Fetal hemoglobin (Hgb F)		X	X	X	X		

REVISED TEXT

Time and Events Table: Part 2 – Expansion Cohort

	SCR	First Treatment Phase (28 days)				Continuation Phase	EOT[11]
		D 1	D 8	D 15	D 22		
Fetal hemoglobin (Hgb F)[12]		X	X	X	X		

12. Korea only: Hgb F not required

PREVIOUS TEXT

Table 7 List of Clinical Laboratory Tests

Hematology			
Platelet Count	*RBC Indices*:		*Automated WBC Differential:*
Red blood cell (RBC) Count	Mean corpuscular volume (MCV)		Neutrophils
White blood cell (WBC) Count (absolute)	Mean corpuscular hemoglobin (MCH)		Lymphocytes
Reticulocyte Count	Mean corpuscular hemoglobin concentration (MCHC)		Monocytes
Hemoglobin			Eosinophils
Hematocrit			Basophils
Mean platelet volume (MPV)			
Clinical Chemistry			
Blood urea nitrogen (BUN)	Potassium	Aspartate aminotransferase (AST)	Total and direct bilirubin[1]
Creatinine	Chloride	Alanine aminotransferase (ALT)	Uric Acid
Glucose	Total carbon dioxide (CO_2)	Gamma glutamyl transferase (GGT)	Albumin
Sodium	Calcium	Alkaline phosphatase	Total Protein
Phosphorus	Lactate Dehydrogenase (LDH)	Thyroid Stimulating Hormone	T4
Vitamin B12			
Other tests			
Coagulation Panel including PT, PTT, INR			
Fetal hemoglobin (Hgb F)			
Other screening tests			
Follicle stimulating hormone (FSH) and estradiol (as needed in women of non-child bearing potential only)			

1. Direct bilirubin should be assessed only if total bilirubin is elevated beyond the upper limit of normal (ULN)

REVISED TEXT

Table 7 List of Clinical Laboratory Tests

Hematology			
Platelet Count	*RBC Indices*:		*Automated WBC Differential:*
Red blood cell (RBC) Count	Mean corpuscular volume (MCV)		Neutrophils
White blood cell (WBC) Count (absolute)	Mean corpuscular hemoglobin (MCH)		Lymphocytes
Reticulocyte Count	Mean corpuscular hemoglobin concentration (MCHC)		Monocytes
Hemoglobin			Eosinophils
Hematocrit			Basophils
Mean platelet volume (MPV)			
Clinical Chemistry			
Blood urea nitrogen (BUN)	Potassium	Aspartate aminotransferase (AST)	Total and direct bilirubin[1]
Creatinine	Chloride	Alanine aminotransferase (ALT)	Uric Acid
Glucose	Total carbon dioxide (CO_2)	Gamma glutamyl transferase (GGT)	Albumin
Sodium	Calcium	Alkaline phosphatase	Total Protein
Phosphorus	Lactate Dehydrogenase (LDH)	Thyroid Stimulating Hormone	T4
Vitamin B12			
Other tests			
Coagulation Panel including PT, PTT, INR			
Fetal hemoglobin (Hgb F)[2]			
Other screening tests			
Follicle stimulating hormone (FSH) and estradiol (as needed in women of non-child bearing potential only)			

1. Direct bilirubin should be assessed only if total bilirubin is elevated beyond the upper limit of normal (ULN)
2. Korea only: fetal Hgb F not required

AMENDMENT 3

Where the Amendment Applies

Protocol Amendment 3 applies to all sites participating in the conduct of the study

Summary of Amendment

Additional eligibility criteria and safety monitoring measures are put in place to address recent safety findings. Primary end point and futility criteria for Part 2 are modified based on the compound's mechanism of action. Other changes include additional urine and plasma sample collection for metabolite profiling (at the highest dose cohort in Part 1 PK/PD expansion), update in concomitant medications, clarification on the timing for pre- and post-dose optional biopsies, and addressing the inconsistencies in the definition of febrile neutropenia.

LIST OF SPECIFIC CHANGES

Section 1.3.1 GSK2879552 Background

PREVIOUS TEXT

An overview of the pre-clinical studies of GSK2879552 is provided below. Detailed information concerning the biology, pharmacology, pharmacokinetics (PK), and safety can be found in the Investigators' Brochure (IB) [GlaxoSmithKline Document Number 2013N168888_00].

GSK2879552 is a potent, selective, mechanism-based inactivator of LSD1/CoREST activity (K_i = 767 nM, k_{inact} = 0.1 min^{-1}). While the initial reversible potency (K_i) of GSK2879552 is moderate, complete inhibition of the enzyme is achieved over time due to the irreversible, mechanism-based nature of the inhibition. GSK2879552 induces the expression of putative LSD1 target genes and has potent, predominantly cytostatic, anti-proliferative activity in small cell lung carcinoma (SCLC) with median EC_{50} = 25 nM, range = 2 - 240 nM. In total, 9/28 SCLC lines were found to be sensitive to GSK2879552 treatment while the sensitivity of an additional 7 SCLC lines could not be determined.

REVISED TEXT

An overview of the pre-clinical studies of GSK2879552 is provided below. Detailed information concerning the biology, pharmacology, pharmacokinetics (PK), and safety can be found in the Investigators' Brochure (IB) [GlaxoSmithKline Document Number 2013N168888_0~~0~~**1**].

GSK2879552 is a potent, selective, mechanism-based inactivator of LSD1/CoREST activity (K_i = **1.7 µM** ~~767 nM~~, k_{inact} = 0.1 min^{-1}). While the initial reversible potency (K_i) of GSK2879552 is moderate, complete inhibition of the enzyme is achieved over time due to the irreversible, mechanism-based nature of the inhibition. GSK2879552 induces the expression of putative LSD1 target genes and has potent, predominantly cytostatic, anti-proliferative activity in small cell lung carcinoma (SCLC) with median EC_{50} = 25 nM, range = 2 - 240 nM. In total, 9/28 SCLC lines were found to be sensitive to GSK2879552 treatment while the sensitivity of an additional 7 SCLC lines could not be determined.

Section 1.4 Benefit : Risk Assessment

PREVIOUS TEXT

Summaries of findings from non-clinical studies conducted with GSK2879552 can be found in the Investigator's Brochure (IB) [GlaxoSmithKline Document Number 2013N168888_00]. Toxicology studies performed in dogs, rats and mice suggest that the primary toxicities of GSK2879552 are hematologic. The following Section outlines the risk assessment and mitigation strategy for this protocol.

Potential Risk of Clinical Significance	**Data/Rationale for Risk**	**Mitigation Strategy**
Lymphoid/hematologic and associated bleeding and infection risks	The primary toxicity with GSK2879552 is a dose-dependent mild-to-severe thrombocytopenia, observed in mice, rats and dogs. A dose-dependent mild-to-severe neutropenia was observed in rats, but not dogs, and was not associated with systemic infections. Mild effects on the erythron were observed in rats and dogs which may reflect both a direct and indirect (i.e., secondary to bleeding/hemorrhage) effect on the erythroid lineage. In general, there was not hypocellularity observed in the bone marrow of these animals.	Informed Consent Form includes the risk of hematologic toxicity. Protocol specifies: - laboratory assessments (complete blood count [CBC]) - Exclusion criteria for subjects with recent history of significant bleeding or elevated bleeding risk - Monitoring for bleeding - Monitoring for infection - Dose stopping/modification criteria - Anticoagulants (e.g., warfarin above 1 mg once daily, direct thrombin inhibitors, etc) at therapeutic doses or platelet inhibitors (e.g., aspirin above 100 mg once daily, clopidogrel) are prohibited from fourteen days prior to the first dose of study drug through completion of the Final Study Visit. - Guideline for platelet transfusion

REVISED TEXT

Summaries of findings from non-clinical studies conducted with GSK2879552 can be found in the Investigator's Brochure (IB) [GlaxoSmithKline Document Number 2013N168888_0~~0~~**1**]. Toxicology studies performed in dogs, rats and mice suggest that the primary toxicities of GSK2879552 are hematologic. The following Section outlines the risk assessment and mitigation strategy for this protocol.

