Division: Worldwide Development
Information Type: Protocol Amendment

Title:	A phase I open-label, dose escalation study to investigate the safety, pharmacokinetics, pharmacodynamics and clinical activity of GSK2879552 given orally in subjects with relapsed/refractory acute myeloid leukemia

Compound Number: GSK2879552

Development Phase: I

Effective Date: 06-OCT-2017

Protocol Amendment Number: 5

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Revision Chronology

GlaxoSmithKline Document Number	**Date**	**Version**
2013N163643_00	2014-MAY-02	Original
2013N163643_01	2014-OCT-01	Amendment No. 1
DLT criteria are revised according to the regulatory agency request. PD sampling requirements and subject populations are also clarified.		
2013N163643_02	2015-MAY-27	Amendment No. 2
Additional eligibility criteria and safety monitoring measures are put in place to address recent safety findings.		
2013N163643_03	2016-MAY-09	Amendment No. 3
A combination arm with ATRA is added. One of the Dose Limiting Toxicities criteria has been revised according to the NCI criteria. Pharmacodynamic/exploratory sample collection and processing have been changed. Pharmacogenetic sample has been added. The criteria for Progressive Disease and Stable Disease have been added in the response criteria. Concomitant medications have been updated.		
2013N163643_04	2017-MAY-02	Amendment No. 4
Add language to include a stopping rule that halts enrollment upon the occurrence of any encephalopathy, unless clearly attributable to central nervous system disease involvement or intercurrent illness.		
2013N163643_05	2017-OCT-06	Amendment No. 5
Modify renal entrance criteria to align with regulatory agencies. Add additional dose adjustment language for hematologic toxicities. Optimize DLT criteria and safety management for retinoic acid syndrome. Add de-escalation language for both GSK2879552 and ATRA. Move PD secondary objective and endpoint to exploratory. Clarified definition of objective response rate (ORR). Included duration of response (DoR), time to response (TTR) and progression-free survival (PFS) as the secondary objectives in the expansion cohort. Updated statistical section to clarify data from Part 1 and Part 2 may be combined for analyses if appropriate. Deleted “dose limiting toxicity” as the safety endpoint of expansion cohort. Update and clarify inconsistencies within protocol: update dose escalation committee language to align with new standard language, define the “baseline” MOCA, baseline assessment of vitamin B12, TSH, free T3 or free T4 added at screening visit, define time window for informed consent, clarify urine metabolite and PK sample collections, add morphology to analysis of bone marrow aspirates, clarify use of azoles permitted on study and other administrative updates.		

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06OCT2017

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Regulatory Agency Identifying Number(s):

Compound Number	IND Number
GSK2879552	121577

INVESTIGATOR PROTOCOL AGREEMENT PAGE

For protocol number 200200

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)
AML	Acute Myeloid Leukemia
ALP	Alkaline Phosphatase
ALT	Alanine aminotransferase
ANC	Absolute Neutrophil Count
AST	Aspartate aminotransferase
ATRA	All-Trans Retinoic Acid
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
CV	Coefficient of Variance
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
FACTS	Fixed and Adaptive Clinical Trial Simulator
FSH	Follicle Stimulating Hormone
FTIH	First Time In Humans

GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
GGT	Gamma Glutamyl Transferase
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
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
PARP	poly ADP ribose polymerase
PCI	Potential Clinical Importance
PCR	Polymerase Chain Reaction
PD	Progressive Disease or Pharmacodynamic
PI	Principal Investigator
PK	Pharmacokinetic
PR	Partial Response
PT	Prothrombin Time
PTS	Platform Technology and Science
PTT	Partial Thromboplastin Time
QTc	Corrected QT interval duration
QTcF	QT interval corrected for heart rate by Fridericia's formula
RAP	Reporting and Analysis Plan
RBC	Red Blood Cells
RNA	Ribonucleic acid
Ro	Accumulation ratio
RP2D	Recommended Phase 2 Dose
SAE	Serious Adverse Event(s)
SCLC	Small Cell Lung Cancer
SD	Standard Deviation
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 acute myeloid leukemia
PROTOCOL NUMBER	200200
CLINICAL PHASE	I
COMPOUND(S)	GSK2879552
STUDY RATIONALE	GSK2879552 is a potent, selective, mechanism-based inactivator of LSD1/CoREST activity. Preclinical studies have shown that GSK2879552 induces the expression of putative LSD1 target genes and has potent, predominantly cytostatic, anti-proliferative activity in AML cell lines. Changes in the expression of cell surface markers suggest that GSK2879552 treatment results in a pro-differentiation effect in both in vitro and in vivo studies. The proposed Phase I study will evaluate the safety and tolerability, pharmacokinetics, pharmacodynamics, and clinical activity to determine the recommended Phase 2 Dose (RP2D) and regimen of GSK2879552, alone or in combination with ATRA, given orally in adult subjects with relapsed/refractory AML.

STUDY OBJECTIVES, ENDPOINTS AND HYPOTHESES

PART 1: Escalation Cohort		
	Objectives	**Endpoints**
Primary	1. To determine the safety, tolerability, MTD and/or RP2D and regimen of GSK2879552, alone or in combination with ATRA, given orally in adult subjects with AML.	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 PK of GSK2879552, alone or in combination with ATRA, after single- and repeat-dose oral administration. 2. To evaluate clinical response after treatment with GSK2879552, alone or in combination with ATRA. 3. To characterize the PK of ATRA in combination with 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, tmax, t½ (terminal phase and/or effective half-life), accumulation ratio, and time invariance. 2. Objective response rate defined as the percentage of subjects achieving complete remission (CR), partial remission (PR), CRp (as per CR but platelet count <100 x 109/L) and morphologic leukemia-free state per response criteria (Cheson, 2003). 3. ATRA PK parameters following single and repeat-dose administration of ATRA and GSK2879552, including AUC, Cmax, tmax, t½ (terminal phase).
Exploratory	1. To explore markers of differentiation (including morphology assessment) in response to GSK2879552, alone or in combination with ATRA. 2. To investigate the mechanism of action and indicators of sensitivity and resistance to GSK2879552, alone or in combination with ATRA. 3. To evaluate the relationship between GSK2879552 exposure, alone or in combination with ATRA, and safety/efficacy/ PD parameters 4. To characterize the metabolite profile of GSK2879552 after oral single and repeat-dosing in some subjects 5. To determine the amount of GSK2879552 excreted in urine after oral single and repeat-dosing in some subjects treated with GSK2879552	1. Change from baseline expression in cell surface markers in AML cells derived from bone marrow and/or peripheral blood. 2. Analysis of morphology, DNA, RNA and/or protein markers in blasts cells in bone marrow aspirates and/or peripheral blood. 3. Relationship between GSK2879552 exposure markers (e.g. dose, concentration, Cmax, Cmin or AUC (0-tau)) and safety/efficacy/PD parameters. PD parameters assessed by change from baseline in select biomarkers, e.g. CD86 and CD11b 4. GSK2879552 metabolites in plasma and/or urine 5. Concentration of GSK2879552 in urine

	6. To investigate the relationship between genetic variants in candidate genes,PK and safety profile of GSK2879552, alone or in combination with ATRA.	measured with an investigational bio-analytical method and extrapolated to total amount excreted in urine over time 6. Pharmacogenomic (PGx) study using buccal samples
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 alone or in combination with ATRA, at the respective RP2D given orally in adult subjects with AML.	1. Objective response rate defined as the percentage of subjects achieving complete remission (CR), partial remission (PR), CRp (as per CR but platelet count <100 x 109/L) and morphologic leukemia-free state) per response criteria (Cheson, 2003)
Secondary	1. To evaluate the safety and tolerability of respective RP2D of GSK2879552, alone or in combination with ATRA. 2. To characterize the population PK of GSK2879552, alone or in combination with ATRA. 3. To evaluate clinical activity in terms of duration of response (DoR), time to response (TTR) and progression-free survival (PFS)	1. AEs, SAEs, dose reductions or delays, withdrawals due to toxicities and changes in safety assessments (e.g., laboratory parameters, vital signs, ECGs, 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. Duration of response (DoR), defined as the time from first documented evidence of PR or better until disease progression (PD) or death, among responders, i.e. confirmed PR or better.

		Time to Time to Response is defined as the time from first dose to the first documented evidence of response (PR or better). Progression-free survival (PFS), defined as the time from first dose until the earliest date of disease progression (PD), or death due to any cause.
Exploratory	1. To investigate the mechanism of action and indicators of sensitivity and resistance to GSK2879552, alone or in combination with ATRA. 2. To evaluate the exposure response (PK/PD) relationship between GSK2879552, alone or in combination with ATRA and safety/efficacy/PD parameters. 3. To investigate the relationship between genetic variants in candidate genes, PK and safety profile of GSK2879552, alone or in combination with ATRA.	1. Analysis of morphology, DNA, RNA and/or protein markers in blast cells from bone marrow aspirate and/or peripheral blood sample 2. Relationship between GSK2879552 exposure markers (e.g. dose, concentration, Cmax or AUC (0-tau)) and safety/efficacy/PD parameters. PD parameters assessed by change from baseline in select biomarkers, e.g. CD86 and CD11b 3. Pharmacogenomic (PGx) study using buccal samples
Hypothesis	Clinical response will be defined as Objective Response Rate (% of subjects achieving CR, PR, CRp or morphologic leukemia-free state) per response criteria. The null hypothesis is: H_0: RR ≤10% The alternative hypothesis is: H_A: ≥30%	

STUDY DESIGN	This is a Phase I, open-label, multi-center, non-randomized, 2-part study. Part 1 is a dose escalation phase to determine the MTD and/or RP2D for GSK2879552, alone or in combination with ATRA 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 safety, tolerability, PK and PD. Once MTD and/or RP2D is identified, an expansion cohort (Part 2) of up to 30 subjects will be enrolled to further evaluate the efficacy and tolerability of GSK2879552, alone or in combination with ATRA in subjects with relapsed/refractory AML. The proposed treatment schedule of GSK2879552 is continuous daily dosing. The starting dose for GSK2879552 mono therapy arm will be 0.25 mg/day or the highest dose determined to be safe in the ongoing SCLC study, whichever is higher with a maximum of 1 mg/day (see Section 1.4.3.2 for details). The starting dose of GSK2879552 in combination with ATRA will be 1-2 dose levels below the highest dose determined to be safe in the GSK2879552 mono therapy arm in this study, i.e., 2 mg once daily. Alterations to the dose and schedule may be incorporated based on emerging PK, PD, and tolerability data. Dose reduction and/or truncated dose scheduling may be considered for subjects with recurrent/ persistent toxicity or according to the institutional guideline.
NUMBER OF SUBJECTS	It is estimated that approximately 55 subjects will be enrolled into Part 1 dose-escalation and additional 25 subjects into PK/PD expansion cohorts in GSK2879552 mono therapy and combination with ATRA arm. Up to 60 subjects will be enrolled in Part 2 (expansion cohort) of GSK2879552 alone and combination with ATRA arm. A total of approximately 140 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. ≥18 years of age and provided signed written informed consent.

2. Subjects must have relapsed/refractory acute myeloid leukemia by WHO classification for which no standard therapies are available or anticipated to result in a durable remission. FAB subtype M3 will be excluded.

3. Subjects ≥ 60 years of age with AML who are not candidates for or have refused standard chemotherapy.

4. Subjects who have previously received an autologous stem cell transplant are allowed if a minimum of 3 months has elapsed from the time of transplant and the subject has recovered from transplant-associated toxicities prior to the first dose of GSK2879552.

5. Subjects with a history of allogeneic stem cell transplant are eligible for study participation provided the following eligibility criteria are met:

    - transplant was >60 days prior to study enrollment.
    - subject has not taken immunosuppressive medications (including but not limited to: cyclosporine, tacrolimus, methotrexate, or mycophenolate mofetil) for at least 1 month
    - no signs or symptoms of graft versus host disease other than Grade 1 skin involvement
    - no active infection

6. Eastern Cooperative Oncology Group (ECOG) performance status of 0-1.

7. Subjects must be stable and, in the opinion of the investigator, be expected to complete 4 week treatment period.

8. Able to swallow and retain orally administered medication and does not have any clinically significant gastrointestinal abnormalities that may alter absorption such as malabsorption syndrome or major resection of the stomach or bowels,

9. 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).

10. Adequate baseline organ function defined by:

System	Laboratory Values
Hematologic	
White blood cell count (absolute)	≤30,000/uL
Coagulation assays (PT/INR and aPTT)	≤1.3 X ULN
Hepatic	
Total bilirubin	≤ 1.5 X ULN[1]
ALT and AST	≤2.5 × ULN
Renal	
Calculated creatinine clearance by Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (Appendix 3) or measured from 24hr urine	≥ 40 mL/min
Cardiac	
Ejection fraction	≥ LLN by Echocardiogram (ECHO) or MUGA
Lipid (ATRA combination ONLY)	
Triglyceride (fasting)	≤ 300 mg/dL
Cholesterol (fasting)	≤ 300 mg/dL

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

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.

11. 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 (Section 11.1), during the study and for 7 days (GSK2879552 mono therapy) or 30 days (combination with ATRA), following the last dose of study treatment.

12. Men with a female partner of childbearing potential must have either had a prior vasectomy or agree to use effective contraception (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.

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

1. Active Human Immunodeficiency Virus (HIV), Hepatitis B Virus (HBV) or Hepatitis C Virus (HCV) infections at the time of screening. Subjects with laboratory evidence of HCV clearance (HCV RNA PCR is negative) may be enrolled.
2. History of or concurrent malignancy of solid tumours, except for below.

   Exception: Subjects who have been disease-free for 5 years, or subjects with a history of completely resected non-melanoma skin cancer or successfully treated in situ carcinoma are eligible. Subjects with second malignancies that are indolent or definitively treated may be enrolled even if less than 5 years have elapsed since treatment. Consult GSK Medical Monitor if unsure whether second malignancies meet requirements specified above
3. Currently receiving cancer therapy (chemotherapy, radiation therapy, immuno- therapy, biologic therapy, hormonal therapy, surgery, and/or tumour embolization)

   Note: HYDREA (hydroxyurea) will be allowed.
4. Received major surgery, radiotherapy, or immunotherapy within 4 weeks of GSK2879552 administration.
5. Prior treatment with temozolomide, dacarbazine or procarbazine
6. Prior treatment with poly ADP ribose polymerase (PARP) inhibitors (e.g., olaparib, ABT-888)
7. Screening Montreal Cognitive Assessment (MOCA) score of 22 or lower
8. Evidence of severe or uncontrolled systemic diseases (e.g., severe/chronic infection, unstable or uncompensated respiratory, 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
9. Current active liver or biliary disease (with the exception of Gilbert's syndrome or asymptomatic gallstones, liver

metastases or otherwise stable chronic liver disease per investigator's assessment).

10. Patients at risk of non-AML related major bleeding (e.g. recent GI hemorrhage or neurosurgery).
11. Symptomatic or untreated CNS leukemia. Subjects are permitted to enroll if previously treated for CNS disease, free of symptoms at the time of screening, and have not required intrathecal chemotherapy at least 1 month prior to study Day 1.
12. 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, Appendix 2).