Potential Risk of Clinical Significance	**Data/Rationale for Risk**	**Mitigation Strategy**
Lymphoid/hematologic and associated bleeding and infection risks	The primary toxicity with GSK2879552 is a dose-dependent mild-to-severe thrombocytopenia, observed in mice, rats and dogs. A dose-dependent mild-to-severe neutropenia was observed in rats, but not dogs, and was not associated with systemic infections. Mild effects on the erythron were observed in rats and dogs which may reflect both a direct and indirect (i.e., secondary to bleeding/hemorrhage) effect on the erythroid lineage. In general, there was not hypocellularity observed in the bone marrow of these animals.	Informed Consent Form includes the risk of hematologic toxicity. Protocol specifies: - laboratory assessments (complete blood count [CBC]) - Exclusion criteria for subjects with recent history of significant bleeding or elevated bleeding risk - Monitoring for bleeding - Monitoring for infection - Dose stopping/modification criteria - Anticoagulants (e.g., warfarin above 1 mg once daily, direct thrombin inhibitors, etc) at therapeutic doses or platelet inhibitors (e.g., aspirin above 100 mg once daily, clopidogrel) are prohibited from fourteen days prior to the first dose of study drug through completion of the Final Study Visit. - Guideline for platelet transfusion
Mental status change	**Two (out of 16) subjects enrolled in 200858 study experienced encephalopathy.**	**Informed Consent Form is updated to include the risk of mental status change.** **Protocol eligibility and monitoring criteria are modified:** - **subjects who have received prior treatment with temozolomide, dacarbazine, procarbazine or PARP inhibitors are excluded** - **Subjects should have baseline thyroid function, vitamin B12 level and metabolic panel within acceptable limits** - **Montreal Cognitive Assessment (MOCA) at baseline and weekly for the first 4 weeks and monthly thereafter.** - **Subjects with baseline MOCA score of ≤ 22 are excluded** **Protocol stopping criteria is modified:** - **Dosing will be held and neurology consult will be required if a decrease of 3 points or more from baseline MOCA score or any score of < 22 occurs or in case of any other indication of early encephalopathy as determined by patient history or physical exam**

Section 2.1 Part 1 Dose Escalation

PREVIOUS TEXT

PART 1: Escalation Cohort		
	Objectives	**Endpoints**
Secondary	2. To evaluate clinical response after treatment with GSK2879552.	2. Objective response rate (% of subjects achieving complete response [CR], partial response [PR]) per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1
Exploratory	6. To characterize the metabolite profile of GSK2879552 after oral repeat-dosing in some subjects 7. To determine the amount of GSK2879552 excreted in urine after oral repeat-dosing	6. GSK2879552 metabolites in plasma and/or urine 7. Concentration of GSK2879552 in urine measured with an investigational bio-analytical method and extrapolated to total amount excreted in urine over time

REVISED TEXT

PART 1: Escalation Cohort		
	Objectives	**Endpoints**
Secondary	2. To evaluate clinical ~~response~~ **activity** after treatment with GSK2879552.	2. **Disease Control Rate (DCR) (CR + PR + SD) at week 16 based on** ~~Objective response rate (% of subjects achieving complete response [CR], partial response [PR]) per~~ Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1
Exploratory	6. To characterize the metabolite profile of GSK2879552 after oral **single and/or** repeat-dosing in some subjects 7. To determine the amount of GSK2879552 excreted in urine after oral **single and/or** repeat-dosing	6. GSK2879552 metabolites in plasma and/or urine 7. Concentration of GSK2879552 in urine measured with an investigational bio-analytical method and extrapolated to total amount excreted in urine over time

Section 2.2 Part 2 Expansion

PREVIOUS TEXT

	Objectives	**Endpoints**
Primary	1. To evaluate clinical activity of GSK2879552 given orally in adult subjects with SCLC.	1. Objective response rate (% of subjects achieving CR, PR) per RECIST 1.1

	Objectives	**Endpoints**
Secondary	1. To evaluate the safety and tolerability of RP2D of GSK2879552	1. AEs, SAEs, dose limiting toxicities, dose reductions or delays, withdrawals due to toxicities and changes in safety assessments (e.g., laboratory parameters, vital signs, physical examinations).
	2. To characterize the population PK of GSK28795522.	2. Population PK parameters for GSK2879552 such as clearance (CL/F) and volume of distribution (V/F), and relevant covariates which may influence exposure (e.g., age, weight, or disease associated covariates).
	3. To evaluate the relationship between GSK2879552 exposure and safety/efficacy/PD parameters.	3. Relationship between GSK2879552 exposure markers (e.g. dose, Cmin, Cmax or AUC [0-tau]), and ProGRP, platelet levels in blood, and safety/efficacy parameters.
	4. To evaluate duration of response and progression free survival (PFS)	4. Duration of response and PFS
Hypothesis	Clinical response will be defined as Objective Response Rate (CR + PR) based on RECIST 1.1. The null hypothesis is: H0: RR ≤10% The alternative hypothesis is: HA: RR ≥25%	

REVISED TEXT

	Objectives	**Endpoints**
Primary	1. To evaluate clinical activity of GSK2879552 given orally in adult subjects with SCLC.	1. **Disease Control Rate (DCR) (CR + PR + SD) at week 16 based on** ~~Objective response rate (% of subjects achieving CR, PR)~~ per RECIST 1.1
Secondary	1. To evaluate the safety and tolerability of RP2D of GSK2879552	1. AEs, SAEs, dose limiting toxicities, dose reductions or delays, withdrawals due to toxicities and changes in safety assessments (e.g., laboratory parameters, vital signs, physical examinations).
	2. To characterize the population PK of GSK28795522.	2. Population PK parameters for GSK2879552 such as clearance (CL/F) and volume of distribution (V/F), and relevant covariates which may influence exposure (e.g., age, weight, or disease associated covariates).
	3. To evaluate the relationship between GSK2879552 exposure and safety/efficacy/PD parameters.	3. Relationship between GSK2879552 exposure markers (e.g. dose, Cmin, Cmax or AUC [0-tau]), and ProGRP, platelet levels in blood, and safety/efficacy parameters.
	4. To evaluate duration of response and progression free survival (PFS)	4. Duration of response and PFS

	Objectives	**Endpoints**
	5. To evaluate objective response rate (ORR)	**5. % of subjects achieving complete response and partial response**
Hypothesis	Clinical response will be defined as **Disease Control** ~~Objective Response~~ Rate **(DCR)** (CR + PR**+SD**) **at week 16** based on RECIST 1.1. The null hypothesis is: H0: **DCR**~~RR~~ **≤15**~~10~~**% at week 16** The alternative hypothesis is: HA: **DCR**~~RR~~ **≥30**~~25~~**% at week 16**	

Section 3.11 Safety Management Guideline

NEW SECTION ADDED

3.11.3 Mental Status Stopping Criteria

Study treatment will be held and neurology consult obtained if:

- **A decrease of 3 pointsor more from baseline MOCA score occurs and/or**
- **Any other indication of early encephalopathy as determined by patient history or physical exam**

The treatment may resume if one of the following criteria is met:

- **A reversible cause is identified and MOCA score returns to normal or symptoms return to baseline.**
- **Evaluated by a neurologist and found to have no clear signs/symptoms of encephalopathy or other cognitive dysfunction. This is applicable only in the absence of decrease in MOCA score.**

The treatment should be permanently discontinued for subjects with documented symptoms with no other cause, even if they return to baseline.

Section 3.12.2 Management of Thrombocytopenia

PREVIOUS TEXT

Table 9 Thrombocytopenia management guideline

Grade	Platelet count	Monitoring	Dose Adjustment*
G3	<50,000 - 25,000/mm^3	Twice weekly for 2 weeks. Then, • if stable, monitor per protocol. • if falling, continue to monitor twice weekly until stable.	• If platelet count is < 50K but > 25K for more than 3 days and stable, continue at the same dose. • If platelet count is < 50K but > 25K for more than 3 days and falling, interrupt dosing and resume treatment once platelet count >50K ➢ at the same dose if platelet count recovers to > 50K within 7 days.** If grade 3 thrombocytopenia recurs, reduce dose by at least 25%. ➢ with reduced dose by at least 25% if platelet count recovers to > 50K after 7 days.**.

REVISED TEXT

Grade	Platelet count	Monitoring	Dose Adjustment*
G3	<50,000 - 25,000/mm^3	Twice weekly for 2 weeks. Then, • if stable, monitor per protocol. • if falling, continue to monitor twice weekly until stable.	• If platelet count is < 50K but > 25K for more than 3 days and stable, continue at the same dose. • If platelet count is < 50K but > 25K for more than 3 days and falling, interrupt dosing and resume treatment once platelet count >50K ➢ at the same dose if platelet count recovers to > 50K within 7 days.** **For subjects receiving daily dosing on a continuous schedule**, ~~If grade 3 thrombocytopenia recurs,~~ reduce dose by at least 25% **if grade 3 thrombocytopenia recurs** ➢ with reduced dose by at least 25% if platelet count recovers to > 50K after 7 days.**.

Section 3.12.3 Management of Neutropenia

PREVIOUS TEXT

For the following, dose should be interrupted and the treatment should resume with dose reduced by at least 25% when neutrophil count is > 1000/mm^3 and the temperature <38.5°C for over 24 hrs:

- febrile neutropenia (defined as concurrent Grade 4 neutropenia and fever >38.5°C and lasting >24 hr)
- Grade 4 neutropenia

Grade 3 neutropenia lasting >7 days

REVISED TEXT

For the following, dose should be interrupted and the treatment should resume with dose reduced by at least 25% ~~when neutrophil count is > 1000/mm^3 and the temperature <38.5°C for over 24 hrs:~~

- febrile neutropenia (**as defined by CTCAE v.4** ~~defined as concurrent Grade 4 neutropenia and fever >38.5°C and lasting >24 hr~~)
- Grade 4 neutropenia
- Grade 3 neutropenia lasting >7 days

Section 3.12 Guidelines for Events of Special Interest and Dose Modifications

NEW SECTION ADDED

3.12.6.1 CBC monitoring and PK sampling Guideline for Dose interruptions/modifications

When the treatment is held due to an AE, CBC and PK sample should be collected on the first day of dose interruption and 3-4 days after. If the treatment is held for more than a week, additional PK and CBC sample should be collected at 1 week after the dose interruption.

When the dose resumes at the same or reduced dose, a pre-dose PK sample and CBC should be collected on the day and twice weekly for the first 3 weeks. On Week 2, two post-treatment PK samples should be collected between 0.5-1 hr and between 4-6 hours from dosing, in addition to the pre-dose PK sample. Pre-dose and weekly CBC monitoring should continue on weeks 4, 6, and 8 of the resumed dosing.

Less frequent CBC monitoring and PK sample collection may be allowed for individual subjects, if warranted.

Section 5.2.1 Inclusion Criteria, #8

PREVIOUS TEXT

8. Adequate baseline organ function defined by

System	Laboratory Values
Hematologic	
Absolute neutrophil count (ANC)	≥ 1.5 X 10^9/L
Hemoglobin	≥ 10 g/dL
Platelets	≥ 125 X 10^9/L
Prothrombin time (PT)/International normalized ratio (INR) and Partial thromboplastin time (PTT)	≤ 1.5 X ULN
Hepatic	
Total bilirubin ALT and AST	≤ 1.25 X ULN[1] ≤2.5 × ULN without liver metastasis ≤5 x ULN if documented liver metastasis
Renal	
Creatinine OR Calculated creatinine clearance by Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (Appendix 2) or measured from 24hr urine	≤1.5 X ULN ≥ 50 mL/min
Cardiac	
Ejection fraction	≥ LLN by Echocardiogram (ECHO)

1. Isolated bilirubin >1.5 X ULN is acceptable if bilirubin is fractionated and direct bilirubin <35% or subject has a diagnosis of Gilbert's syndrome

REVISED TEXT

8. Adequate baseline organ function defined by

System	Laboratory Values
Hematologic	
Absolute neutrophil count (ANC) Hemoglobin Platelets Prothrombin time (PT)/International normalized ratio (INR) and Partial thromboplastin time (PTT)	≥ 1.5 X 10^9/L ≥ 10 g/dL ≥ 125 X 10^9/L ≤ 1.5 X ULN
Hepatic	
Total bilirubin ALT and AST	≤ 1.25 X ULN[1] ≤2.5 × ULN without liver metastasis ≤5 x ULN if documented liver metastasis
Renal	
Creatinine OR Calculated creatinine clearance by Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (Appendix 2) or measured from 24hr urine	≤1.5 X ULN ≥ 50 mL/min
Cardiac	
Ejection fraction	≥ LLN by Echocardiogram (ECHO)
Metabolic	
TSH, T4 **Vitamin B12** **BUN** **Na, K^2, Ca, Cl, CO_2** **Glucose (fasting)**	**WNL** **≥ LLN** **≤1.5 X ULN** **WNL** **≤1.25 X ULN**

1. Isolated bilirubin >1.5 X ULN is acceptable if bilirubin is fractionated and direct bilirubin <35% or subject has a diagnosis of Gilbert's syndrome
2. **Replacement of K is allowed if below LLN**

Section 5.2.2 Exclusion Criteria

NEW TEXT ADDED

3. Prior treatment with temozolomide, dacarbazine or procarbazine

4. Prior treatment with poly ADP ribose polymerase (PARP) inhibitors (e.g., olaparib, ABT-888)

5. Baseline Montreal Cognitive Assessment (MOCA) score of 22 or lower

Section 7 STUDY ASSESSMENTS AND PROCEDURES

PREVIOUS TEXT

Visit Window

Baseline disease assessment should be completed within 35 days prior to dosing start and pregnancy testing 7 days prior. All other screening assessments should be completed within 14 days prior to dosing start.

Visits in the first 3 weeks will be allowed ± 1 day window. The only exceptions are pre- and post -treatment biopsies on Day 1 and 15 where 3 days and ± 3 days window will be allowed, respectively.

REVISED TEXT

Baseline disease assessment **and ECHO/MUGA** should be completed within 35 days prior to dosing start and pregnancy testing 7 days prior. All other screening assessments should be completed within 14 days prior to dosing start.

Visits in the first 3 weeks will be allowed ± 1 day window. The only exceptions are pre- and post -treatment biopsies on Day 1 and 15 where ~~3~~**7** days and ± 3 days window will be allowed, respectively.

Section 7.1 Time and Events Table(s)

PREVIOUS TEXT

Time and Events Table: Part 1 – Dose Escalation

	SCR	First Treatment Phase (28 days)									Continuation Phase	EOT
		D 1	D 2	D 4	D 8	D 11	D 15	D 16	D 18	D 22		
ECHO	X											
Blood for metabolite evaluation							X[9]	X[9]				
Urine for metabolite							X[15]	X[15]				

1. A blood sample will be collected for PK analysis on D1 at following time points: pre-dose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 hrs post dose. Additional samples may be collected at 33 and 48 hrs post dose in subjects not receiving a dose on Day 2 to better characterize the terminal half-life ofGSK2879552, if needed.
15. On D15, 24hr urine will be collected and measured, and 400 mL urine from at least 6 subjects at the highest dose cohort in PK/PD expansion will be collected for metabolite identification purposes.
16. In a subset of subjects in PK/PD cohorts, fresh pre-treatment and post-treatment biopsies are required. Pre-treatment and post-treatment biopsies are optional for all subjects not enrolled in PK/PD expansion cohorts. Day 1 biopsy (-3 days window) should be collected pre-dose, Day 15 (±3 days window) biopsy can be collected pre- or post- dose.

Time and Events Table: Part 2 – Expansion Cohort

	SCR	First Treatment Phase (28 days)				Continuation Phase	EOT[11]
		D 1	D 8	D 15	D 22		
Blood samples for PD[3] (whole blood)	X	X	X				
Blood samples for circulating biomarkers[3] (plasma)		X			X		X
Blood samples for translational research[3] (PBMCs)	X			X			X

10. Baseline tumor tissue collection is mandatory for all subjects. Archival tissue will be acceptable. In the absence of available archival tissue, fresh tissue biopsy will be required. Fresh biopsies on Day 1, Day 15 and at disease progression are optional for all subjects in Part 2. Day 1 biopsy (-3 days window) should be collected pre-dose, Day 15 (±3 days window) biopsy can be collected pre- or post- dose.