    - History of acute coronary syndromes (including unstable angina and myocardial infarction), coronary angioplasty, or stenting within the past 3 months.
    - Baseline QTc interval using Fridericia'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.
13. Administration of an investigational drug within 14 days or 5 half-lives, whichever is ***shorter*** with a minimum of 14 days preceding the first dose of study treatment(s) in this study.
14. Have a known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to GSK2879552 or LSD1 inhibitors that contraindicates their participation.
15. Lactating female.
16. 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.
17. Current use of a prohibited medication including anticoagulants or platelet inhibitors (Section 10.2) or expected to require any of these medications during treatment with the investigational drug.

	18. Previous treatment with GSK2879552 **For ATRA Combination arm ONLY** 19. Known hypersensitivity to ATRA, parabens (preservatives in the gelatin capsule) or other retinoids. 20. ATRA capsule contains sorbitol. Subjects with rare hereditary problems of fructose intolerance are excluded. 21. History of seizure within 12 months or brain tumor (primary) 22. History of taking mega-dose vitamin A (>25,000 USP U/day) within 3 months from the dosing start.
STUDY TREATMENT DOSE/ROUTE/REGIMEN	
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 and ATRA 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 for GSK2879552 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 blood samples for PD, exploratory and biomarker will be collected at planned visits as listed in the Time and Event Table. For subjects in the highest dose of Part 1 PK/PD expansion cohort, additional blood samples for GSK2879552 metabolite profiling will be collected on Day 1 and Day 15 at the same time points as listed in the Time and Event Table (Section 7.1). In addition, pre-dose urine sample will be collected on Day 1, and 24 hour urine sample will be collected starting from post-dose on Days 1 and 15 until dosing on Days 2 and 16, respectively. For all subjects in Part 2 expansion cohorts, serial blood samples for analysis of GSK2879552 and ATRA 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

	and every 4 week thereafter. Pre-dose blood samples for PD, exploratory and biomarker will be collected at planned visits as listed in the Time and Event Table. 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 assessments will be made by physical examination and laboratory evaluation. Bone marrow aspiration/biopsy will be performed as stated in the Time and Event Table (Section 7.1). Response criteria are listed in Appendix 6. Laboratory evaluation will include a complete blood count with differential and blood smear to measure blasts.
TRANSLATIONAL RESEARCH	Blood and/or bone marrow aspirates will be collected at various times, throughout the study in order to support research aimed at understanding the biological effect of GSK2879552 alone or in combination with ATRA in AML as well as identifying indicators of sensitivity or resistance
STATISTICAL METHODS	In Part 1 Dose Escalation Phase, No formal statistical hypotheses are being tested. The sample size depends on the actual number of cohorts of subjects treated. 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. The primary goal of Part 2 is to detect a clinically meaningful response rate (defined as the percentage of subjects that have achieved a CR, CRp, PR or a morphologic leukemia-free state) of 30% relative to a 10% response rate suggesting no activity. Symbolically, the null hypothesis is: H_0: $_{RR} \leq 10\%$ The alternative hypothesis is: H_A:$_{RR} \geq 30\%$ 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.

After 10 subjects have been enrolled to examine safety and efficacy, the number of observed confirmed objective responses will guide further enrolment according to the rules summarized in Figure 3. A maximum of **30** subjects will be enrolled at the respective RP2D for GSK2879552 mono therapy and in combination with ATRA. All available data will be considered in making enrollment decisions.

Analysis Population

All Treated 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.

1. INTRODUCTION

1.1. Background – LSD1

LSD1 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.

Multiple roles for LSD1 have been described in the literature. 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 plays a critical role in normal hematopoietic differentiation by mediating repression of a key gene expression program in hematopoietic progenitors [Saleque, 2007]. In AML, LSD1 knockdown or small molecule inhibition has a pro-differentiation effect both in vitro and in vivo [Harris, 2012]. Sub-lethally irradiated (syngeneic) mice transplanted with LSD1 knockdown mouse derived MLL-AF9 AML cells showed a prolonged survival relative to mice engrafted with control cells [Harris, 2012]. In a separate study, LSD1 inhibition extended survival of mice transplanted with mouse derived MLL-AF9 leukemia cells. In this study, mice were treated for 17 days with an LSD1 inhibitor and a survival benefit was apparent for weeks beyond the treatment duration [Kruger, 2013]. Together these studies suggest LSD1 is a regulator of expression programs and its role may depend on the complex in which it resides as well as the susceptibility of specific genes to transcriptional modulation.

GSK2879552 is a potent, selective inhibitor of LSD1/CoREST. GSK2879552 causes an increase in histone 3 lysine 4 di-methylation (H3K4me2) at promoters of putative LSD1 target genes and has predominantly cytostatic effect on small cell lung cancer (SCLC) and acute myeloid leukemia (AML) cell lines (Refer to the Investigator Brochure (IB) for GSK2879552 [GlaxoSmithKline Document Number 2013N168888_03).

1.2. Unmet Medical Needs for Relapsed/Refractory AML

Acute myeloid leukemia (AML) is the most common acute leukemia in adults with a median age at diagnosis of 67 years old. No standard regimen exists for the treatment of patients with relapsed AML, particularly in patients with the first remission duration of less than 1 year. For refractory AML patients, overall survival at 1 year is less than 10% and the median survival is a few months only [Schmid, 2006]. Older patients with AML have significant comorbidities, a poorer performance status, more unfavorable cytogenetic abnormalities, and a higher incidence of secondary AML than their younger counterparts [Klepin, 2009]. The median overall survival of elderly AML patients remains on the order of months with few long-term survivors [Dombret, 2008]. There is a clear unmet medical need for treatment options in relapsed/refractory AML and elderly

AML patients who are not eligible for chemotherapy. Agents like decitabine, which alter the chromosomal methylation status, have been approved for the treatment of advanced myelodysplastic syndromes and AML in elderly patients who are not eligible for induction chemotherapy. GSK2879552, which can induce differentiation in AML cell lines has the potential to be an effective treatment for AML.

1.3. GSK2879552

1.3.1. GSK2879552 - Background

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 mechanism-based nature of the inhibition by which the enzyme-bound FAD cofactor becomes irreversibly covalently modified. For an irreversible inhibitor, the inhibition is predicted to be relieved upon new protein synthesis. In vitro results suggest that the half-life ($t_{1/2}$) of LSD1 protein is greater than 24 hrs. The growth inhibitory effects of GSK2879552 were assessed in a diverse panel of cell lines representing a range of tumor types. The activity was specific primarily to SCLC and AML cell lines suggesting that GSK2879552 is not a generally cytotoxic agent.

GSK2879552 induces the expression of putative LSD1 target genes and has potent, predominantly cytostatic, anti-proliferative activity in sensitive SCLC (median EC_{50} = 25 nM, range 2 – 240 nM)) and AML (median EC_{50} = 26 nM, range = 3 – 102 nM) cell lines. In a 6 day assay, GSK2879552 has potent anti-proliferative activity in 20 of 29 cell lines representing multiple sub-types of AML (M0 - M7). Eight of the 9 lines resistant in the 6 day assay were further characterized and are sensitive in an extended duration 10 day assay, suggesting that prolonged LSD1 inhibition may result in greater efficacy. Treatment of bone marrow cells derived from AML patients revealed inhibition of AML blast colony formation, demonstrating that the anti-proliferative activity of GSK2879552 may extend beyond established cell lines.

Consistent with literature reports [Harris, 2012], a pro-differentiation effect was observed upon GSK2879552 treatment of AML cells both in vitro and in vivo. *In vitro*, GSK2879552 treatment resulted in growth inhibition of AML cell lines as well as increased expression of differentiation associated cell surface markers (CD11b EC_{50} = 7.1 nM and CD86 EC_{50} = 13 nM at 24 hours in SKM-1) across cell lines representing multiple subtypes of AML.

In vivo studies using MV-4-11 AML cells engrafted into irradiated mice demonstrated an increase in expression of cell surface markers by 8 hours that continued to increase through 72 hours following daily administration of GSK2879552 (CD86, EC_{50} = 1.4 mg/kg and CD11b, EC_{50} = 2.1 mg/kg at 24 hrs). The pro-differentiation response observed in the MV-4-11 model provides evidence that GSK2879552 had biological efficacy in vivo, however, this did not translate into increased survival in this model. In a MLL-$AF9^+$ murine model of AML, treatment with GSK2879552 led to a significant delay in leukemia onset in treated mice relative to vehicle treated controls.

In the mouse MV-4-11 AML engraftment model, severe thrombocytopenia with bleeding resulted in increased morbidity. Macroscopic and histopatholgic examination suggested that the severity of the thrombocytopenia was likely due to the combined effects of irradiation, engraftment of injected AML cells into marrow and multiple other organs, and the effect of GSK2879552 on platelets.

1.3.2. LSD1 inhibitor and All-Trans Retinoic Acid

Retinoic acid regulates normal embryonic cell differentiation and development of many tissues including the brain, lungs, and other organs [Niederreither, 2008]. All-*trans*-retinoic acid (ATRA) induced differentiation has been explored in cancers that appear to retain stem-like cells as well as those in which molecular features of differentiation have been characterized. Sarcoma cells including osteosarcoma and rhabdomyosarcoma display morphological changes and alterations in molecular markers consistent with osteoblast and myogenic differentiation in response to ATRA [Luo, 2010; Barlow, 2006]. The presence of cancer stem cells in glioblastoma has been associated with therapeutic resistance and tumor initiating potential. Pre-clinical models have been developed to reveal this subpopulation and, in this setting, glioblastoma cells exposed to ATRA undergo reduced proliferation and self-renewal, differentiation into glial and neuronal lineages, and ultimately apoptosis [Karsy, 2010; Choschzick, 2014]. Despite the pre-clinical data suggesting ATRA treatment can promote differentiation in a number of tumor models, ATRA therapy has not proven efficacious in solid tumors clinically.

ATRA has been used successfully in hematological malignancies and is the current standard of care for acute promyelocytic lekemia (APL), a subtype of acute myeloid leukemia (AML). ATRA therapy promotes complete remission in more than 90% of patients through differentiation of leukemic blasts, however, this efficacy has not translated to non-APL subtypes of AML. The selective response to ATRA in APL is associated with the expression of PML-RAR, the fusion protein that results from chromosomal translocation t(15,17)(q22;q21). In this setting, ATRA can induce expression changes in genes associated with myeloid differentiation through relief of repression of the myeloid expression program imposed by the PML-RAR fusion protein [Melnick, 1999; Johnson, 2015]. These data suggest that targeting a differentiation mechanism may also provide an effective therapy in AML if expression of myeloid gene programs can be achieved.

Inhibition of LSD1 by GSK2879552 can promote differentiation in AML cells as evaluated by several measures including gene expression and cell surface marker changes consistent with myeloid differentiation. LSD1 has been implicated in regulation of the ATRA driven response through increases in H3K4me2 at key genes involved in the ATRA pathway [Schenk, 2012; Sakamoto, 2014]. Given the overlapping mechanism associated with each single agent, and the potentiating effect of LSD1 inhibition on the ATRA pathway, treatment of AML may demonstrate greater response to ATRA when combined with GSK2879552.

1.3.3. Pre-Clinical PK and Safety of GSK2879552

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 and a comparison of systemic exposures achieved in these studies are presented in the IB for GSK2879552 [GlaxoSmithKline Document Number2013N168888_03]. A summary of principal toxicological findings are discussed below.

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 maturation block of 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)].

1.3.4. Pharmacokinetics of GSK2879552 in Humans

GSK2879552 pharmacokinetics (PK) will be evaluated in a limited number of subjects in the first time in human study in small cell lung cancer patients (GSK study 200858, NCT# 02034123) prior to the initiation of this study. PK 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.

As of 20-NOV-2015, the PK of GSK2879552 was evaluated following administration of single (N=18) and repeated (N=16) oral administration of 0.25 mg to 3 mg of GSK2879552 in subjects with SCLC in Study 200858 and following single (N=11) and repeated (N=8) oral administration of 1 mg to 8 mg in subjects with AML in Study 200200. GSK2879552 pharmacokinetics are characterized by a rapid absorption with

maximum concentration occurring typically within the first hour after dosing. GSK2879552 is eliminated slowly with an average terminal phase half-life of 12 to 38 hours, leading to a moderate average increase in exposure of 72% for AUC at 2 mg daily. Following single and repeated administration of 0.25 mg to 4 mg of GSK2879552, Cmax and AUC tended to increase in a dose proportional fashion.

1.3.5. Clinical Safety of GSK2879552

Summary of findings from clinical studies conducted with GSK2879552 can be found in the Investigator Brochure for GSK2879552 [GlaxoSmithKline Document Number 2013N168888_03].

As of 20-NOV-2015, 11 subjects have been enrolled in Part 1 at once daily doses of 1 mg (n=1), 2 mg (n=2), 4 mg (n=7), and 8 mg (n=1). All 11 subjects (100%) had experienced AEs. The most frequently reported AEs (>20%) were fatigue, febrile neutropenia, nausea, anemia, decreased appetite, hypotension, rash, cellulitis, hypokalemia, and local edema. All Grade 4 AEs were hematological and included thrombocytopenia and neutropenia. Treatment-related AEs reported in at least 10% of subjects were nausea, decreased appetite, and thrombocytopenia. The treatment-related thrombocytopenia AEs were Grade 4 in both subjects; one of these subjects also had Grade 3 febrile neutropenia and Grade 3 anemia. Other treatment-related events that were Grade 3 or 4 included anemia and nausea. There were no fatal AEs.

All 11 subjects in Study 200200 have experienced SAEs. The most common SAE was febrile neutropenia. All cases of febrile neutropenia resolved. No other SAEs occurred in more than 1 subject. One subject had fatal pleural effusion secondary to disease under study, which was considered by the investigator to be not related to study treatment.

1.3.6. Combination Agent

1.3.6.1. All-Trans Retinoic Acid (ATRA)

All-trans retinoic acid (ATRA, tretinoin) is indicated for the induction of remission in patients with acute promyelocytic leukemia (APL) at 45 mg/m^2/day, or according to the French-American-British (FAB) classification the M3 subtype of acute myeloid leukemia (AML-M3).

The most frequently reported adverse events of ATRA are similar to those described in patients taking high doses of vitamin A and included headache (86%), fever (83%), skin/mucous membrane dryness (77%), bone pain (77%), nausea/vomiting (57%), rash (54%), mucositis (26%), pruritus (20%), and increased sweating (20%) [ATRA Prescribing Information, 2004].