REVISED TEXT

Time and Events Table: Part 1 – Dose Escalation

	SCR	First Treatment Phase (28 days)									Continuation Phase	EOT
		D 1	D 2	D 4	D 8	D 11	D 15	D 16	D 18	D 22		
Montreal Cognitive Assessment	**X**	**X**			**X**		**X**			**X**	**Wk 4 and every 4 wks**	
ECHO/**MOCA**	X											
Vitamin B12, TSH, T4	**X**											
Blood for metabolite evaluation		**X[9]**	**X[9]**				X[9]	X[9]				
Urine for metabolite		**X[15]**	**X[15]**				X[15]	X[15]				

1. A blood sample will be collected for PK analysis on D1 at following time points: pre-dose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 hrs post dose. Additional samples may be collected at 33 **(optional)** and 48 hrs post dose in subjects not receiving a dose on Day 2 to better characterize the terminal half-life ofGSK2879552, if needed.
15. **On Day 1, pre-dose urine (~100 ml) will be collected for metabolite study.** On **Days 1 and** 15, 24hr urine will be collected and measured, and 400 mL urine from at least 6 subjects at the highest dose cohort in PK/PD expansion will be collected for metabolite identification purposes.
16. In a subset of subjects in PK/PD cohorts, fresh pre-treatment and post-treatment biopsies are required. Pre-treatment and post-treatment biopsies are optional for all subjects not enrolled in PK/PD expansion cohorts. Day 1 biopsy (-~~3~~**7** days window) should be collected pre-dose, Day 15 (± 3 days window) biopsy can be collected pre- or post- dose. **Optional post-treatment biopsy can be collected at a later time point, if desired.**

Time and Events Table: Part 2 – Expansion Cohort

	SCR	First Treatment Phase (28 days)				Continuation Phase	EOT[11]
		D 1	D 8	D 15	D 22		
Montreal Cognitive Assessment	**X**		**X**	**X**	**X**	**Wk 4 and every 4 weeks**	
Vitamin B12, TSH, T4	**X**						

	SCR	First Treatment Phase (28 days)				Continuation Phase	EOT[11]
		D 1	D 8	D 15	D 22		
~~Blood samples for PD[3] (whole blood)~~	~~X~~	~~X~~	~~X~~				
Blood samples for translational research[3] (~~PBMCs~~ **CTC**)	X			X		**Wk 8**	X
10. Baseline tumor tissue collection is mandatory for all subjects. Archival tissue will be acceptable. In the absence of available archival tissue, fresh tissue biopsy will be required. Fresh biopsies on Day 1, Day 15 and at disease progression are optional for all subjects in Part 2. Day 1 biopsy (-3 days window) should be collected pre-dose, Day 15 (±3 days window) biopsy can be collected pre- or post- dose. **Optional post-treatment biopsy can be collected at a later time point, if desired.**							

Section 7.2. Demographic/Medical History and Baseline Assessments

PREVIOUS TEXT

Baseline (Screening) assessments will include:

- Complete physical examination, including height (in cm) and weight (in kg).
- Vital signs (blood pressure, temperature, respiratory rate, pulse rate)
- Eastern Cooperative Oncology Group (ECOG) performance status
- 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
- Echocardiogram (ECHO) or multi-gated acquisition (MUGA) scan
- Baseline disease assessment: computed tomography (CT) scan (with IV contrast) of chest, abdomen and pelvis (if applicable)
- Brain magnetic resonance imaging (MRI) with contrast or a CT scan (with/without contrast) if MRI is contraindicated
- Fresh tumor biopsy (preferred) or archival tumor tissue collection

REVISED TEXT

Fasting will be required for screening clinical laboratory tests.

Baseline (Screening) assessments will include:

- Complete physical examination, including height (in cm) and weight (in kg).
- Vital signs (blood pressure, temperature, respiratory rate, pulse rate)
- Eastern Cooperative Oncology Group (ECOG) performance status
- Clinical laboratory tests: hematology, clinical chemistry, coagulation parameters, **vitamin B12, thyroid (TSH, T4)**
- Serum beta-human chorionic gonadotropin (β-HCG) pregnancy test for female subjects of childbearing potential only
- 12-lead ECG
- Echocardiogram (ECHO) or multi-gated acquisition (MUGA) scan
- Baseline disease assessment: computed tomography (CT) scan (with IV contrast) of chest, abdomen and pelvis (if applicable)
- Brain magnetic resonance imaging (MRI) with contrast or a CT scan (with/without contrast) if MRI is contraindicated
- Fresh tumor biopsy (preferred) or archival tumor tissue collection
- **Montreal Cognitive Assessment**

Section 7.3 Safety Evaluations

NEW SECTION ADDED

7.3.3 Montreal Cognitive Assessment

Montreal Cognitive Assessment (MOCA) was designed as a rapid screening instrument for mild cognitive dysfunction. It assesses different cognitive domains: attention and concentration, executive functions, memory, language, visuoconstructional skills, conceptual thinking, calculations, and orientation. Time to administer the MOCA is approximately 10 minutes.

The test and administration instructions are freely accessible for clinicians at www.MOCAtest.org. English version 7.1 is shown in Appendix 7.

Section 7.3.7. Laboratory Assessments

PREVIOUS TEXT

Table 10 List of Clinical Laboratory Tests

Clinical Chemistry			
Blood urea nitrogen (BUN)	Potassium	Aspartate aminotransferase (AST)	Total and direct bilirubin[1]
Creatinine	Chloride	Alanine aminotransferase (ALT)	Uric Acid
Glucose	Total carbon dioxide (CO_2)	Gamma glutamyl transferase (GGT)	Albumin
Sodium	Calcium	Alkaline phosphatase	Total Protein
Phosphorus	Lactate Dehydrogenase (LDH)		

REVISED TEXT

Table 11 List of Clinical Laboratory Tests

Clinical Chemistry			
Blood urea nitrogen (BUN)	Potassium	Aspartate aminotransferase (AST)	Total and direct bilirubin[1]
Creatinine	Chloride	Alanine aminotransferase (ALT)	Uric Acid
Glucose	Total carbon dioxide (CO_2)	Gamma glutamyl transferase (GGT)	Albumin
Sodium	Calcium	Alkaline phosphatase	Total Protein
Phosphorus	Lactate Dehydrogenase (LDH)	**Thyroid Stimulating Hormone**	**T4**
Vitamin B12			

Section 7.5 Pharmacodynamics

PREVIOUS TEXT

- Changes from baseline in circulating ProGRP levels will be assessed in blood
- Change from baseline in a gene expression panel, including but not limited to GFI1B, KCNJ5, RND2, SERPINE2, ASB4, CACNB3, CD59A, SPARC, and STAB1 will be assessed in whole blood
- The impact of GSK2879552 treatment on platelet levels will also be assessed by complete blood count (CBC) analysis
- Changes in markers including, but not limited to, ProGRP and SCLC-specific LSD1 target genes or proteins in paired baseline and post-treatment tumor tissue will be assessed

REVISED TEXT

- Changes from baseline in circulating ProGRP levels will be assessed in blood
- Change from baseline in a gene expression panel, including but not limited to GFI1B, KCNJ5, RND2, SERPINE2, ASB4, CACNB3, CD59A, SPARC, and STAB1 will be assessed in whole blood
- ~~The impact of GSK2879552 treatment on platelet levels will also be assessed by complete blood count (CBC) analysis~~
- Changes in markers including, but not limited to, ProGRP and SCLC-specific LSD1 target genes or proteins in paired baseline and post-treatment tumor tissue will be assessed

Section 7.6.3 Circulating biomarker analysis, 2nd paragraph

PREVIOUS TEXT

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 GSK2879552.

REVISED TEXT

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 **in cell-free DNA and circulating tumor cells (CTCs) along with burden** may be evaluated in plasma and correlated with clinical outcome to treatment with GSK2879552.

Section 10.2.1 Drugs that may alter the Pharmacokinetics of GSK2879552

PREVIOUS TEXT

The precise in vivo metabolic and transporter liability for GSK2879552 has yet to be assessed. In vitro data in human microsomes and hepatocytes suggests that GSK2879552 has a negligible turnover. GSK2879552 may be a substrate for liver and/or kidney transporters.

Therefore, substances that potently inhibit gut, liver and/or kidney transporters (Table 8) 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 GSK2879552. Substances that moderately inhibit gut, liver

and/or kidney transporters (Table 9) should be used with caution during the course of the study.