About 25% of patients with APL treated with ATRA have experienced the retinoic acid-APL (RA-APL) syndrome. The syndrome generally occurs during the first month of treatment, with some cases reported following the first dose of ATRA. During ATRA treatment, about 40% of patients will develop rapidly evolving leukocytosis which is associated with a higher risk of life threatening complications. Retinoids have been associated with pseudotumor cerebri (benign intracranial hypertension), especially in

pediatric patients. Up to 60% of patients experienced hypercholesterolemia and/or hypertriglyceridemia, which were reversible upon completion of treatment. Elevated liver function test results occur in 50% to 60% of patients during treatment. However, the majority of these abnormalities resolve without interruption of ATRA or after completion of treatment. ATRA has teratogenic and embryotoxic effects and there is a high risk that severe fetal abnormalities may result with ATRA administration during pregnancy. Cases of thrombosis involving various sites have been reported rarely [ATRA Prescribing Information, 2004].

In a Phase I study conducted in subjects with solid tumor, ATRA was administered at doses ranging from 45 to 309 mg/m^2 per day [Conley, 1997]. Hypertriglyceridemia was dose-limiting at 269 mg/m^2 per day. Other frequent toxicities included mucocutaneous dryness and headache. The recommended once-daily ATRA dose was 215 mg/m^2. In another Phase I study conducted in subjects with solid tumor, ATRA dose ranged from 45 to 200 mg/m^2 per day [Lee, 1993]. Skin toxicities were dose limiting in this study at 175 mg/m^2 or higher dose. Headache was one of the most common toxicities and nausea/vomiting were frequent at dose levels higher than 100 mg/m^2. The recommended once daily ATRA dose was 150 mg/m^2. In a Phase I study conducted in patients with head and neck squamous cell carcinoma with prior surgical resection [Park, 2000], ATRA was administered at 45, 90, or 150 mg/m^2 either once daily or as divided doses. A similar toxicity profile was observed with headache, mucocutaneous dryness, and hypertriglyceridemia as the frequent toxicities. The maximum tolerable dose of ATRA in this population was established at 45 mg/m2/day, although the reason for the lower tolerance in this subject population is not clear.

ATRA is available in a 10 mg soft gelatin capsule for oral administration. The recommended dose in APL is 45 mg/m^2/day administered as two divided doses, as equally as feasible.

Pharmacokinetics of ATRA

ATRA (tretinoin) is rapidly absorbed following oral administration with peak concentration observed within 1 to 2 hours after dosing. ATRA is eliminated rapidly, with a terminal half-life of 0.5 to 2 hours following the first dose in patients with APL or CML. Cytochrome P450 3A4, 2C8 and 2E enzymes have been implicated in the oxidative metabolism of ATRA. There is evidence that ATRA induces its own metabolism. Plasma ATRA concentrations decrease on average to one-third of their day 1 values during 1 week of continuous therapy. Mean ± SD peak ATRA concentrations decreased from 394 ± 89 to 138 ± 139 ng/mL, while area under the curve (AUC) values decreased from 537 ± 191 ng·h/mL to 249 ± 185 ng·h/mL following 45 mg/m2 daily dosing in 7 APL patients [ATRA Prescribing Information, 2004]. This reduction in exposure was reverted following a one week dose interruption [Russo, 1998].

1.4. Rationale

1.4.1. Rationale for Study

Relapsed/refractory AML is an area of significant unmet need. Induction of differentiation is a clinically proven therapeutic mechanism in a subset of AML (APL-

AML), and targeting LSD1 could provide a new opportunity in AML treatment by inducing differentiation in non-APL AML. Preclinical studies have shown that GSK2879552 induces the expression of putative LSD1 target genes and has potent, predominantly cytostatic, anti-proliferative activity in AML cell lines. Changes in the expression of cell surface markers suggest that GSK2879552 treatment results in a pro-differentiation effect in both in vitro and in vivo studies. The proposed Phase I study will evaluate the safety and tolerability, pharmacokinetics, pharmacodynamics, and clinical activity to determine the recommended Phase 2 Dose (RP2D) and regimen of GSK2879552, alone or in combination with ATRA, given orally in adult subjects with relapsed/refractory AML.

1.4.1.1. Rationale for Combination with ATRA

Previous studies indicated that, when combined with ATRA, knockdown of LSD1 or treatment of AML cells with a non-selective LSD1 inhibitor, tranylcypromine, resulted in a greater anti-leukemic effect *in vitro* and *in vivo*. The addition of LSD1 inhibitor potentiated ATRA induced cell surface marker changes, myeloid differentiation gene expression, and *in vivo* engraftment of AML cells. These effects were observed in both ATRA sensitive and insensitive cells [Schenk, 2012].

Several approaches were undertaken to evaluate the combination effects of GSK2879552 with ATRA. As described, growth inhibition by GSK2879552 alone is cytostatic and does not invoke cell death mediated by apoptosis. Evaluation of proliferation in AML cell lines showed that ATRA alone has growth inhibitory effects. Co-treatment of AML cell lines with fixed concentrations of ATRA (0, 1, 10, 100, or 1000 nM) with GSK2879552A (3000 nM-0.152 nM) decreased the EC_{50} associated with GSK2879552 growth inhibition and resulted in cytotoxicity at earlier timepoints than ATRA alone in MOLM-13 cells and OCI-AML3 cells. Overall, percent maximum inhibition increased in combination relative to GSK2879552 alone in 5 of 6 cell lines tested. Using a similar study paradigm, caspase activation, a hallmark of apoptotic cell death was measured to further evaluate the mechanism of cytotoxicity invoked by the combination. GSK2879552 in combination with ATRA resulted in increased caspase activation when compared to activity of either single agent and supra -additive effects were observed in 5 of 6 AML cell lines tested. Five of 6 cell lines tested reached a supra-additive effect at 100 nM and 1000 nM ATRA while 3 cell lines, HL-60, MV-4-11 and SIG-M5, reached a supra-additive effect at 10 nM ATRA. Supra-additive effects occurred at GSK2879552A concentrations $\geq$ 37 nM except in SIG M5 cells where the supra-additive were only evident at lower doses of GSK2879552A (0.46 nM to 37 nM).

In a separate study using samples derived from bone marrow of AML patients, AML blast colony forming ability was evaluated with the combination of GSK2879552 with fixed concentrations of ATRA (0-1000nM). While each single agent did inhibit AML blast colony number to varying degrees in a 6 of 9 samples, co-treatment with 0.1 µM or 1 µM ATRA in combination with GSK2879552 resulted in a greater anti-leukemic effect as revealed by a lower GSK2879552 IC_{50} or greater maximal inhibition of AML blast colony forming ability than either single agent alone. Supra-additive effects were observed in 2 of 6 evaluable samples.

Finally, flow cytometric evaluation of cell surface markers of 2 AML cell lines (KG-1 and KG-1a) revealed increased CD11b and CD86 expression above single agent activity in 1 of the 2 cell lines. Taken together, these studies indicate that the combination of LSD1 inhibition with ATRA can enhance in vitro growth inhibition of AML cells beyond that achievable by either agent alone.

In this study, a combination arm will be included to evaluate safety, tolerability, PK, PD and clinical activity of GSK2879552 in combination with ATRA.

1.4.2. Rationale for Population

Acute myeloid leukemia (AML) is a clonal disorder characterized by arrest of differentiation in the myeloid lineage coupled with an accumulation of immature progenitors in the bone marrow, resulting in hematopoietic failure. AML is defined as the involvement of more than 20% of the blood and/or bone marrow by leukemic myeloblasts (per WHO) and is the most common acute leukemia in adults, with estimated 14,590 new cases and 10,370 deaths in US in 2013 [American Cancer Society, 2013]. The incidence of AML increases with age, with a median age at diagnosis of 67 years old.

Approximately 60% to 70% of adults with AML can be expected to attain complete remission following appropriate induction therapy. More than 25% of adults with AML can be expected to survive 3 or more years and may be cured. However, no standard regimen exists for the treatment of patients with relapsed AML, particularly in patients with the first remission duration of less than 1 year. For refractory AML patients, the chance to achieve a CR with standard treatment is 10% to 20% at best, and overall survival at 1 year is less than 10% with a median survival of 4 months only [Schmid, 2006].

Remission rates in adult AML are also inversely related to age and the older patients have a median overall survival on the order of months with few long-term survivors [Dombret, 2008]. A few population-based studies have reported 3-year survival rates of only 9-10% and 5-year survival of 3-8% in patients aged 60 years and older, compared with 5-year survival rates of up to 50% for younger patients [Alibhai, 2009; Juliusson, 2009]. These subjects tolerate intensive chemotherapy poorly, and often have AML with poor-prognosis karyotypes. There is a clear unmet medical need for treatment options in relapsed/refractory AML and elderly AML patients who are not eligible for chemotherapy. Hypomethylating agents have been approved for the treatment of advanced myelodysplastic syndromes and AML in elderly patients who are not eligible for induction chemotherapy which may highlight the potential for these agents.

1.4.3. Rationale for Dose – GSK2879552 Monotherapy

1.4.3.1. Predicted Effective Dose

The potential therapeutic dose for GSK2879552 in humans with relapsed/refractory AML was derived using available preclinical PK, in vitro AML cell line data and in vivo PD and efficacy data from AML tumor xenograft studies.

In vitro, GSK2879552 showed inhibition of proliferation of AML cells with median EC50 = 26 nM (range = 3 - 102 nM). In SKM-1 AML cell lines, GSK2879552 treatment results in increased expression of cell surface markers consistent with a pro-differentiation mechanism (CD11b EC50 = 7.1 nM or 2.6 ng/mL and CD86 EC50 = 13 nM or 4.7 ng/mL at 24 hours). GSK2879552 is a mechanism-based irreversible inhibitor of LSD1 suggesting that enzyme inhibition is predicted to be relieved upon new protein synthesis. In vitro results suggest that the $t_{1/2}$ of LSD1 protein is greater than 24 hrs, and therefore once daily regimen should be adequate even though the predicted half-life of GSK2879552 is less than 4 hours.

In vivo studies using MV-4-11 AML cells engrafted into mice revealed an increase in expression of both CD11b and CD86 cell surface markers by 8 hours that continued to increase through 72 hours following daily administration of GSK2879552 (CD86, dose for 50% effect, ED_{50} of 1.4 mg/kg at 24 hrs, and ED75 of 4.9 mg/kg at 24 hours).

The anticipated effective daily doses in humans based on a predicted clearance of 5.4 mL/min/kg are around 10 mg to 11 mg, computed to provide a free average steady-state concentration of 26 nM (median in vitro EC50) and a free AUC similar to the one predicted for mice receiving 4.9 mg/kg (in vivo EC75 for CD86 in MV-4-11 model), respectively. A daily dose of 40 mg would provide a free average steady-state concentration of 102 nM, the maximum in vitro EC50 observed in AML cell lines. The prediction based on in vivo mouse data has taken into account the 25% difference in plasma protein binding between human and mouse and assume 100% oral bioavailability.

1.4.3.2. Starting Dose

Four approaches have been considered to establish the starting dose for GSK2879552 in AML patients assuming a 70 kg adult with a surface area of 1.7 m^2.

1. One tenth of the rat 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/m^2. 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/m^2) 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/m^2 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 free exposure in rats and dogs is predicted to be 1.6 mg and 0.6 mg, respectively.

4. The highest dose determined to be safe in the ongoing first in human study of GSK2879552 in subjects with small cell lung cancer (GSK study 200858, NCT# 02034123).

The highest dose determined to be safe is the highest dose that has cleared the DLT observation period (first 4 weeks of treatment) without any observed DLT as defined in that study. It is expected that while the Grade 3 or 4 non-hematologic toxicities that constitute DLTs are likely to be similar in SCLC and AML subjects, the hematologic Grade 3 or 4 toxicities constituting the DLT criteria are likely to be observed earlier in SCLC subjects. Since AML subjects have disease-induced suppressed bone marrow function and pancytopenia, the definition of hematologic dose limiting toxicity is different in the AML study compared with the SCLC study: Hematologic toxicities would be considered dose limiting if prolonged suppression is observed (See Section 4.2.5). Therefore, a dose determined to be safe in SCLC subjects, i.e., without hematologic or non-hematologic DLTs, is expected to be safe for AML subjects and will allow for a starting dose that is likely to be nearer to MABEL dose.

Taking all approaches into consideration, the target population of relapsed/refractory AML subjects and the nature of the dose-limiting toxicity in animals, a starting dose of 0.25 mg daily (same starting dose as in the FTIH in SCLC study) is proposed. However, to minimize the number of subjects exposed to sub-therapeutic doses, a higher starting dose will be considered if the following conditions are met:

- A higher dose has been established to be safe in the ongoing FTIH study of single agent GSK2789552 in small cell lung cancer (GSK study 200858; NCT# 02034123). Safety and PK data from all patients treated up to the highest safe dose level in the small cell lung cancer study has been reviewed by the 200858 study Investigators with GSK Medical Monitor, clinical team, safety physician and PK representative.
- Safety and PK data mentioned above is summarized in a supplemental document, not requiring protocol amendment, with the rationale for starting at a higher dose. The supplemental document will be submitted for review and approval by Investigators and site IRB/EC for the present study in AML subjects, and communicated to regulatory authorities as appropriate.

If all of the above conditions are met, the present study can start at a higher dose than 0.25 mg daily, but not exceeding a starting dose of 1 mg once daily. In the absence of meeting all three conditions, the starting dose will remain 0.25 mg daily.

1.4.4. Rationale for Dose – GSK2879552 and ATRA combination

1.4.4.1. Predicted Effective Dose

Effective doses for GSK2879552 in combination with ATRA are anticipated to be at or below the predicted single agent effective doses of 10 to 40 mg daily.

ATRA dose of 45 mg/m2/day as two divided doses (as equally as feasible) would provide maximum concentrations around 500 nM, average steady-state concentrations around 80 nM and concentrations above 100 nM for around 6 hours. ATRA concentrations at 100 to 1000 nM ranges in combination with up to 2 μM GSK2879552 resulted in a greater anti-leukemic effect in *in vitro* studies.

1.4.4.2. Starting Dose

ATRA dose will be fixed at 45 mg/m^2/day as two divided doses, as equally as feasible. The starting dose for GSK2879552 will be 2 mg. These starting doses were chosen based on the following considerations:

- GSK2879552 and ATRA do not have overlapping toxicity profiles based on the nonclinical toxicology and clinical safety profile of GSK2879552 at doses up to 4 mg daily.
- GSK2879552 mono-therapy has been well tolerated in this study at up to 4 mg daily dose. 2 mg daily dose of GSK2879552 represents a 50% reduction from the highest cleared dose of 4 mg daily as of 20-NOV-2015.
- A dose of 45 mg/m^2/day for ATRA represents the recommended dose in APL as a single agent, well below the MTD of 150-215 mg/m^2/day.
- The risk of GSK2879552 altering ATRA PK is low. In-vitro data suggests that GSK2879552 has a very low potential to inhibit or induce CYP enzymes, and to inhibit Pgp, BCRP, OATP1B1 or OATP1B3 transporters.
- The risk for ATRA to increase GSK2879552 exposure is very low. ATRA has only been reported to be an enzyme inducer.

1.4.5. Benefit Risk Assessment

Summaries of findings from non-clinical and clinical studies conducted with GSK2879552 can be found in the Investigator Brochure (IB) for GSK2879552 [GlaxoSmithKline Document Number 2013N168888_03]. The following section outlines the risk assessment and mitigation strategy for this protocol

1.4.5.1. Risk Assessment

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. Reduced platelet aggregation has been observed in rats following repeat dosing at a time when there was significant thrombocytopenia. 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, hypocellularity was not observed in the bone marrow of these animals.	Informed Consent Form includes the risk of hematologic toxicity. Protocol specifies: - Exclusion criteria for non-AML related major bleeding (e.g. recent GI hemorrhage or neurosurgery) - Laboratory assessments (complete blood count [CBC]) - Dose stopping/modification criteria Signs and symptoms of bleeding or infection will be closely monitored during the study.
Encephalopathy	Three (out of 18) 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

Potential Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy
ATRA Combination ONLY		
RA-APL syndrome or respiratory compromise	About 25% of patients with APL treated with ATRA have experienced the retinoic acid-APL (RA-APL) syndrome.	Protocol provides the guideline for RA-APL syndrome management.
Leukocytosis	About 40% of patients may develop rapidly evolving leukocytosis during ATRA treatment	Subjects with an increased risk of a further rapid increase in WBC counts, i.e., WBC >30,000/uL, are excluded.
Pseudotumor cerebri/ intracranial hypertension.	ATRA may cause pseudotumor cerebri/intracranial hypertension.	Concomitant administration of ATRA and agents known to cause pseudotumor cerebri/intracranial hypertension (e.g., tetracycline) will be prohibited.
Hypercholesterolemia/ hypertriglyceridemia	Up to 60% of patients experienced hypercholesterolemia and/or hypertriglyceridemia with ATRA treatment.	Subjects with hypertriglyceridemia or hypercholesterolemia >300 mg/dL are excluded. Lipid panel will be checked weekly for the first 4 weeks and then q 4 weeks thereafter.
Liver function test elevation	Elevated liver function test results occur in 50% to 60% of patients during ATRA treatment.	LFT is monitored twice weekly for the first 2 weeks, weekly for the next 2 weeks and then q 4 weeks thereafter. Treatment stopping criteria based on elevation in LFT is in place and the safety management guideline is also provided.
Hypervitaminosis A	Chemically, ATRA is all-trans retinoic acid and is related to retinol (Vitamin A).	Vitamin A or multivitamins including vitamin A are prohibited.
Teratogenic effect	There is a high risk that a severely deformed infant will result if ATRA is administered during pregnancy.	Female subjects with child bearing potential will be required to use 2 reliable forms of contraception methods simultaneously during the treatment and until 30 days after the last dose of ATRA or 7 days after the last dose of GSK2879552, whichever is later. Contraception counselling will be repeated monthly throughout ATRA treatment. Serum pregnancy test will be performed at screening and end of treatment visit, and urine pregnancy test at week 4 and every 4 weeks thereafter.
Thrombosis	Cases of fatal thrombotic complications have been reported rarely in patients concomitantly treated with ATRA and anti-fibrinolytic agents.	CBC and coagulation panel are monitored weekly for the first 4 weeks and then every 4 weeks thereafter. Concomitant administration of antifibrinolytic agents (such as tranexamic acid, aminocaproic acid, or aprotinin) will be prohibited.

1.4.5.2. Benefit Assessment

This is an open-label, dose escalation and the first time in human study of this agent to be conducted in subjects with relapsed/refractory AML for which no standard therapies are anticipated to result in a durable remission. GSK2879552 has promising preclinical activity in AML cell lines, however it is unknown whether GSK2879552 will have efficacy in subjects with AML, thus any potential beneficial effect for an individual subject attributable to GSK2879552 is unknown.

ATRA is indicated for acute promyelocytic leukemia (APL). While there has been significant success in the utility of ATRA as a differentiation therapy in APL, ATRA has not been found to invoke a similar mechanism in other AML subtypes. GSK2879552 promotes differentiation in AML cell lines leading to the hypothesis that, through an overlapping mechanism, treatment of AML may demonstrate a greater response to ATRA when combined with GSK2879552. Any potential beneficial effect for an individual subject attributable to the combination of ATRA with GSK2879552 in non-APL type AML is unknown.

Data obtained in this study may assist in progressing the knowledge base on AML 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

1.4.5.3. Overall Risk Benefit Conclusion

Current data from GSK2879552 preclinical studies, alone or in combination with ATRA, indicate a potential for clinical activity by induction of differentiation in AML. Taking into account the measures taken to minimise risks to subjects participating in this Phase I clinical trial, the potential risks identified in association with GSK2879552, alone or in combination with ATRA, are justified by the anticipated benefits that may be afforded to subjects with relapsed/refractory AML, for whom there are currently no effective available therapies.

2. OBJECTIVES, ENDPOINTS AND HYPOTHESES

PART 1: Escalation Cohort		
	Objectives	**Endpoints**
Primary	1. To determine the safety, tolerability, MTD and/or RP2D and regimen of GSK2879552, alone or in combination with ATRA, given orally in adult subjects with AML.	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 PK of GSK2879552, alone or in combination with ATRA, after single- and repeat-dose oral administration. 2. To evaluate clinical response after treatment with GSK2879552, alone or in combination with ATRA. 3. To characterize the PK of ATRA in combination with 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, tmax, t½ (terminal phase and/or effective half-life), accumulation ratio, and time invariance. 2. Objective response rate defined as the percentage of subjects achieving complete remission (CR), partial remission (PR), CRp (as per CR but platelet count <100 x 109/L) and morphologic leukemia-free state per response criteria (Cheson, 2003) 3. ATRA PK parameters following single and repeat-dose administration of ATRA and GSK2879552, including AUC, Cmax, tmax, t½ (terminal phase).
Exploratory	1. To explore markers of differentiation (including morphology) in response to GSK2879552, alone or in combination with ATRA. 2. To investigate the mechanism of action and indicators of sensitivity and resistance to GSK2879552, alone or in combination with ATRA. 3. To evaluate the relationship between GSK2879552 exposure, alone or in combination with ATRA and safety/efficacy/PD parameters. 4. To characterize the metabolite profile of GSK2879552 after oral single and repeat-dosing in some subjects 5. To determine the amount of GSK2879552 excreted in urine after oral single and repeat dosing in some subjects treated with GSK2879552	1. Change from baseline expression in cell surface markers in AML cells derived from bone marrow and/or peripheral blood. 2. Analysis of morphology, DNA, RNA and/or protein markers in blasts cells in bone marrow aspirates and/or peripheral blood. 3. Relationship between GSK2879552 exposure markers (e.g. dose, concentration, Cmax, Cmin or AUC (0-tau)) and safety/efficacy/PD parameters. PD parameters assessed by change from baseline in select biomarkers, e.g. CD86 and CD11b 4. GSK2879552 metabolites in plasma and/or urine 5. Concentration of GSK2879552 in urine measured with an investigational bio-analytical method and extrapolated to total amount excreted in urine over time 6. Pharmacogenomic (PGx) study using

	6. To investigate the relationship between genetic variants in candidate genes, PK and safety profile of GSK2879552, alone or in combination with ATRA.	buccal samples.
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, alone or in combination with ATRA at the respective RP2D given orally in adult subjects with AML.	1. Objective response rate defined as the percentage of subjects achieving complete remission (CR), partial remission (PR), CRp (as per CR but platelet count <100 x 109/L) and morphologic leukemia-free state per response criteria (Cheson, 2003).
Secondary	1. To evaluate the safety and tolerability of respective RP2D of GSK2879552, alone or in combination with ATRA. 2. To characterize the population PK of GSK2879552, alone or in combination with ATRA. 3. To evaluate clinical activity in terms of duration of response, time to response (TTR) and progression-free survival (PFS)	1. AEs, SAEs, dose reductions or delays, withdrawals due to toxicities and changes in safety assessments (e.g., laboratory parameters, vital signs, ECGs, 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. Duration of response (DoR), defined as the time from first documented evidence of PR or better until disease progression (PD) or death, among responders, i.e. confirmed PR or better.Time to Time to Response is defined as the time from first dose to the first documented evidence of response (PR or better). Progression-free survival (PFS), defined as the time from first dose until the earliest date of disease progression (PD), or death due to any cause.
Exploratory	1. To investigate the mechanism of action and indicators of sensitivity and resistance to GSK2879552, alone or in combination with ATRA. 2. To evaluate the exposure response (PK/PD) relationship between GSK2879552, alone or in combination with ATRA and	1. Analysis of morphology, DNA, RNA and/or protein markers in blast cells from bone marrow aspirate and/or peripheral blood sample 2. Relationship between GSK2879552 exposure markers (e.g. dose, concentration, Cmax or AUC (0-tau)) and safety/efficacy/PD parameters. PD

	safety/efficacy/PD parameters. 3. To investigate the relationship between genetic variants in candidate genes, PK and safety profile of GSK2879552, alone or in combination with ATRA.	parameters assessed by change from baseline in select biomarkers, e.g. CD86 and CD11b 3. Pharmacogenomic (PGx) study using buccal samples
Hypothesis	Clinical response will be defined as Objective Response Rate (% of subjects achieving CR, PR, CRp or morphologic leukemia-free state) per response criteria. The null hypothesis is: H_0: RR ≤10% The alternative hypothesis is: H_A: ≥30%	

3. STUDY POPULATION

3.1. 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 55 subjects will be enrolled into Part 1 dose-escalation and additional 25 subjects may be enrolled into PK/PD expansion cohorts in GSK2879552 mono therapy and combination with ATRA arm. Up to 60 subjects will be enrolled in Part 2 (expansion cohort) of GSK2879552 alone and combination with ATRA arm. A total of approximately 140 subjects will be enrolled in the study. Additional subjects/cohorts may be enrolled to allow for evaluation of additional dose levels.

In Part 1, 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.

3.2. Subject Selection Criteria

3.2.1. 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) for GSK2879552 [GlaxoSmithKline Document Number 2013N168888_03]

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. ≥18 years of age and provided signed written informed consent.

2. Subjects must have relapsed/refractory acute myeloid leukemia by WHO classification for which no standard therapies are available or anticipated to result in a durable remission. FAB subtype M3 will be excluded.

3. Subjects ≥ 60 years of age with AML who are not candidates for or have refused standard chemotherapy.

4. Subjects who have previously received an autologous stem cell transplant are allowed if a minimum of 3 months has elapsed from the time of transplant and the subject has recovered from transplant-associated toxicities prior to the first dose of GSK2879552.

5. Subjects with a history of allogeneic stem cell transplant are eligible for study participation provided the following eligibility criteria are met:

    - transplant was >60 days prior to study enrollment.
    - subject has not taken immunosuppressive medications (including but not limited to: cyclosporine, tacrolimus, methotrexate, or mycophenolate mofetil) for at least 1 month
    - no signs or symptoms of graft versus host disease other than Grade 1 skin involvement
    - no active infection

6. Eastern Cooperative Oncology Group (ECOG) performance status of 0-1.

7. Subjects must be stable and, in the opinion of the investigator, be expected to complete 4 week treatment period.

8. Able to swallow and retain orally administered medication and does not have any clinically significant gastrointestinal abnormalities that may alter absorption such as malabsorption syndrome or major resection of the stomach or bowels,

9. 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).

10. Adequate baseline organ function defined by:

System	Laboratory Values
Hematologic	
White blood cell count (absolute) Coagulation assays (PT/INR and aPTT)	≤30,000/uL ≤1.3 X ULN
Hepatic	
Total bilirubin ALT and AST	≤ 1.5 X ULN[1] ≤2.5 × ULN
Renal	
Calculated creatinine clearance by Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (Appendix 3) or measured from 24hr urine	≥ 40 mL/min
Cardiac	
Ejection fraction	≥ LLN by Echocardiogram (ECHO) or MUGA
Lipid (ATRA combination ONLY)	
Triglyceride (fasting) Cholesterol (fasting)	≤ 300 mg/dL ≤ 300 mg/dL

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

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.

11. 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 (Section 11.1), during the study and for 7 days (GSK2879552 mono therapy) or 30 days (combination with ATRA), following the last dose of study treatment.

12. Men with a female partner of childbearing potential must have either had a prior vasectomy or agree to use effective contraception (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.

3.2.2. 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. Active Human Immunodeficiency Virus (HIV), Hepatitis B Virus (HBV) or Hepatitis C Virus (HCV) infections at the time of screening. Subjects with laboratory evidence of HCV clearance (HCV RNA PCR is negative) may be enrolled.
2. History of or concurrent malignancy of solid tumours, except for below.

   Exception: Subjects who have been disease-free for 5 years, or subjects with a history of completely resected non-melanoma skin cancer or successfully treated in situ carcinoma are eligible. Subjects with second malignancies that are indolent or definitively treated may be enrolled even if less than 5 years have elapsed since treatment. Consult GSK Medical Monitor if unsure whether second malignancies meet requirements specified above

3. Currently receiving cancer therapy (chemotherapy, radiation therapy, immuno-therapy, biologic therapy, hormonal therapy, surgery, and/or tumour embolization)

Note: HYDREA (hydroxyurea) will be allowed.

4. Received major surgery, radiotherapy, or immunotherapy within 4 weeks of GSK2879552 administration.
5. Prior treatment with temozolomide, dacarbazine or procarbazine
6. Prior treatment with poly ADP ribose polymerase (PARP) inhibitors (e.g., olaparib, ABT-888)
7. Screening Montreal Cognitive Assessment (MOCA) score of 22 or lower
8. Evidence of severe or uncontrolled systemic diseases (e.g., severe/chronic infection, unstable or uncompensated respiratory, 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
9. Current active liver or biliary disease (with the exception of Gilbert's syndrome or asymptomatic gallstones, liver metastases or otherwise stable chronic liver disease per investigator's assessment).
10. Patients at risk of non-AML related major bleeding (e.g. recent GI hemorrhage or neurosurgery).
11. Symptomatic or untreated CNS leukemia. Subjects are permitted to enroll if previously treated for CNS disease, free of symptoms at the time of screening, and have not required intrathecal chemotherapy at least 1 month prior to study Day 1.
12. 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, Appendix 2).
    - History of acute coronary syndromes (including unstable angina and myocardial infarction), coronary angioplasty, or stenting within the past 3 months.

- Baseline QTc interval using Fridericia'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.

13. Administration of an investigational drug within 14 days or 5 half-lives, whichever is ***shorter*** with a minimum of 14 days preceding the first dose of study treatment(s) in this study.
14. Have a known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to GSK2879552 or LSD1 inhibitors that contraindicates their participation.
15. Lactating female.
16. 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.
17. Current use of a prohibited medication including anticoagulants or platelet inhibitors (Section 10.2) or expected to require any of these medications during treatment with the investigational drug.
18. Previous treatment with GSK2879552

For ATRA Combination arm ONLY

19. Known hypersensitivity to ATRA, parabens (preservatives in the gelatin capsule) or other retinoids.
20. ATRA capsule contains sorbitol. Subjects with rare hereditary problems of fructose intolerance are excluded.
21. History of seizure within 12 months or brain tumor (primary)
22. History of taking mega-dose vitamin A (>25,000 USP U/day) within 3 months from the dosing start.