Table 12 Prohibited Drugs Potentially Affecting GSK2879552 PK Resulting in Increased or Decreased GSK2879552 Exposure

PROHIBITED – strong inhibitors of gut, liver or kidney transporters since levels of GSK2879552 may be decreased/increased	
Drug	**Therapeutic Area**
quinidine	Antiarrhythmics
clarithromycin, erythromycin, rifamycin class agents (e.g. rifampin, rifabutin, rifapentine)	Antibiotics
itraconazole	Antifungals
lopinavir, nelfinavir, ritonavir	Antiretrovirals, Protease Inhibitors
gemfibrozil	Hyperlipidemia
cyclosporine, valspodar	Miscellaneous

Table 13 Use with Caution – Drugs Potentially Increase/Decrease GSK2879552 Exposure

WITH CAUTION – moderate inhibitors of gut, liver or kidney transporters since levels of GSK2879552 may be decreased/increased	
Drug	**Therapeutic Area**
probenecid	Anti gout/hyperuricemia
Diflunisal, probenecid	Non-steroidal anti-inflammatory drug (NSAIDs)

REVISED TEXT

All co-meds should be used with caution since little is known about the mechanism of clearance of GSK2879552. In vitro data in human microsomes and hepatocytes suggest that GSK2879552 has a negligible turnover.

~~The precise in vivo metabolic and transporter liability for GSK2879552 has yet to be assessed. In vitro data in human microsomes and hepatocytes suggests that GSK2879552 has a negligible turnover. GSK2879552 may be a substrate for liver and/or kidney transporters.~~

~~Therefore, substances that potently inhibit gut, liver and/or kidney transporters (Table 8) 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 GSK2879552. Substances that moderately inhibit gut, liver and/or kidney transporters (Table 9) should be used with caution during the course of the study.~~

~~Table 14 Prohibited Drugs Potentially Affecting GSK2879552 PK Resulting in Increased or Decreased GSK2879552 Exposure~~

~~PROHIBITED – strong inhibitors of gut, liver or kidney transporters since levels of GSK2879552 may be decreased/increased~~	
~~Drug~~	**~~Therapeutic Area~~**
~~quinidine~~	~~Antiarrhythmics~~
~~clarithromycin, erythromycin, rifamycin class agents (e.g. rifampin, rifabutin, rifapentine)~~	~~Antibiotics~~
~~itraconazole~~	~~Antifungals~~
~~lopinavir, nelfinavir, ritonavir~~	~~Antiretrovirals, Protease Inhibitors~~
~~gemfibrozil~~	~~Hyperlipidemia~~
~~cyclosporine, valspodar~~	~~Miscellaneous~~

~~Table 15 Use with Caution – Drugs Potentially Increase/Decrease GSK2879552 Exposure~~

~~WITH CAUTION – moderate inhibitors of gut, liver or kidney transporters since levels of GSK2879552 may be decreased/increased~~	
~~Drug~~	**~~Therapeutic Area~~**
~~probenecid~~	~~Anti gout/hyperuricemia~~
~~Diflunisal, probenecid~~	~~Non-steroidal anti-inflammatory drug (NSAIDs)~~

Section 10.2.2 Drugs that may have their PKs altered by GSK2879552

PREVIOUS TEXT

The potential for pharmacokinetic interactions with drugs likely to be co-administered with GSK2879552 in vivo has not been assessed. In vitro data suggests that GSK2879552 has very low potential to inhibit CYP enzymes. GSK2879552 has also been shown to not activate human PXR which is known to induce several drug metabolizing enzymes.

These results suggest that co-administration of sensitive and narrow therapeutic index medications affected by strong inhibitors of transporters should be used with caution (Table 10).

Table 16 Use with Caution - Drugs Potentially Affected by GSK2879552

USE WITH CAUTION – Monitor for side effects since levels of these drugs may be increased. Consider dose reduction.	
Transporter Substrate	**Therapeutic Area**
atorvastatin, fluvastatin, pitavastatin,pravastatin, rosuvastatin,simvastatin	HMG-CoA Reductase Inhibitors
glyburide, repaglinide	Antidiabetics
bosentan	Pulmonary hypertension
dofetillide, pilsicainide, procainamide	Antiarrythmic
digoxin	Congestive heart failure

REVISED TEXT

The potential for pharmacokinetic interactions with drugs likely to be co-administered with GSK2879552 in vivo has not been assessed. In vitro data suggests that GSK2879552 has very low potential to inhibit CYP enzymes. GSK2879552 has also been shown to not activate human PXR which is known to induce several drug metabolizing enzymes.

GSK2879552 is not an inhibitor of human efflux transporters P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) and uptake transporters organic anion transporting polypeptide 1B1 (OATP1B1) and OATP1B3.

Co-administration of sensitive and narrow therapeutic index medications affected by strong inhibitors of OCT and MATE should be avoided when possible or monitored carefully. Examples of such drugs are dofetillide, pilsicainide and procainamide.

~~These results suggest that co-administration of sensitive and narrow therapeutic index medications affected by strong inhibitors of transporters should be used with caution (Table 10).~~

~~**Table 17 Use with Caution - Drugs Potentially Affected by GSK2879552**~~

~~**USE WITH CAUTION – Monitor for side effects since levels of these drugs may be increased. Consider dose reduction.**~~	
~~**Transporter Substrate**~~	~~**Therapeutic Area**~~
~~*atorvastatin, fluvastatin, pitavastatin,pravastatin, rosuvastatin,simvastatin*~~	~~HMG-CoA Reductase Inhibitors~~
~~*glyburide, repaglinide*~~	~~Antidiabetics~~
~~*bosentan*~~	~~Pulmonary hypertension~~
~~*dofetillide, pilsicainide, procainamide*~~	~~Antiarrythmic~~
~~*digoxin*~~	~~Congestive heart failure~~

Section 13.1.2 Part 2: Expansion Cohort

PREVIOUS TEXT

Clinical response will be defined as Objective Response Rate (ORR) (CR + PR) based on RECIST 1.1.

The null hypothesis is:

H0: RR ≤10%

The alternative hypothesis is:

HA:RR ≥25%

After 10 subjects have been enrolled to examine safety and efficacy, the number of observed unconfirmed objective responses will guide further enrolment according to the rules summarized in Figure 3. In order to stop for futility as quickly as possible as long as there is no sign of efficacy, the responses don't need to be confirmed. A maximum of **30** subjects will be enrolled in Part 2 expansion cohort. All available data will be considered in making enrollment decisions.

Figure 4 Stopping Rules for Cohort Expansion: GSK2879552

	Number of Responses					
Number of Subjects	**0**	**1**	**2**	**3**	**4**	**≥5**
10						
11						
12						
13						
14						
15						
16						
17						
18						
19						
20						
21						
22						
23						
24						
25						
26						
27						
28						
29						
30						

1. The shaded regions are the specific regions for stopping the study for futility. For instance, if there is no 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

REVISED TEXT

Clinical response will be defined as **disease control rate (DCR)** ~~Objective Response Rate (ORR)~~ (CR + PR+**SD**) based on RECIST 1.1 **at week 16**. **Biologic activity of cytostatic agents is characterized by the stabilization of the disease rather than the shrinkage of tumor lesions. As they slow or stop the growth of tumors and the developmentof metastases, DCR may be a more appropriate end point in the evaluation of cytostatic agents [Van Glabbeke M, 2009] such as GSK2879552.**

The null hypothesis is:

H0: **DCR**~~RR~~ ≤**15**~~10~~%

The alternative hypothesis is:

HA:**DCR**~~RR~~ ≥**30**~~25~~%

After **12**~~10~~ subjects have been enrolled to examine safety and efficacy, the ~~number of~~ observed unconfirmed **disease control rate at week 16** ~~objective responses~~ will guide further enrolment according to the rules summarized in Figure 3. In order to stop for futility as quickly as possible ~~as long as~~ **if** there is no sign of efficacy, ~~the~~ **confirmation of** responses **is not required** ~~don't need to be confirmed~~. A maximum of **30** subjects will be enrolled in **the** Part 2 expansion cohort. All available data will be considered in making enrollment decisions.