4. INVESTIGATIONAL PLAN

4.1. Discussion of Study Design

This is a Phase I, open-label, multi-center, non-randomized, 2-part study. Part 1 is a dose escalation phase to determine the MTD and/or RP2D for GSK2879552, alone or in combination with ATRA, based on the safety, tolerability, pharmacokinetic, and pharmacodynamic profiles observed after oral administration of GSK2879552. Eligible subjects with relapsed/refractory acute myeloid leukemia or elderly subjects who are ineligible for or refuse induction therapy will be enrolled. Any dose level(s) may be expanded up to 12 subjects in order to collect additional data on safety, tolerability, PK and PD.

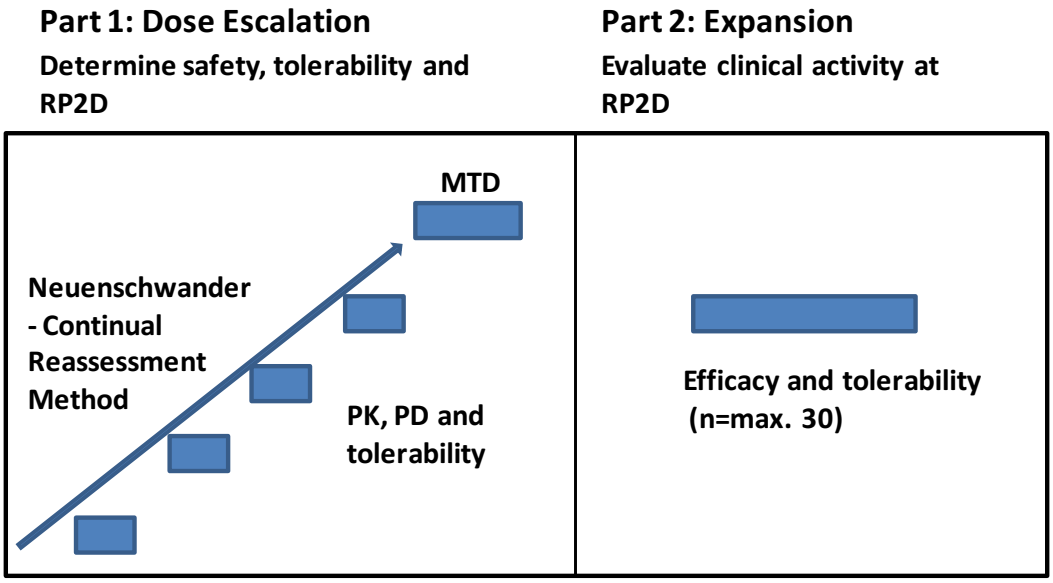
Once MTD and/or RP2D is identified, an expansion cohort (Part 2) of up to 30 subjects each will be enrolled to further evaluate the efficacy and tolerability of GSK2879552, alone or in combination with ATRA, in subjects with relapsed/refractory AML.

The proposed treatment schedule of GSK2879552 is continuous daily dosing. The starting dose for GSK2879552 mono therapy arm will be 0.25 mg/day or the highest dose determined to be safe in the ongoing SCLC study, whichever is higher with a maximum of 1 mg/day (see Section 1.4.3.2 for details). The starting dose of GSK2879552 in combination with ATRA will be 1-2 dose levels below the highest dose determined to be safe in the GSK2879552 mono therapy arm in this study, i.e., 2 mg once daily. Alterations to the dose and schedule may be incorporated based on emerging PK, PD, and tolerability data.

Dose reduction and/or truncated dose scheduling may be considered for subjects with recurrent/ persistent toxicity or according to the institutional guideline. For example, once the disease control (CR, CRp, PR or a morphologic leukemia-free state) is attained, ATRA may be given in an intermittent schedule, e.g., 2 week on/2 weeks off.

Subjects may continue treatment in the study until disease progression, unacceptable toxicity, or withdrawal of consent. The duration of study will depend on recruitment rates, and timing of subjects' duration on study. The study will end 2 years from the last subject first dose or earlier if all patients are off study drug. Patients may be allowed to continue on study drug after the end of the study if the Investigator, in consultation with the sponsor's Medical Monitor, determines that continuing treatment will benefit the patient.

Figure 1 Study Schema



- **PK/PD expansion: Any dose level could be expanded up to 12 subjects during dose escalation.**
- **Alternative dosing schedule may be explored.**

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.

4.2. Part 1: Dose-Escalation Phase

4.2.1. GSK2879552 Mono-therapy

In Cohort 1, a single subject will receive a dose of GSK2879552 0.25 mg once daily or the highest dose determined to be safe in FTIH in SCLC study (GSK study 200858), whichever is higher with a maximum of 1 mg/day.

The subject in Cohort 1will be evaluated for dose limiting toxicities (DLTs) during the first 4 weeks of treatment (DLT observation window), and the safety and PK data will be reviewed prior to a dose escalation decision and starting Cohort 2. If the first subject becomes unevaluable 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 DLT observation window 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 4 weeks for reasons other than toxicity will be replaced.

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
- Any Grade 2 or higher non-hematologic adverse event that is considered related to the study medication with the following exceptions:
    - Grade ≤ 3 fatigue, asthenia, and nausea that respond to standard medical care within 72hrs, significant electrolyte abnormalities unrelated to underlying malignancy and corrected within 24 hrs, and alopecia
- 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.

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 the toxicity was seen in the initial subject and no additional toxicity meeting the above criteria is seen in either of the 2 new subjects.
- No subjects treated at next higher dose level have toxicity meeting the above criteria.

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.

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 DLT or any Grade 2 or higher non-hematologic adverse event that is considered related to the study medication (with the exceptions as above) is observed. The maximum allowable dose increment will be determined based on the prior dose level data.

Completion of Dose Escalation

The dose escalation will complete when MTD and/or 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. Up to 12 additional subjects will be enrolled at the dose to further define the safety and tolerability of the dose and schedule. 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 data. Quality control of critical safety data will be described in the Dose Escalation Plan, which includes ongoing study monitoring visits, Sponsor review of the clinical database, and confirmation by site investigators and/or delegate that the data is accurate and complete.

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/de-escalation should continue as recommended by the N-CRM. The dose-escalation decision and

rationale for each cohort will be discussed with investigators during teleconference(s) and documented in writing, with copies maintained at each study site and in the study master file.

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

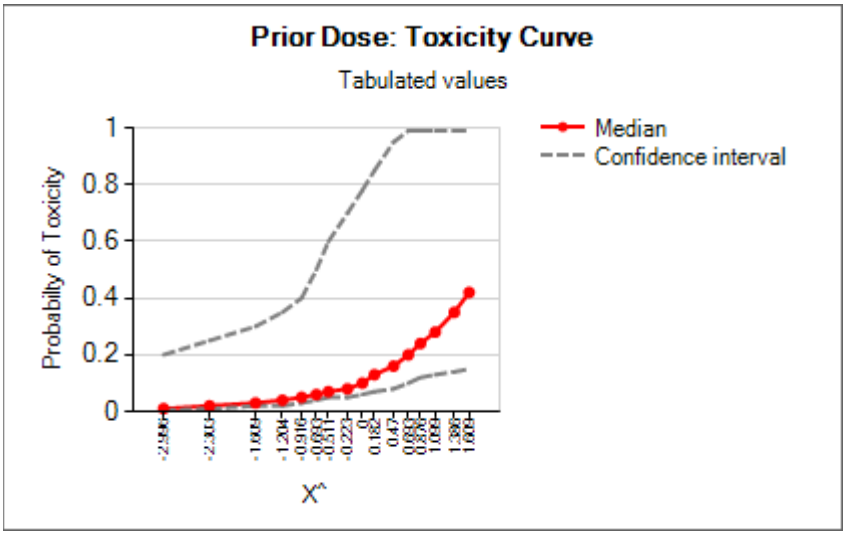
The N-CRM methodology requires that a Bayesian prior for the toxicity curve be pre-specified. The Bayesian prior used for this design was determined using the quantile method. For each possible dose, an estimate of the median probability of DLT was specified, along with a 95% credible interval. The 95% credible intervals are intentionally wide due to limited information about the toxicity profile of GSK2879552 in humans. Table 1 shows the median prior probability of experiencing a DLT at a given dose along with a 95% credible interval around the median. This table does not imply that all doses will be studied:

Table 1 Specified Prior Probability of DLT

Dose level (mg)	2.5% Quantile for Probability of Toxicity	Median Probability of Toxicity	97.5% Quantile for Probability of Toxicity
0.25 mg	0.005	0.01	0.2
0.5 mg	0.01	0.02	0.25
1 mg	0.02	0.03	0.3
1.5 mg	0.02	0.04	0.35
2 mg	0.03	0.05	0.4
2.5 mg	0.04	0.06	0.5
3 mg	0.05	0.07	0.6
4 mg	0.05	0.08	0.7
5 mg	0.06	0.1	0.78
6 mg	0.07	0.13	0.85
8 mg	0.08	0.16	0.95
10 mg	0.1	0.2	0.99
12 mg	0.12	0.24	0.99
15 mg	0.13	0.28	0.99
20 mg	0.14	0.35	0.99
25 mg	0.15	0.42	0.99

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 5 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



4.2.2. GSK2879552 and ATRA combination

In Cohort 1, three subjects will receive GSK2879552 2 mg once daily dose with ATRA 45 mg/m^2/day as two divided doses. After all three subjects complete the first 4 weeks of treatment, the safety data will be reviewed for DLT. Available PK and PD data will be also reviewed prior to a dose escalation decision and starting Cohort 2. Each cohort will enroll 3 or more subjects to obtain sufficient data. If any subject becomes unevaluable for reasons other than toxicity, a replacement subject will be enrolled. In addition, subjects who fail to take at least 75% of their scheduled doses of each drug in the first 4 weeks for reasons other than toxicity will be replaced. Starting with Cohort1, the dose escalation will use the N-CRM with prior DLT information of GSK2879552 and ATRA mono-therapies and follow the same rule with regards to the number of subjects, maximum dose increment, and the completion of dose escalation as described in Section 4.2.1. The details of priors used in N-CRM model is described in Section 13.2.

Starting at dose level 1, the following GSK2879552 dose levels are planned for evaluation in combination with ATRA..

Dose level	GSK2879552	ATRA
1	2 mg/day	45 mg/m^2/day
2	4 mg/day	45 mg/m^2/day
3	8 mg/day	45 mg/m^2/day
4	12 mg/day	45 mg/m^2/day
5	20 mg/day	45 mg/m^2/day

A reduced dose of GSK2879552 or ATRA may be considered if the combination is not well tolerated at dose level 1. The initial dose level reductions allow for either drug to be reduced. Subsequent dose levels are based on the totality of data and upon discussion with the investigators.

Dose level	GSK2879552 ATRA fixed at 45mg/m^2
-1	1 mg/day
-2	0.5 mg/day

Dose level	GSK2879552 ATRA <30mg/m^2
1a	2 mg/day
-1a	1 mg/day
-2a	0.5 mg/day

4.2.3. 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. However, PD sample (peripheral blood and bone marrow aspirate) collection may be stopped early at the sponsor's discretion. Subjects may be enrolled at previously completed dose levels for the purpose of obtaining additional data. 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.

4.2.4. Alternative Dosing and PK/PD Sampling Schedules

In Part 1 Dose Escalation phase, subjects will initially receive daily dosing of GSK2879552. If the terminal half-life is longer than 5 hours, some subjects may be requested to withhold Day 2 and Day 3 dosing to obtain blood samples for PK analysis at timed intervals up to 72 hours after dosing. Once their final PK sample on Day 4 is obtained, these subjects would begin repeat dosing on Day 4. In Part 2, subjects will begin repeat dosing per RP2D and regimen from Day 1.

Further alterations may be made to the dosing schedule and/or PK/PD sampling schedule of GSK2879552 or ATRA based on the results of emerging PK, PD, efficacy and safety data, and documented in the SPM. These changes will be communicated to IRB/EC, but would not constitute a protocol amendment.

Schedules that incorporate a recovery period may be explored (e.g., 4 days on/3 days off). Alternatively, a drug holiday after continuous dosing may be explored for GSK2879552 and/or ATRA. 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.

4.2.5. Dose-Limiting Toxicity

An event will be considered a DLT if it occurs within the first 28 days of treatment (with exception of myelosuppression as stated below), and meets one of the following criteria unless it can be clearly established that the event is unrelated to treatment.

Subjects unable to receive at least 75% of scheduled doses within the DLT period for reasons other than toxicity (e.g., acute illness, disease progression) will not be evaluable

- Hematologic DLT: Myelosuppression (as defined by absolute neutrophil count (ANC) <500/μl AND platelets ≤25,000/μl) with bone marrow hypoplasia (cellularity ≤ 5%) without evidence of leukemia (<5% blasts) for ≥ 42 days after drug cessation.
- Grade ≥3 non-hematologic toxicity that is considered clinically significant and lasts >72 hours. Fatigue, asthenia, or nausea that respond to standard medical care within 72 hours and new electrolyte disturbance that respond within 24 hours are exceptions. In addition, electrolyte disturbances associated with underlying malignancy are not considered DLT.
- Grade 2 toxicity that in the judgment of the investigator and GSK Medical Monitor is dose-limiting.
- Treatment delay of ≥42 days due to unresolved toxicity (without evidence of leukemia (<5% blasts)).

4.2.6. Maximum Tolerated Dose and Recommended Phase 2 Dose

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. The RP2D may be different for mono-therapy and for the combination therapy with ATRA.

Data considered for RP2D selection will include, but not be limited to: safety, available PK profile, and observed signs of clinical activity from Part 1.

4.3. Part 2: Expansion Cohort

Once the respective RP2D have been determined, an expansion cohort of up to 30 subjects each, GSK2879552 mono-therapy or in combination with ATRA, will be enrolled in order to better characterize the clinical activity and safety profile of the RP2D.

Additional expansion cohorts may be initiated to test the efficacy of i) GSK2879552 at RP2D in ≥60 years old treatment naïve subjects, and ii) GSK2879552 in combination with other agents (demonstrated synergy in pre-clinical studies) in relapsed/refractory or ≥60 years old treatment naïve subjects.

The statistical design and number of subjects to be enrolled in the dose expansion cohort is based on the predictive probability of success if enrollment continues until all planned subjects are recruited [Lee, 2008]. The predictive probability design allows for evaluation of stopping rules after each subject once a minimum number of subjects are evaluable. In this particular study, we will stop only for futility. Final decisions on stopping enrolment will depend on the totality of the data collected.

4.4. 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 a higher dose level cohort has been cleared without a DLT.

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.

Subjects approved for intra-subject dose escalation will require additional limited PK sampling at the higher dose as determined by GSK Clinical Pharmacology.

4.5. Study Treatment

4.5.1. 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.

4.6. Dosage and Administration of Study Treatment(s)

See Section 5.1 for the dosage and administration of GSK2879552 and ATRA.

4.6.1. Meals and Dietary Restrictions

Subject should refrain from consumption of Seville oranges, grapefruit, grapefruit hybrids, grapefruit juice, pomelos, or exotic citrus fruits, which may inhibit efflux transporters, from 1 day prior to the first dose of study treatment(s) until the last dose of study drug.

GSK2879552 will be administered under fasting conditions, either 1 hour before or 2 hours after a meal. Subjects should take their morning ATRA dose fasted, at the same time as GSK2879552. If ATRA concentrations are lower than anticipated following fasted administration, subjects may be asked to take their morning ATRA dose with food. Subject should take their evening ATRA dose with food.

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 study medication.

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.

4.6.2. Blinding

This is an open-label study.

4.7. Safety Management Guidelines

4.7.1. 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) ≥5 X (times) upper limit of normal (ULN) and bilirubin ≥2 Xs ULN (or ALT ≥5 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 ≥8 X ULN.
3. ALT ≥5 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 ≥5X ULN persists for ≥4 weeks.
5. ALT ≥5 X ULN and cannot be monitored weekly for 4 weeks.

Subjects with ALT ≥5 X ULN **and** <8 Xs 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 following section for details on weekly follow-up procedures for these subjects.

4.7.1.1. Liver Chemistry Follow-up Procedures

Refer to the diagram in Appendix 5 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 4.7.1:

- 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 approval as described in Section 9.

Safety Follow-Up Procedures for subjects with ALT ≥3 times 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 ≥5 times ULN and bilirubin ≥2 times ULN (or ALT ≥5 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 ≥5 times ULN, every attempt must be made to also obtain the following:

- Viral hepatitis serology including:
  - Hepatitis A Immunoglobulin M (IgM) antibody.
  - Hepatitis B surface antigen and Hepatitis B Core Antibody (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 120 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 ≥5 times ULN **and** bilirubin ≥2 times ULN (>35% direct) or ALT ≥ 5 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 HPLC assay (quantifies potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week [James, 2009]). **NOTE: not required in China**
- Only in those with underlying chronic hepatitis B at study entry (identified by positive hepatitis B surface antigen): quantitative hepatitis B DNA and hepatitis delta antibody. . **NOTE**: if hepatitis delta antibody assay cannot be performed, it can be replaced with a PCR of hepatitis D RNA virus (where needed) – as outlined in: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1153793.

4.7.2. QTc Stopping Criteria

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

- QT interval corrected for heart rate by Fridericia's formula (QTcF = QT / CubeRootRR) >500 msec
- Increase of QTcF by ≥60 msec from baseline
- For patients with underlying **bundle branch block**, follow the discontinuation criteria listed below:

Baseline QTc with Bundle Branch Block	Discontinuation QTc with Bundle Branch Block
< 450 msec	> 500 msec
450 – 480 msec	≥ 530 msec

1Based 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.

If the QTc prolongation resolves to Grade 1 or baseline, 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 7 for the French specific QTc stopping criteria.

4.7.3. Mental Status Stopping Criteria

Enrollment will be stopped upon the occurrence of any encephalopathy, unless clearly attributable to central nervous system disease involvement or intercurrent illness.

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 (Pre-dose Day 1) 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 or to the MOCA score before the decrease.
- 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.

4.8. Guidelines for Events of Special Interest and Dose Modifications

The severity of adverse events (AEs) will be graded utilizing the National Cancer Institute- Common Toxicity Criteria for Adverse Events (NCI-CTCAE), version v4.03. Guidelines for dose modifications and interruptions for management of common toxicities associated with the study treatment(s) are provided in this section.

4.8.1. Events of Special Interest

Any signs of bleeding, bruising and infection will be monitored closely throughout the study. Platelet transfusion will be administered following institutional guidelines and practices. Neutropenia and anemia management and fungal or bacterial prophylaxis will also follow institutional guidelines.

4.8.2. Dose Adjustment for Non-Hematologic Toxicity

See Table 2 Dose Adjustment Guideline for drug related non-hematologic toxicities based on worst grade.

Table 2 Dose Adjustment Guideline for Drug Related Non-Hematologic Toxicity

Worst Grade	Dose Adjustment
G1	No change in dose
G2†	Continue dosing with no change OR Consider holding for up to 2 weeks for toxicity to resolve to baseline or ≤ Grade 1, then continue at the same dose OR dose reduce by at least 25% if the toxicity is considered a DLT.
G3 and 4†	Hold for up to 2 weeks for toxicity to resolve to baseline or ≤ Grade 1, then dose reduce by at least 25%. If no recovery to ≤Grade 1* or baseline after 14 days, patient should be withdrawn.

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

†In combination cohort, consider holding ATRA dosing first for skin related toxicity (dryness, rash), nausea, vomiting, pain, headache, and mucositis. With fever, consider holding LSD1 first to allow neutrophil count to recover.

If the non-hematologic toxicity or event resolves to baseline or ≤ Grade 1 within 14 days of stopping therapy, treatment with GSK2879552 and/or ATRA 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 non-hematologic toxicity does not resolve to ≤ Grade 1 or baseline within 14 days, the subject should be withdrawn from the treatment permanently (Section 6.3). However, if the investigator and GSK Medical Monitor agree that further treatment will benefit the subject, treatment can restart with at least **25%** dose reduction once the toxicity resolves to ≤ Grade 1 or baseline.

4.8.3. Dose Adjustment For Hematologic Toxicity

Toxicity	Dose Adjustment/ Stopping Criteria	Management Guidelines
At all thrombocytopenia grades, implement fall precautions to avoid bleeding due to trauma, e.g. trauma to head can cause a subdural hematoma. This risk increases with higher grades of thrombocytopenia		
Thrombocytopenia regardless of blast count	Grade 1, 2 & 3 (platelets ≥25,000/mm^3)	Continue dosing at same dose level with more frequent monitoring as necessary.
Thrombocytopenia if blasts >5%	Grade 4 (platelets <25,000/mm^3) and/or any grade accompanied by severe bleeding related to thrombocytopenia	If platelet count <25,000/mm^3 but ≥10,000/mm^3: 1. Use clinical judgement to institute more frequent monitoring as necessary 2. Institute platelet transfusion as appropriate. If platelet count <10,000/mm^3: 1. Continue treatment and start platelet transfusion as per institutional guidelines. 2. If repeat platelet transfusions are not able to rescue platelet count, then consider irradiated, leukapherised or HLA-matched platelets as clinically appropriate 3. If still unable to rescue platelet count, investigator may consider treatment interruption in discussion with medical monitor. 4. Use of concomitant therapies (tranexamic acid) is permitted. Please note tranexamic acid is prohibited for subjects receiving GSK2879552 in combination with ATRA. 5. Use of hydroxyurea in the setting of increased blast counts in conjunction with decreased platelet counts is permitted.
Thrombocytopenia if blasts <5%	Grade 4 (platelets <25,000/mm^3) and/or any grade accompanied by severe bleeding related to thrombocytopenia	If platelet count <25,000/mm^3 but ≥10,000/mm^3: 1. Use clinical judgement to institute more frequent monitoring as necessary 2. Institute platelet transfusion as appropriate. If platelet count <10,000/mm^3 (or ≤25,000/mm^3 with accompanying fever, sepsis, or minor bleeding): 1. Treatment may be held for up to 4 weeks and resume* as soon as count recovery has occurred (i.e., neutrophils ≥0.5 and platelets ≥25 x 10^9/L). Use clinical judgement to institute more frequent monitoring as necessary. 2. The treatment may be held for additional 1-2 weeks if the neutrophil and platelet counts do not recover after the initial 2 weeks. 3. After a total of 5-6 consecutive weeks, if there is no evidence of recovering blood counts, a repeat bone marrow examination should be performed

Toxicity	Dose Adjustment/ Stopping Criteria	Management Guidelines
		during that period (approximately -35-42 days after drug cessation) to evaluate for the possibility of hematologic DLT. 4. If persistent for 6 weeks and not attributed to disease or requires platelet transfusions for bleeding in the absence of the disease, the subject will be withdrawn from the study. *If treatment resumes, the dose and schedule may be adjusted based on platelet count, i.e., dose can be reduced by at least 25% increments up to two times.

4.8.4. Safety Management for ATRA Combination

4.8.4.1. Retinoic Acid syndrome

About 25% of patients with APL treated with ATRA have experienced the retinoic acid-(RA) syndrome characterized by fever, dyspnea, acute respiratory distress, weight gain, radiographic pulmonary infiltrates, pleural and pericardial effusions, edema, and hepatic, renal, and multi-organ failure [ATRA Prescribing Information, 2004]. This syndrome has occasionally been accompanied by impaired myocardial contractility and episodic hypotension. The syndrome generally occurs during the first month of treatment, with some cases reported following the first dose of ATRA.

Retinoic Acid Syndrome should be strongly suspected if the following signs or symptoms (without any other clear or established etiology) emerge during treatment with GSK2879552:

- New or worsening progressive dyspnea or hypoxemia, with increasing demands for supplemental oxygen; respiratory distress refractory to treatment for the initially suspected cause
- Radiologic evidence of new or worsened bilateral pulmonary involvement (infiltrates or opacities) with or without presence of infection, refractory to treatment with anti-infectives (antibiotics, antivirals, antifungals)
- Radiologic evidence of new or worsened pleural or pericardial effusion that is refractory to treatment for an initially suspected cause
- New or worsened peripheral edema, with rapid weight gain (e.g., >5 kg/11 pounds over 7 days)
- Increase in serum creatinine (e.g., >2-fold from baseline)
- The following symptoms or signs may be features of retinoic acid syndrome but if isolated and not accompanied by pulmonary or renal manifestations, may not require rapid initiation of retinoic acid syndrome treatment (unless sufficiently severe and prolonged):
    - Unexplained fever $\geq 38^{o}C$ ($100.4^{o}F$)
    - Rash of unknown origin
    - Bone pain

- Lymphadenopathy

The measures below are recommended to be taken at the earliest manifestations of suspected retinoic acid syndrome:

- Patients with severe or rapidly progressing retinoic acid syndrome should be hospitalized for continued observation
- In case of uncertainty with the diagnosis, e.g., presence of less specific symptoms of moderate severity, patients should be closely monitored, as the condition may rapidly worsen
- Corticosteroids should be promptly initiated (e.g., 10 mg of dexamethasone every 12 hours until resolution of retinoic acid syndrome). Once resolved the corticosteroid dose can be progressively reduced over 1-2 weeks
- GSK2879552 and/or ATRA may be withheld at the physician's discretion. Due to the long half-life of GSK2879552 (about 16 hours), treatment interruption may not immediately reverse the symptoms of retinoic acid syndrome. If interrupted, GSK2879552 treatment may be reinitiated at the original or a reduced dose, once the signs and symptoms resolve and the patient's clinical condition improves
- In patients with elevated WBC counts, prompt initiation of hydroxyurea is suggested, or treated as per standard local practice (e.g., dose of 2 to 3g PO 2- or 3-times daily for WBC $>30x10^9$/L)
- In cases of severe leukocytosis, use of leukapheresis may be appropriate
- For substantial fluid accumulation, initiation of furosemide may be appropriate, as per local standard practice
- Patients with pericardial effusion (a less common manifestation of retinoic acid syndrome) can require urgent cardiac intervention due to it being a life-threatening condition
- Patients with increasing serum creatinine levels should be evaluated for tumor lysis syndrome
- Patients experiencing a rapid increase in peripheral blood cells should be monitored for disseminated intravascular coagulopathy and hemorrhage
- Imaging techniques such as standard or high-resolution computerized tomography (CT) scan and chest X-ray are useful for establishing a diagnosis of retinoic acid syndrome by identifying pulmonary infiltrates or effusions; noting that a CT scan is more sensitive in detecting early radiological signs of retinoic acid syndrome-associated changes

4.8.4.2. Liver Function Test Elevation

If ALT ≥5 X ULN, ATRA dose should be held while GSK2879552 dosing continues

- If resolved in 14 days, ATRA dose should resume at full dose
- If not resolved in 14 days, GSK2879552 dose should be also held.
    - If resolved in another 14 days, resume GSK2879552 at a reduced dose by minimum 25% and ATRA at full dose
    - If not resolved in another 14 days, withdraw the subject from the study.

4.8.4.3. Pseudotumor Cerebri (benign intracranial hypertension)

Early signs and symptoms include papilledema, headache, nausea, vomiting, and visual disturbances. Subjects with these symptoms should be evaluated for pseudotumor cerebri, and, if present, appropriate care should be instituted including high dose steroid. ATRA dose should be held for moderate to severe pseudotumor cerebri.

5. INVESTIGATIONAL PRODUCT(S)

The term 'study treatment' is used throughout the protocol to describe investigational product(s) (IP) received by the subject as per the protocol design. Study treatment may therefore refer to the individual study treatments or the combination of those study treatments.

5.1. Description of Investigational Product(s)

Product name:	**GSK2879552 Capsule**
Formulation description*:	GSK2879552 capsules contain 0.5 mg, 2 mg or 5 mg of GSK2879552 as parent.
Dosage form:	Capsule
Unit dose strength(s)	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:	0.5 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.

* NOTE: 0.25 mg strength of GSK2879552 capsule is no longer being used and is removed from the table.

GSK2879552 will be provided to sites by GSK, whereas ATRA will be locally supplied and prepared according to local standards. The contents of the label will be in accordance with all applicable regulatory requirements.

Product name:	**Tretinoin (ATRA) Capsule**
Formulation description:	ATRA is supplied as a 10 mg capsule for oral administration.
Dosage form:	Capsule
Unit dose strength(s)	10 mg
Route/Regimen	Oral/The initial dosing regimen will be continuous oral twice daily dosing, i.e., morning and evening. ATRA dose may be divided evenly 2-4 times a day, as needed. Subjects should take their morning dose fasted, at the same time as GSK2879552. If ATRA concentrations are lower than anticipated following fasted administration, subjects may be asked to take their morning ATRA dose with food. Subject can take their evening ATRA dose with food.

5.2. Preparation/Handling/Storage of 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 Study Procedures Manual (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. See package insert for ATRA storage conditions.

Maintenance of a temperature log (manual or automated) is required at the clinical sites.

5.3. 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.

5.4. Treatment Compliance

On clinic days, GSK2879552 and ATRA 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 IP 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 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.

5.5. 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.

The MTD of ATRA in patients with myelodysplastic syndrome or solid tumors was 195mg/m2/day. Overdosage with other retinoids has been associated with transient headache, facial flushing, cheilosis, abdominal pain, dizziness and ataxia. These symptoms have quickly resolved without apparent residual effects. There is no specific treatment in the case of an overdose, however, it is important that the patient be treated in a special hematological unit [ATRA Prescribing Information, 2004].

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.

6. COMPLETION OR WITHDRAWAL OF SUBJECTS

6.1. Screen and Baseline Failures

Screen failures are defined as subjects who consent to participate in the clinical trial but are never subsequently randomized. In order to ensure transparent reporting of screen failure subjects, meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, and respond to queries from Regulatory authorities, a minimal set of screen failure information is required including Demography, Screen Failure details, Eligibility Criteria, and any Serious Adverse Events.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. Rescreened participants should be assigned the same participant number as for the initial screening if rescreening for same arm of study (monotherapy to monotherapy or ATRA combination to ATRA combination.) If rescreening for a different arm of the study, (monotherapy to ATRA combination or ATRA combination to monotherapy) participants will need a new screening number. Please refer to the Study Procedures Manual for more details.