Figure 5 Stopping Rules for Cohort Expansion: GSK2879552

	Number of **Subjects Responding (i.e., controlled disease)** ~~Responses~~ **at 16 weeks**					
Number of Subjects	0	1	2	3	4	≥5
~~10~~						
~~11~~						
12						
13						
14						
15						
16						
17						
18						
19						
20						
21						
22						
23						
24						
25						
26						
27						
28						
29						
30						

1. The shaded regions are the specific regions for stopping the study for futility. For instance, if there is no response in fourteen subjects, then the predictive probability for success will be 5.0% or less (the futility criterion) and **consideration should be given to stop enrolment** ~~the study will be stopped~~

Section 13.2.2 Part 2: Expansion Cohort

PREVIOUS TEXT

An initial dose escalation will be used to establish the RP2D for GSK2879552. Once the final dose is confirmed, at least 10 and up to 30 subjects will be enrolled at that dose, using decision rules defined in Figure 3. The sample size and stopping rules are based on

the methodology of Lee et al. [Lee, 2008]. The assumptions underlying the design are detailed below.

H_0: $p \leq 10\%$

The alternative hypothesis is:

H_A:$p \geq 25\%$

Starting with 10 subjects and allowing for a maximum sample size of 30, this design will have a type I error rate (α) of 0.15 and 85% power. 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 20 subjects and probability of early termination (PET) is 76%. Under the alternative hypothesis, if the true response rate is 25%, the expected sample size of the design is 29.0 subjects and PET is 11.4%.

REVISED TEXT

An initial dose escalation will be used to establish the RP2D for GSK2879552. Once the final dose is confirmed, at least **12** ~~10~~ and up to 30 subjects will be enrolled at that dose, using decision rules **based on the disease control rate (DCR)** as defined in Figure 3. The sample size and stopping rules are based on the methodology of Lee et al. [Lee, 2008]. The assumptions underlying the design are detailed below.

H_0: ~~p~~**DCR**$\leq$**15** ~~10~~%

The alternative hypothesis is:

H_A:~~p~~**DCR**$\geq$**30** ~~25~~%

Starting with **12**~~10~~ subjects and allowing for a maximum sample size of 30, this design will have a type I error rate (α) of 0.15 and **80** ~~85~~% power. 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 design will have a type I error rate of less than 0.15 and a power greater than 80% for a sample size exceeding 30 subjects.** 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~~ **DCR at 16 weeks** is **15**~~10~~%, the expected sample size of the design is **24**~~20~~ subjects and probability of early termination (PET) is

75~~76~~%. Under the alternative hypothesis, if the true **DCR at 16 weeks** ~~response rate~~ is **30**~~25~~%, the expected sample size of the design is 29~~.0~~ subjects and PET is **10** ~~11.4~~%.

Section 13.5.2 Part 2: Expansion Cohort

PREVIOUS TEXT

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 13.1.2.

REVISED TEXT

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 13.1.2.

Section 13.6.1 Anti-Cancer Activity Analyse

PREVIOUS TEXT

The primary aim of Part 2 is to detect a clinically meaningful response rate of 30% relative to a 10% response rate suggesting no activity.

Response rate is defined as the percentage of subjects who achieved CR and PR among subjects who received at least one dose of treatment. Response rate and the associated 2-sided 95% exact confidence limits will be provided.

REVISED TEXT

Clinical response will be defined as disease control rate (DCR) (CR + PR + SD) based on RECIST 1.1 at week 16. The primary aim of Part 2 is to detect a clinically meaningful ~~response~~ **disease control** rate of 30% relative to a **15**~~10~~% ~~response~~ **disease control** rate suggesting no activity.

~~Response rate is defined as the percentage of subjects who achieved CR and PR among subjects who received at least one dose of treatment. Response rate and the associated 2-sided 95% exact confidence limits will be provided.~~

AMENDMENT 2

Where the Amendment Applies

Protocol Amendment 2 applies to all sites participating in the conduct of the study

Summary of Amendment

The protocol is amended to add two new dose strengths that will reduce the pill burden for subjects. The sponsor/medical monitor contact information is also updated.

List of Specific Changes

Medical Monitor and Sponsor Contact Information:

PREVIOUS TEXT

Role	Name	Day Time Phone Number	After-hours Phone/Cell/ Pager Number	Fax Number	GSK Address
Primary Medical Monitor	PPD PPD MD, PhD	PPD			GlaxoSmithKline 1250 South Collegeville Rd Mailstop UP 4210 Collegeville, PA 19426, USA PPD
Secondary Medical Monitor	PPD MD	PPD			GlaxoSmithKline 1250 South Collegeville Rd Mailstop UP 4401 Collegeville, PA 19426, USA PPD

REVISED TEXT

Role	Name	Day Time Phone Number	After-hours Phone/Cell/ Pager Number	~~Fax Number~~	GSK Address
Primary Medical Monitor	PPD **M.D.** PPD ~~MD, PhD~~	PPD			GlaxoSmithKline 1250 South Collegeville Rd Mailstop UP **4410** ~~4210~~ Collegeville, PA 19426, USA PPD
Secondary Medical Monitor	PPD **MD, PhD** PPD ~~MD~~	PPD			GlaxoSmithKline 1250 South Collegeville Rd Mailstop UP**4210** ~~4401~~ Collegeville, PA 19426, USA PPD

Section 4.1 Description of Investigational Product

PREVIOUS TEXT

Product name:	**GSK2879552 Capsule**
Formulation description:	GSK2879552 capsules contain 0.25 mg or 2 mg of GSK2879552 as parent.
Dosage form:	Capsule
Unit dose strength(s)	0.25 mg and 2 mg
Route/ Regimen	Oral The initial dosing regimen will be continuous oral daily dosing. Subjects should take their doses fasted with approximately 200 mL of water.
Physical description:	0.25 mg GSK2879552: Opaque Size 3 capsule composed of a white body and a white cap with no identifying markings containing a white to slightly coloured powder. 2 mg GSK2879552: Opaque Size 1 capsule composed of a pink body printed with two black lines and a pink cap printed with two black lines, containing a white to slightly coloured powder.

REVISED TEXT

Product name:	**GSK2879552 Capsule**
Formulation description:	GSK2879552 capsules contain 0.25 mg**, 0.5 mg, 2 mg** or **5**~~2~~ mg of GSK2879552 as parent.
Dosage form:	Capsule
Unit dose strength(s)	0.25 mg**, 0.5 mg, 2 mg** and **5**~~2~~ mg
Route/ Regimen	Oral The initial dosing regimen will be continuous oral daily dosing. Subjects should take their doses fasted with approximately 200 mL of water.
Physical description:	0.25 mg GSK2879552: Opaque Size 3 capsule composed of a white body and a white cap with no identifying markings containing a white to slightly coloured powder. **0.5 mg GSK2879552: Opaque Size 1 capsule composed of a light green body and a light green cap with no identifying markings containing a white to slightly coloured powder.** 2 mg GSK2879552: Opaque Size 1 capsule composed of a pink body printed with two black lines and a pink cap printed with two black lines, containing a white to slightly coloured powder. **5 mg GSK2879552: Opaque Size 1 capsule composed of a Swedish Orange body and a Swedish Orange cap with no identifying markings containing a white to slightly coloured powder.**

AMENDMENT 1

Where the Amendment Applies

Protocol Amendment 1 applies to all sites participating in the conduct of the study

Summary of Amendment

The original protocol is amended to incorporate changes in the starting dose, DLT criteria, and safety management following the regulatory input. One of the eligibility criteria is also modified to allow enrolment of patients without tumor tissues at baseline. Other changes are to clarify one of the exploratory objectives and endpoints, correct the investigational product storage conditions, clarify the definition of subject completion and allow flexibility in the timing of assessments.