6.2. Subject Completion Criteria

In Part 1, a subject will be considered to have completed the study if:

- they complete screening assessments, the 28-day DLT observation period, and taking a minimum of 75% of planned doses,
- they progress or die while receiving study treatment, or
- they are receiving ongoing study treatment at the time of the Sponsor's decision to close the study.

In Part 2, a subject will be considered to have completed the study if:

- they die while receiving study treatment,
- they progress while receiving study treatment and are followed until death, or
- they are receiving ongoing study treatment at the time of the Sponsor's decision to close the study.

Subjects who have not died, and are no longer being followed for survival are considered to have discontinued the study. The End of Study eCRF should only be completed when a subject is no longer being followed.

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 4.7.1. The investigator may discuss with a GSK Medical Monitor continuing a subject who is receiving benefit but has met the criteria for disease progression, if the following criteria are met: Investigator-determined clinical benefit (e.g. symptomatic improvement), lack of

significant toxicity (no drug related non-hematologic grade 3/4 AEs within the last 4 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
- A clinically significant hematologic adverse event leading to an interruption of treatment for greater than 28 days. Subjects will be allowed up to a 28-day delay in dosing for hematologic toxicity to resolve or for scheduling difficulties. If the investigator and GSK Medical Monitor conclude that the benefit: risk supports continued treatment of a subject who has had a > 28 day treatment delay, then the subject may continue therapy with the approval of the GSK Medical Monitor.
- A clinically significant non-hematologic adverse event leading to an interruption of treatment for greater than 14 days. Subjects will be allowed up to a 14-day delay in dosing for non-hematologic toxicity to resolve or for scheduling difficulties. If the investigator and GSK Medical Monitor conclude that the benefit: risk supports continued treatment of a subject who has had a > 14 day treatment delay, then the subject may continue therapy with the approval of the GSK Medical Monitor.
- Persistent G4 thrombocytopenia for 4 weeks not attributed to disease or requires platelet transfusions for bleeding in the absence of the disease.
- 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

The study will be considered completed, having met the study objectives, when 80% or more subjects in Part 2 have withdrawn from the study. 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 assessments. 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.

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.

Detailed procedures for obtaining each assessment are provided in the Study Procedures Manual (SPM).

Visit Window

Informed consent should be signed within 35 days prior to dosing.

Baseline disease assessment should be completed within **21 days** prior to dosing start.

ECHO/MUGA should be completed within **35 days** prior to dosing start.

Pregnancy testing should be completed **7 days** prior to dosing start and all other screening assessments should be completed within **14 days** prior to dosing start.

Visits in the first 4 weeks will be allowed ± **1** day window. Bone marrow on Day 15 can be done between Day 8 and Day 21.

Visits beyond the first 4 weeks will have ± **3 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, 8, and 10 hours post dose sampling: ±30 minutes

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

48 and 72 hours post dose sampling: ±3 hours. The 72 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.

Table 3 Time and Events, Part 1 Dose Escalation

		First Treatment Phase (28 days)										Continuation Phase	EOT	SFU Q12W
	SCR	D 1	D 2	D 4	D 8	D 11	D 15	D 16	D 18	D22	D25			
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													
Review subject dosing diary				X	X		X					every 4 wks	X	
Study Drug Dosing[14]		< ---------- Daily or per dosing schedule ----------→												
Study Drug Dispensing		X										every 4 wks		
Complete physical exam	X												X	
Brief physical exam		X[11]			X							every 4 wks		
Montreal Cognitive Assessment	X	X			X		X			X		Wk 4 and every 4 wks		
Performance status	X	X[11]			X							every 4 wks	X	
Vital Signs	X	X[11]		X	X		X					every 4 wks	X	
Height and weight[10]	X	X[11]			X							every 4 wks	X	
ECHO or MUGA	X												**x**	
12-lead ECGs	X	X			X							every 4 wks	X	
HIV, HBsAg and HCV Ab testing	X													
CBC	X	X[11]		X	X	X	X		X	X	X	Every week x 4(wk 4-7), wk 8 then every 4 wks[16]	X	
Chemistry Panel including liver function tests	X			X[22]	X	X[22]	X			X		every 4 wks	X	

	SCR	First Treatment Phase (28 days)										Continuation Phase	EOT	SFU Q12W
		D 1	D 2	D 4	D 8	D 11	D 15	D 16	D 18	D22	D25			
Fasting Lipid panel (triglyceride, cholesterol)[22]	X				X		X			X		every 4 wks		
Coagulation Panel (PT, PTT, INR, fibrinogen)	X				X		X			X		every 4 wks	X	
Vitamin B12, TSH, Free T4 or Free T3[23]	X													
Fetal hemoglobin (Hgb F)		X			X		X							
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), wk 8, then every 4 wks[4]		
Blood samples for PD[6, 21] **(peripheral blood)**	X		X	X	X	bone marrow day[6]						Wk 4, between Wk 6- 8, Wk 12 and then every 12 wks.	X	
Blood samples for exploratory studies[6, 21] **(peripheral blood)**	X			X										
Bone marrow aspirate for PD[21]	X[7]					X[18]						Wk 4, between Wk 6- 8, Wk 12 and then every 12 wks	X[17]	
Bone marrow aspirate for exploratory studies [21]	X[7]					X[18]						Wk 4, between Wk 6- 8, Wk 12 and then every 12 wks.	X[17]	
Blood smear to measure blasts	X			X	X		X					Every week x 4 (wk 4-7), Wk8, then every 4 wks		
Bone marrow aspirate/biopsy for disease assessment[24, 25]	X[20]					X[18]						Wk 4, between Wk 6- 8[19], Wk 12 and then every 12 wks.		
Telephone call for survival status[26]														X
PGX sample (buccal swab)	X													
PK blood sample on bone marrow day [15]						X (bone marrow day)						Wk 4, between Wk 6- 8, Wk 12 and then every 12 wks		
Transfusion Asssessment[13]	X				X		X			X		Every week x 4 (wk 4-7), wk 8, then every 4 wks		

	SCR	First Treatment Phase (28 days)										Continuation Phase	EOT	SFU Q12W
		D 1	D 2	D 4	D 8	D 11	D 15	D 16	D 18	D22	D25			
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 evaluation		X[5, 12]	X[5]				X[5]	X[5]						
Urine for PK		X[5, 12]	X[5]				X[5]	X[5]						

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, 10, and 24 hrs post dose. In the combination cohort, a blood sample for ATRA PK analysis will be also collected at the same time points except for the 0.25, 10 and 24 hour sample. Additional samples may be collected at 48 and 72 hrs post dose in subjects not receiving a dose on Days 2 and 3 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. In the combination cohort, a blood sample for ATRA PK analysis will be also collected at the same time points.
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, 10, and 24 hrs post dose. In the combination cohort, a blood sample for ATRA PK analysis will be also collected at the same time points except for the 0.25, 10 and 24 hour sample.
4. PK blood sample should be taken pre-dose around 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 Days 1 and 15, 24hr urine will be collected in the highest dose cohort in PK/PD expansion cohorts starting from post-dose on Day 1 and 15, and for 24 hours, i.e., until dosing on Days 2 and 16, respectively. The 24hr urine will be measured and samples collected for PK and metabolite evaluation.
6. Blood samples for PD and exploratory studies should be collected pre-dose.
7. A fresh bone marrow aspirate is requested from all subjects. This requirement is mandatory for all subjects participating in the PK-PD cohorts.
8. For women of child bearing potential only. Serum pregnancy test is required for screening and EOT 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 3 subjects. The plasma samples will be collected at following time points on Days 1 and 15: pre-dose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 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 and metabolite evaluation at pre-dose on D1 in the highest dose cohort in PK/PD expansion cohorts.
13. Platelet and blood transfusions to be assessed at designated visits and summarized per unit on a weekly cumulative basis.
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. PK blood sample should be collected pre-dose on the day of bone marrow biopsy. This sample should be collected if the bone marrow biopsy was performed on the non-planned visit days and the “PK blood sample” was not collected,

16. Twice weekly CBC monitoring may continue per institutional guidelines.
17. Bone marrow aspirate at the time of progression is optional for all subjects.
18. Between D8 and D21, timing to be optimized based on emerging data.
19. The assessment of response should occur between 1 – 4 weeks of count recovery (ANC > 1000/μl and platelets > 100,000/μl). Subjects should be off cytokine support (GCSF or GMCSF) for a minimum of 7 days before obtaining bone marrow to document remission.
20. Baseline disease assessment should be completed within 21 days prior to dosing start. Cytogenetics testing should be performed as part of disease assessment at baseline. Cytomorphology is the preferred method to determine bone marrow blast counts. However, if a bone marrow aspirate cannot be obtained for cytomorphology review, a bone marrow biopsy is strongly recommended to determine the bone marrow blast count.
21. In PK/PD expansion cohorts, PD and/or exploratory sample (peripheral blood and BMA) collection may be stopped earlier at the sponsor's discretion.
22. ATRA combination arm only.
23. Free T3 to be tested only when clinically indicated
24. At any time point in the study, if a bone marrow aspirate is found to be hemodilute (no spicules) or uninterpretable, then a bone marrow biopsy is strongly recommended to be collected at the next disease assessment time point in addition to the aspirate to ensure the conduct of a disease assessment.
25. BM slides may be evaluated for changes in morphology.
26. The Survival FU visit should be completed every 12 weeks after documented disease progression (or after initiation of another anticancer treatment). Subjects should be contacted every 12 weeks (±2 weeks) until death occurs.

Table 4 Time and Events Table: Part 2 – Expansion Cohort

	SCR	First Treatment Phase (28 days)								Continuation Phase	EOT	SFU
		D 1	D4	D 8	D11	D 15	D18	D22	D25			Q12W
Office Visit	X	X	X	X	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				every 4 wks	X	
Study Drug Dispensing		X								every 4 wks		
Complete physical exam	X										X	
Brief physical exam		X[7]		X						every 4 wks		
Montreal Cognitive Assessment	X	X		X		X		X		Wk 4 and every 4 wks		
ECOG PS	X	X[7]		X						every 4 wks	X	
Vital Signs	X	X[7]		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	
HIV, HBsAg and HCV Ab testing	X											
CBC	X	X[7]	X	X	X	X	X	X	X	Weekly x 4 wks (Wk 4-7), Wk 8 and every 4 wks[12]	X	
Chemistry Panel including LFT	X		X[18]	X	X[18]	X		X		every 4 wks	X	
Fasting Lipid panel (triglyceride, cholesterol)[18]	X			X		X		X		Every 4 wks		
Coagulation Panel including PT, PTT, INR, fibrinogen	X			X		x		X		every 4 wks	X	

	SCR	First Treatment Phase (28 days)								Continuation Phase	EOT	SFU
		D 1	D4	D 8	D11	D 15	D18	D22	D25			Q12W
Vitamin B12, TSH, Free T4 or Free T3[20]	X											
PK Blood samples		X[1]	X[8]	X[8]		X[2]				Weekly x 4 wks (Wk 4-7), Wk 8 and every 4 wks[8]		
Fetal hemoglobin (Hgb F)		X		X		X						
Pregnancy test[4]	X									every 4 wks	X	
Blood samples for PD (peripheral blood)[3, 19]	X		X	X	bone marrow day[14]					Wk 4, between Wk 6-8, Wk 12, then every 12 wks	X	
Blood samples for exploratory studies[3, 19] (peripheral blood)	X		X									
Bone marrow aspirate for PD[19]	X				X[14]					Wk 4, between Wk 6-8, Wk 12, then every 12 wks	X[5]	
Bone marrow aspirate for exploratory studies [19]	X[11]				X[14]					Wk 4, between Wk 6-8, Wk 12, then every 12 wks	X[5]	
Blood smear to measure blasts	X			X		X				Every week x 4 (Wk 4-7), Wk 8 then every 4 wks		
Bone marrow aspirate /biopsy for disease assessment [21, 22]	X[16]				X[14]					Wk 4, between Wk 6-8[13], Wk 12, then every 12 wks		
Telephone call for survival status [23]												X
PGX samples (buccal swab)	X											
PK blood sample on bone marrow day[15]					X (on bone marrow day)					Wk 4, between Wk 6- 8, Wk 12, then every 12 wks.		
Transfusion Assessment[10]	X			X		X		X		Every week x 4 (wk 4-7), Wk 8, then every 4 wks		
Adverse Events		Continuous										
Con Meds		Continuous										

1. A blood sample will be collected for PK analysis on D1 at pre-dose, 0.5, and 3 hrs post dose. . In the combination cohort, a blood sample for ATRA PK analysis will be collected at the same time points.
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. In the combination cohort, a blood sample for ATRA PK analysis will be collected at the same time points.

3. Blood samples for PD, exploratory studies should be collected pre-dose.
4. For women of child bearing potential only. Serum pregnancy test is required for screening and EOT visits. Urine pregnancy test is adequate during study visits.
5. Bone marrow aspirate at the time of progression is optional for all subjects.
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 around the same time as CBC. PK sample will not be collected beyond 48 weeeks.
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.
10. Platelet and blood transfusions to be assessed at designated visits and summarized per unit on a weekly cumulative basis
11. A fresh bone marrow aspirate at baseline is required in Part 2
12. Twice weekly CBC monitoring may continue per institutional guidelines.
13. The assessment of response should occur between 1 – 4 weeks of count recovery (ANC > 1000/μl and platelets > 100,000/μl). Subjects should be off cytokine support (GCSF or GMCSF) for a minimum of 7 days before obtaining bone marrow to document remission.
14. Between D8 and D21, timing to be optimized based on emerging data.
15. PK blood sample should be collected prior to dosing on biopsy days. This sample should be collected if the bone marrow biopsy was performed on the non-planned visit days and the "PK blood sample" was not collected within the time frame
16. Baseline disease assessment should be completed within 21 days prior to dosing start. Cytogenetics testing should be performed as part of disease assessment at baseline. Cytomorphology is the preferred method to determine bone marrow blast counts. However, if a bone marrow aspirate cannot be obtained for cytomorphology review, a bone marrow biopsy is strongly recommended to determine the bone marrow blast count.
17. Sample should be collected at pre-dose on the day of bone marrow aspirate collection.
18. ATRA combination only
19. PD and/or exploratory sample (peripheral blood and BMA) collection may be stopped earlier at the sponsor's discretion
20. Free T3 to be tested only when clinically indicated
21. At any time point in the study, if a bone marrow aspirate is found to be hemodilute (no spicules) or uninterpretable, then a bone marrow biopsy is strongly recommended to be collected at the next disease assessment time point in addition to the aspirate to ensure the conduct of a disease assessment.
22. BM slides may be evaluated for changes in morphology.
23. The Survival FU visit should be completed every 12 weeks after documented disease progression (or after initiation of another anticancer treatment). Subjects should be contacted every 12 weeks (±2 weeks) until death occurs.