List of Specific Changes

Section 2.1 Part 1 Dose Escalation, #1 under Exploratory

PREVIOUS TEXT

	Objectives	Endpoints
Exploratory	1. To assess feasibility of a select LSD1 target gene panel for use as a PD assay for GSK2879552	1. Change from baseline expression in LSD1 target genes in whole blood and tumor

REVISED TEXT

	Objectives	Endpoints
Exploratory	1. To assess feasibility of a select ~~LSD1 target~~ gene panel for use as a PD assay for GSK2879552	1. Change from baseline expression in **select** ~~LSD1 target~~ genes in whole blood and tumor

Section 2.2 Part 2 Expansion, #1 under Exploratory

PREVIOUS TEXT

	Objectives	Endpoints
Exploratory	1. To assess feasibility of a select LSD1 target gene panel for use as a PD assay for GSK2879552	1. Change from baseline expression in LSD1 target genes in whole blood and tumor

REVISED TEXT

	Objectives	Endpoints
Exploratory	1. To assess feasibility of a select ~~LSD1 target~~ gene panel for use as a PD assay for GSK2879552	1. Change from baseline expression in **select** ~~LSD1 target~~ genes in whole blood and tumor

Section 3.1 Discussion of Study Design, 6th paragraph

PREVIOUS TEXT

The proposed treatment schedule of GSK2879552 is continuous daily dosing. The starting dose will be 0.5 mg once daily. Alterations to the dose and schedule may be incorporated based on emerging PK, PD, and tolerability/safety data.

REVISED TEXT

The proposed treatment schedule of GSK2879552 is continuous daily dosing. The starting dose will be **0.25** ~~0.5~~ mg once daily. Alterations to the dose and schedule may be incorporated based on emerging PK, PD, and tolerability/safety data.

Section 3.2 Part 1: Dose Escalation, 1st paragraph

PREVIOUS TEXT

In Cohort 1, a single subject will receive a dose of GSK2879552 0.5 mg once daily.

REVISED TEXT

In Cohort 1, a single subject will receive a dose of GSK2879552 **0.25** ~~0.5~~ mg once daily.

Section 3.2 . Part 1: Dose-Escalation, 3rd bullet point under Number of Subjects in a Cohort

PREVIOUS TEXT

The dose escalation will continue with 1 subject per cohort until any of the following events are observed, and then each subsequent cohort will consist of a minimum of 2 subjects.

- Grade 3 neutropenia lasting over 7 days.

REVISED TEXT

The dose escalation will continue with 1 subject per cohort until any of the following events are observed, and then each subsequent cohort will consist of a minimum of 2 subjects.

- Grade 3 neutropenia ~~lasting over 7 days~~.

Section 3.2 . Part 1: Dose-Escalation, under Bayesian Prior

PREVIOUS TEXT

Table 4 Specified Prior Probability of DLT

Anticipated Dose (mg)	Median Probability of Toxicity	2.5% Quantile for Probability of Toxicity	97.5% Quantile for Probability of Toxicity
0.5	0.05	0.02	0.75
1	0.07	0.04	0.8
1.5	0.1	0.06	0.82
2	0.12	0.08	0.84
2.5	0.15	0.1	0.86
3	0.2	0.12	0.88
4	0.3	0.14	0.9
5	0.42	0.15	0.92
6	0.5	0.16	0.95
8	0.6	0.17	1
10	0.8	0.18	1
12	0.9	0.2	1

A graphical presentation of the prior is displayed in the Figure 2. In the figure, the x-axis is natural log (dose/reference dose), where the reference dose is set to 4 mg. Doses are the projected doses. Actual doses used during the conduct of the trial may vary.

REVISED TEXT

Table 4 Specified Prior Probability of DLT

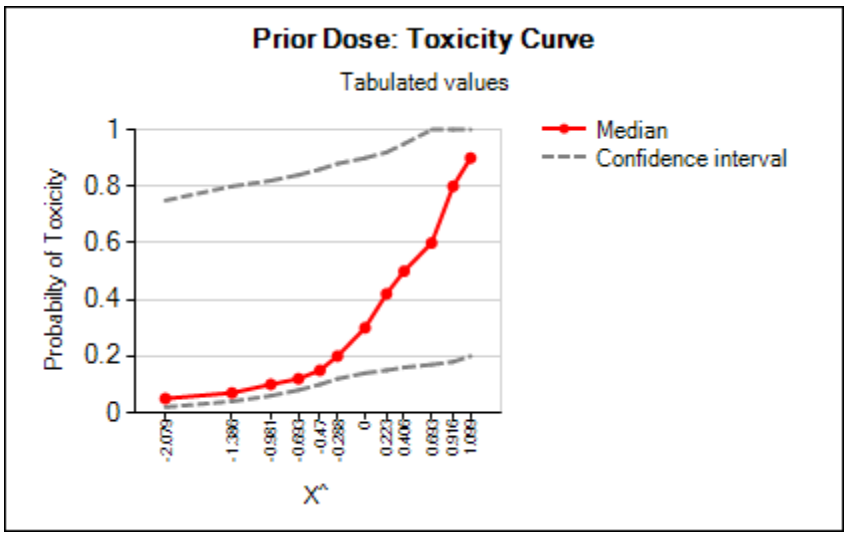
Anticipated Dose (mg)	Median Probability of Toxicity	2.5% Quantile for Probability of Toxicity	97.5% Quantile for Probability of Toxicity
0.25	**0.02**	**0.01**	**0.73**
0.5	0.05	0.02	0.75
1	0.07	0.04	0.8
1.5	0.1	0.06	0.82
2	0.12	0.08	0.84
2.5	0.15	0.1	0.86
3	0.2	0.12	0.88
4	0.3	0.14	0.9
5	0.42	0.15	0.92
6	0.5	0.16	0.95
8	0.6	0.17	1
10	0.8	0.18	1
12	0.9	0.2	1

A graphical presentation of the prior is displayed in the Figure 2. In the figure, the x-axis is natural log (dose/reference dose), where the reference dose is set to **4 3** mg. Doses are the projected doses. Actual doses used during the conduct of the trial may vary.

Section 3.2 . Part 1: Dose-Escalation, under Bayesian Prior

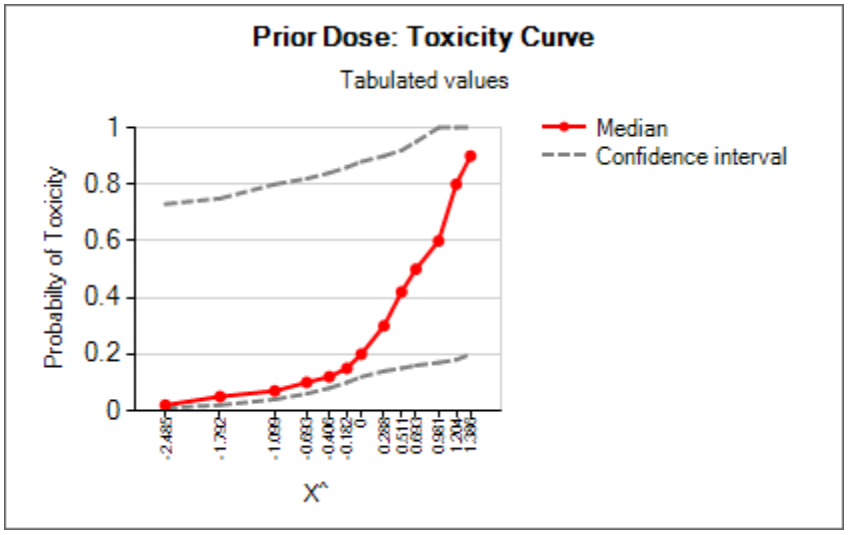
PREVIOUS FIGURE

Figure 2 Prior Distribution For The Probability of DLT Given Dose



REVISED FIGURE

Figure 2 Prior Distribution For The Probability of DLT Given Dose



Section 3.5 Dose-Limiting Toxicity, 2nd bullet point

PREVIOUS TEXT

- Grade 4 neutropenia > 7 days duration
- Febrile neutropenia (defined as concurrent Grade 4 neutropenia and fever >38.5°C and lasting >24 hr)

REVISED TEXT

- Grade ~~4~~ neutropenia ~~> 7 days duration~~
- **Grade 3 neutropenia > 7 days duration**
- Febrile neutropenia **as defined by CTCAE v.4** ~~(defined as concurrent Grade 4 neutropenia and fever >38.5°C and lasting >24 hr)~~

Section 3.9.2.2 Starting Dose, under Conclusion

PREVIOUS TEXT

The proposed starting dose of 0.5 mg was selected with the goal of administering a pharmacologically active dose that is reasonably safe to use, in accordance with ICH S9. This dose is slightly lower than the predicted human MABEL dose range based on exposures in dogs and rats (0.6 to 1.6 mg) and less than half of the predicted human MABEL dose based on human equivalent dose calculation from the rat and dog studies (1.1 mg).

The starting dose of 0.5 mg daily has a predicted total exposure of 22.8 ng.h/mL with a Cmax of 2.8 ng/mL (free AUC of 10.4 ng.h/mL and free Cmax of 1.3 ng/mL)

REVISED TEXT

The proposed starting dose of **0.25** ~~0.5~~ mg was selected with the goal of administering a pharmacologically active dose that is reasonably safe to use, in accordance with ICH S9. ~~This dose is slightly lower than the predicted human MABEL dose range based on exposures in dogs and rats (0.6 to 1.6 mg) and less than a quarterhalf of the predicted human MABEL dose based on human equivalent dose calculation from the rat and dog studies (1.1 mg).~~

The starting dose of **0.25** ~~0.5~~ mg daily has a predicted total exposure of **11.4**~~22.8~~ ng.h/mL with a Cmax of **1.4**~~2.8~~ ng/mL (free AUC of **5.2**~~10.4~~ ng.h/mL and free Cmax of **0.65**~~1.3~~ ng/mL)

Section 3.12.3 Management of Neutropenia, 2nd bullet point

PREVIOUS TEXT

- Grade 4 neutropenia lasting >7 days

REVISED TEXT

- ~~•~~ Grade 4 neutropenia ~~lasting >7 days~~
- **Grade 3 neutropenia lasting >7 days**

Section 4.2 Handling/Storage of GSK2879552, GSK Investigational Product, 2nd paragraph under Storage

PREVIOUS TEXT

GSK2879552 is to be stored at a temperature range of 2-8°C (36-46°F), protected from light. Maintenance of a temperature log (manual or automated) is required.

REVISED TEXT

GSK2879552 is to be stored at a temperature range of 2-8°C (36-46°F), protected from ~~light~~**moisture**. Maintenance of a temperature log (manual or automated) is required.

Section 5.2.1 Inclusion Criteria #6

PREVIOUS TEXT

6. Tumor tissue requirements:

    - Availability of archival tissue, or willingness to undergo fresh biopsy at baseline.

    - Enrollment in PK/PD cohort may be limited to subjects with disease amenable to pre- and post-dose biopsies, and willingness to undergo biopsy.

REVISED TEXT

6. Tumor tissue requirements:

    - Availability of archival tissue, or willingness to undergo fresh biopsy at baseline. **Patients without baseline tissue may be enrolled with approval from the GSK medical monitor.**

    - Enrollment in PK/PD cohort may be limited to subjects with disease amenable to pre- and post-dose biopsies, and willingness to undergo biopsy.

Section 6.2 Subject Completion Criteria

PREVIOUS TEXT

A subject will be considered to have completed the study if they complete screening assessments, at least 28 days of study treatment(s) and the post-treatment follow-up visit.

REVISED TEXT

In Part 1, a~~A~~ subject will be considered to have completed the study if they complete screening assessments, at least 28 days of study treatment(s) and the post-treatment follow-up visit.

In Part 2, a subject will be considered to have completed the study if they are followed until disease progression, death or start of new anticancer treatment.

Section 7 Study Assessments and Procedures

NEW TEXT added after the 3rd paragraph

If the blood draw is done first, there should be at least 15 minute interval before the vital signs and 12-lead ECGs measurements are taken.

Section 7.1 Time and Events Table: Part 1 Dose Escalation, footnote 16

PREVIOUS TEXT

Day 15 (± 3 days window) biopsy should be collected at least 24 hours after the previous dose.

REVISED TEXT

Day 15 (± 3 days window) biopsy ~~should~~ **can** be collected **pre- or post-dose.** ~~at least 24 hours after the previous dose.~~

Section 7.1 Time and Events Table: Part 2 Expansion Cohort, footnote 10

PREVIOUS TEXT

Day 15 (± 3 days window) biopsy should be collected at least 24 hours after the previous dose.

REVISED TEXT

Day 15 (± 3 days window) biopsy ~~should~~ **can** be collected **pre- or post-dose.** ~~at least 24 hours after the previous dose.~~

Appendix 6 Simulation Results of N-CRM in Dose Escalation Phase

PREVIOUS TEXT

The parameters (s.d.) of the explicit distribution are α= -0.3738(1.6211), ln(β)= 0.4401 (0.239), and ρ=-0.9773 where α and ln(β) are distributed as bivariate normal with correlation ρ.

Table 11 Simulation Results Under Various Scenarios

Dose (mg)	Scenario 1: Steep Dose-Toxicity Curve		Scenario 2: Moderate Dose-Toxicity Curve		Scenario 3: Shallow Dose-Toxicity Curve	
	True DLT Rate	Percent of Trials Selecting Dose as MTD (%)	True DLT Rate	Percent of Trials Selecting Dose as MTD (%)	True DLT Rate	Percent of Trials Selecting Dose as MTD (%)
0.5	0.05	4.3	0.05	5	0.02	1
1	0.07	6	0.07	5.1	0.04	2.4
1.5	0.12	11.6	0.1	7.1	0.06	1.5
2	0.16	16.2	0.15	11.3	0.08	2.5
2.5	0.23	17.4	0.17	9.4	0.1	2.9
3	0.25	33.7	0.2	24.4	0.12	16.2
4	0.35	10.3	0.24	16	0.14	14.4
5	0.6	0.5	0.25	8.2	0.17	12.9
6	0.8	0	0.28	12	0.19	28.6
8	0.9	0	0.38	1.4	0.21	12.3
10	0.92	0	0.5	0	0.27	4.1
12	0.95	0	0.6	0.1	0.4	1.2

The average sample size over the 1000 clinical trials simulated under Scenarios 1-3 was 19.2, 19.9, and 22.3 respectively.

REVISED TEXT

The parameters (s.d.) of the explicit distribution are α= **-0.9917 (1.382)** ~~0.3738(1.6211)~~, ln(β)= **0.3615 (0.8838)**, ~~0.4401 (0.239)~~ and ρ= **-0.6808** ~~0.9773~~ where α and ln(β) are distributed as bivariate normal with correlation ρ.

Table 11 Simulation Results Under Various Scenarios

Dose (mg)	Scenario 1: Steep Dose-Toxicity Curve		Scenario 2: Moderate Dose-Toxicity Curve		Scenario 3: Shallow Dose-Toxicity Curve	
	True DLT Rate	Percent of Trials Selecting Dose as MTD (%)	True DLT Rate	Percent of Trials Selecting Dose as MTD (%)	True DLT Rate	Percent of Trials Selecting Dose as MTD (%)
0.25	**0.03**	**1**	**0.03**	**1.1**	**0.01**	**0.1**
0.5	0.05	**1.9** ~~4.3~~	0.05	**1.3** ~~5~~	0.02	**0.3** ~~1~~
1	0.07	**3.4** ~~6~~	0.07	**2.8** ~~5.1~~	0.04	**0.9** ~~2.4~~
1.5	0.12	**9.5** ~~11.6~~	0.1	**6.1** ~~7.1~~	0.06	**1.2** ~~1.5~~
2	0.16	**13.4** ~~16.2~~	0.15	**9.3** ~~11.3~~	0.08	**1.7** ~~2.5~~
2.5	0.23	**17.8** ~~17.4~~	0.17	**13.1** ~~9.4~~	0.1	**6** ~~2.9~~
3	0.25	**46** ~~33.7~~	0.2	**41.5** ~~24.4~~	0.12	**37.3** ~~16.2~~
4	0.35	**6.9** ~~10.3~~	0.24	**14.5** ~~16~~	0.14	**14.9** ~~14.4~~
5	0.6	**0.1** ~~0.5~~	0.25	**6.1** ~~8.2~~	0.17	**11.7** ~~12.9~~
6	0.8	0	0.28	**3.8** ~~12~~	0.19	**15.3** ~~28.6~~
8	0.9	0	0.38	**0.2** ~~1.4~~	0.21	**6.1** ~~12.3~~
10	0.92	0	0.5	**0.2** ~~0~~	0.27	**2.8** ~~4.1~~
12	0.95	0	0.6	**0** ~~0.1~~	0.4	**1.7** ~~1.2~~

The average sample size over the 1000 clinical trials simulated under Scenarios 1-3 was **18.6, 19.3,** ~~19.2, 19.9,~~ and **21** ~~22.3~~ respectively.