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 assessed as related to the eligibility criteria listed in Section 3.2. 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 obtained 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, TSH, free T3 or free T4 (see Table 5 for full list of laboratory tests required at screening). Patients should have baseline thyroid function, vitamin B12, and metabolic panel within acceptable limits (FDA request May 2015).
- Lipid panel (ATRA combination only): triglyceride and cholesterol
- Serum beta-human chorionic gonadotropin (β-HCG) pregnancy test for female subjects of childbearing potential only
- 12-lead electrocardiogram (ECG)
- Echocardiogram (ECHO) or multi-gated acquisition (MUGA) scan
- Baseline disease assessment and bone marrow aspirates
- Review of concomitant medications
- Montreal Cognitive Assessment (MOCA)

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

CBC will be monitored twice weekly in the first 4 weeks, followed by once weekly x 4 weeks and then every 4 wks thereafter. CBC may be monitored more frequently according to the institutional guideline.

Planned time points for all safety assessments will include physical exam, vital signs, clinical laboratory tests including chemistry, hematology, and coagulation panel, ECGs and ECOG performance status. AEs and toxicities will be assessed throughout the study and will be graded according to NCI-CTCAE v. 4.03.

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.

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

7.3.1. Physical Examinations

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

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

7.3.2. ECOG Performance Status

The performance status will be assessed using the Eastern Cooperative Oncology Group (ECOG) scale (Appendix 4) 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 8.

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. 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 4.7.2 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. 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 5 should be performed according to the Time and Events Table (Section 7.1).

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 30 days after the last dose of study treatment should be repeated until the values return to normal or baseline. If such values do not return to normal within a period judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

Hematology, clinical chemistry, coagulation panel and additional parameters to be tested are listed in Table 5:

Table 5 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	
Blast count			
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
Phosphate	Lactate Dehydrogenase (LDH)	Thyroid Stimulating Hormone	Free T4 or Free T3
Vitamin B12			
Lipid			
Triglyceride	Cholesterol		
Other tests			
Coagulation Panel including PT, PTT, INR, fibrinogen			
Fetal hemoglobin (Hgb F)			
Other screening tests			
Follicle stimulating hormone (FSH) and estradiol (as needed in women of non-child bearing potential only)			
HIV, Hepatitis B surface antigen (HBsAg) and Hepatitis C antibody (HCV Ab) testing			

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

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 7 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 and ATRA 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 the highest dose cohort of the PK/PD expansion in 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 PK analysis of GSK2879552 and metabolite profiling will be collected in the highest dose cohort of the PK/PD expansion in 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 urine sample collection will be recorded.

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

7.4.3. Pharmacokinetic Sample Analysis

Plasma sample analysis will be performed under the management of Bioanalysis, Immunogenicity & Biomarkers (BIB), In Vitro/In Vivo Translation (IVIVT), Platform Technology and Science (PTS), GlaxoSmithKline for GSK2879552 and InVentiv Health

Clinical for ATRA. Concentrations of GSK2879552 and ATRA 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 and InVentiv Health Clinical.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 protocol.

Urine sample analysis may be performed under the management of Bioanalysis, Immunogenicity & Biomarkers (BIB), In Vitro/In Vivo Translation (IVIVT), 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 protocol.

7.5. Pharmacodynamics

In Part 1 and Part 2 of the study, blast cell cell-surface markers such as CD11b and CD86 that are indicative of AML sub-population will be assessed in peripheral blood and bone marrow aspirates when possible to determine the effects of GSK2879552 alone or in combination with ATRA. Change from baseline levels will be measured. Details on PD sample collection, processing, storage and shipping procedures are provided in the SPM.

7.6. Translational Research

Blood and/or bone marrow aspirates will be collected at various times, throughout the study in order to support research aimed at understanding the biological effect of GSK2879552 alone or in combination with ATRA in AML as well as identifying indicators of sensitivity or resistance.

- The successful collection of quality tumor specimens will be critical to furthering our understanding the mechanism of action of GSK2879552 alone or in combination with ATRA, and identifying the best way to treat patients with GSK2879552. Specifically, the evaluation of responders, responders at relapse, and non-responders for DNA methylation, gene alteration status, cell surface marker expression and/or pathway activation may lead to the discovery of potential new diagnostic markers or novel combinations. Similarly, pre- and post-dose tumor specimens will be evaluated for markers of target engagement, tumor response, and/or evaluated for changes in gene expression; thus supporting identification of a biologically effective dose and furthering our mechanistic understanding of LSD1 inhibition in these settings.

Performance of these investigations maybe conditional on the results of the clinical trial and samples may be selected for analysis on the basis of the clinical outcome. All samples will be retained for a maximum of 15 years after the last subject completes the study.

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

7.6.1. Tumor Biomarker Analysis

All subjects will be asked to submit peripheral blood and fresh bone marrow aspirate at baseline, during the study and at the end of treatment in order to conduct retrospective tests for the identification of potential markers of sensitivity or resistance through the assessment of DNA, RNA and/or protein.

7.6.2. RNA Expression Changes Pre and Post Treatment

Transcriptomic analysis may be performed for RNA isolated from peripheral blast cells or bone marrow aspirates pre and post treatment of GSK2879552 alone or in combination with ATRA. This will enable the evaluation of changes in RNA expression profiles that may correlate with biological response relating to AML or the action of GSK2879552.

7.7. Evaluation of Anti-Cancer Activity

Disease assessments will be made by physical examination and laboratory evaluation. Bone marrow aspiration and biopsy will be performed as stated in the Time and Event table (Section 7.1). Response criteria are listed in Appendix 6. Laboratory evaluation will include a complete blood count with differential and blood smear to measure blasts. BM slides may be evaluated for morphological changes indicative of differentiation or other potential cellular changes due to the drug.

7.8. Pharmacogenetics

An important objective of the clinical study is pharmacogenetics (PGx) research. Participation in PGx is optional, but all subjects who are eligible for the clinical study will be given the opportunity to participate. Subjects may decline participation without effect on their medical care or care during the clinical study. A separate consent signature is required for PGx research.

Subjects who provide consent will have a buccal swab sample taken for analysis. The presence/absence of genetic variations in selected candidate genes in DNA from saliva will be analysed to determine their relationship with response (safety, tolerability, PK, and efficacy) to treatment with GSK2879552, alone or in combination with ATRA.

Information regarding PGx research is included in Appendix 9. The IRB/ EC and, where required, the applicable regulatory agency must approve the PGx assessments before these can be conducted at the site. The approval(s) must be in writing and will clearly specify approval of the PGx assessments (i.e., approval of Appendix 9). In some cases, approval of the PGx assessments can occur after approval is obtained for the rest of the study. If so, then the written approval will clearly indicate approval of the PGx assessments is being deferred and the study, except for PGx assessments, can be initiated. When PGx assessments will not be approved, then the approval for the rest of the study will clearly indicate this and therefore, PGx assessments will not be conducted.

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) ≥5 times upper limit of normal (ULN) **and** bilirubin ≥2 times ULN (>35% direct) (or ALT ≥5 times ULN and international normalization ratio (INR) >1.5, if INR is measured).

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

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

Any abnormal laboratory test results (hematology, clinical chemistry), 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 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 8.5.

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 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
Pregnancy	2 Weeks	Pregnancy Notification Form	2 Weeks	Pregnancy Follow-up Form
Liver chemistry abnormalities:				
ALT ≥5 times ULN and bilirubin ≥2 times ULN (>35% direct) (or ALT ≥5 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 ≥8 times ULN; ALT ≥5 times ULN with hepatitis or rash **or** 5 times ULN ≥4 weeks	24 hours[a]	Liver Event eCRF[b]	24 hours	Updated Liver Event eCRF[b]
ALT ≥5 times ULN and <8 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 serious adverse events (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, institutional review board (IRB)/ethics committee (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 to 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 to 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 (not including platelet inhibitors), as appropriate.

Some azoles are well known to interact with ATRA; please follow your local institutional guidelines for choosing the best anti-fungal agent while the subject is on ATRA to minimize drug-drug interactions.

10.2. Prohibited Medication(s)

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

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

In the combination arm with ATRA, antifibrinolytic agents (such as tranexamic Acid, aminocaproic acid, or aprotinin), agents known to cause pseudotumor cerebri/intracranial hypertension (e.g., tetracycline) and vitamin A or multivitamin including vitamin A will be prohibited while receiving ATRA.

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 PK 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),uptake transporters organic anion transporting polypeptide 1B1 (OATP1B1) and OATP1B3, organic cation transporters (OCT2) and multidrug and toxin extrusion transporters (MATE1 and MATE2-K) should be used with caution.

10.3. 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%.

Female subjects of childbearing potential receiving ATRA combination treatment must use two reliable forms of contraception simultaneously during treatment and 30 days after the last dose of ATRA or 7 days after the last dose of GSK2879552, whichever is later. **Contraceptive counselling should be repeated monthly** while receiving ATRA and documented in the site source file. **Hormonal contraceptives are NOT considered acceptable form of contraception for female subjects of childbearing potential receiving ATRA combination treatment.** Intrauterine device or intrauterine system, male partner sterilization and double-barrier method as described below are acceptable forms of contraception for female subjects of childbearing potential receiving ATRA combination treatment.

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 7 days prior to first dose of study treatment, through the dosing period, and for at least7 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. – GSK2879552 monotherapy ONLY
- Estrogenic vaginal ring if not contraindicated for this subject population or per local practice. – GSK2879552 monotherapy ONLY
- Percutaneous contraceptive patches if not contraindicated for this subject population or per local practice. – GSK2879552 monotherapy ONLY
- Implants of levonorgestrel if not contraindicated for this subject population or per local practice. – GSK2879552 monotherapy ONLY
- Injectable progesterone if not contraindicated for this subject population or per local practice. – GSK2879552 monotherapy ONLY
- 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 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 which may inhibit efflux transporters, 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.

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

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

13. DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

13.1. Hypothesis(es)

13.2. 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.

Bayesian Prior for Combination Therapy Cohorts

The underlying Bayesian model requires that a Bayesian prior for the DLT rates for the combination be pre-specified. The monotherapy DLT rates on observed data from 200200 study and a prior Phase I ATRA study [Lee, 1993] were incorporated in the DLT prior distribution calculation. Table 6 shows the prior DLT data at a given dose.

Table 6 Prior Monotherapy DLT Data

GSK2879552 Dose level (mg)	# of DLTs / # Subjects	ATRA Dose Level (mg)	# of DLTs / # Subjects
1 mg	0/1	45 mg/m2	1/6
2 mg	0/2	60 mg/m2	0/3
4 mg	0/4	80 mg/m2	0/3
8 mg	0/1		

Additional detail on the model will be provided in the RAP.

13.3. Part 2: Expansion Cohort

The primary goal of Part 2 is to detect a clinically meaningful response rate (defined as the percentage of subjects that have achieved a CR, CRp, PR or a morphologic leukemia-free state) of 30% in AML relative to a 10% response rate suggesting no activity.

Symbolically, the null hypothesis is:

H_0: RR≤10%

The alternative hypothesis is:

H_A:RR≥30%

13.4. Sample Size Determination

13.4.1. Part 1: Dose-Escalation Phase

The total number of subjects to be enrolled into Part 1 will depend on the number of dose escalations required to establish the maximum tolerated dose of GSK2879552 alone or in

combination with ATRA; they are not driven by statistical considerations. To complete dose escalation, it is estimated that approximately 55 evaluable subjects will be enrolled .

Monotherapy doses to be studied in Part 1 will be guided by calculating the posterior probability that the DLT rate falls within an acceptable range for each subsequent dose after each dose cohort observation period. The N-CRM method will be used to calculate posterior probabilities utilizing a pre-specified prior distribution.

Combination doses to be studied in Part 1 will be guided by calculating the posterior probability that the DLT rate is as close to, but below the target toxicity rate of 33% at adjacent dose combinations. The Bayesian logistic regression method will be used to calculate posterior probabilities utilizing the pre-specified prior distribution of the toxicity rates on combinations.

13.4.2. 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.

Bayesian statistics will be employed to calculate the predictive probability that the response rate is greater than the historic response rate at interim analyses using a weak/non-informative prior. A Bayesian analysis expresses uncertainty about a parameter in terms of probability. A prior distribution is defined to characterize the level of knowledge about a parameter before the data are collected. Once the data are collected, a posterior distribution is formed using the prior distribution and the observed data. A very weak prior Beta distribution with a mean response rate equal to the target response rate is assumed. Thus, the posterior distribution for the response rate will be primarily driven by the data and can be derived as follows:

Let p denote the response rate, the number of responses in the current n subjects, x, follows a binomial distribution, Binomial (n, p). Taking the Bayesian method and combining the prior distribution and the observed data x, the posterior distribution of the response rate follows a beta distribution, i.e.

In the following case, 30% is the target response rate.

$$p \sim \text{Beta}\ (0.03 + x,\ 0.07 + n\text{-}x) \text{ with the posterior mean } (0.03+ x)/(0.07 + n).$$

For each cohort, to test hypotheses:

H_0: RR≤10%

H_A: RR≥30%

When maximum sample size is 30, the design will have a Type I error (α) of 0.064 and 89% power with the probability of early termination is 0.88 when the treatment is futile and probability of early termination 0.084 when the treatment is effective (true RR=0.3).Futility analysis for each dose expansion cohort will begin when response data is available for at least 10 evaluable subjects. The dose expansion cohort may be stopped early for futility if the predictive probability of success (response rate ≥ historical response rate) is less than 5%. Futility stopping rules are described below.

After 10 evaluable subjects have been enrolled to examine safety and efficacy, the number of observed objective responses will guide further enrolment according to the rules summarized in Figure 3. A maximum of **30** subjects will be enrolled at the RP2Ds for GSK2879552 and GSK2879552 2 in combination with ATRA, respectively. All available data will be considered in making enrollment decisions. If both cohorts enroll the maximum number of subjects, this will result in 60 subjects total. Data from part 1 may be combined with data from part 2 in the analysis to achieve the above final and interim analysis sample sizes.

Figure 3 Diagram of Stopping Rules for Cohort Expansion: GSK2879552

		Number of Responses					
Number of Subjects	**0**	**1**	**2**	**3**	**4**	**5**	**≥6**
10							
11							
12							
13							
14							
15							
16							
17							
18							
19							
20							
21							
22							
23							
24							
25							
26							
27							
28							
29							
30							

The shaded regions are the specific regions for stopping the study for futility. For instance, if there is only one response in fifteen subjects, then the predictive probability for success will be 5.0% or less (the futility criterion) and the study will be stopped.

13.5. Sample Size Sensitivity

There was no need to perform sample size sensitivity analysis.

13.5.1. Sample Size Re-estimation

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

13.6. Data Analysis Considerations

13.6.1. Analysis Populations

All Treated 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.

13.7. Interim Analysis

13.7.1. Part 1: Dose-Escalation

In Part 1, interim analyses to inform dose escalation will be performed following the completion of each monotherapy and combination dose cohort in part 1. The primary driver for dose escalation decisions in Part 1 will be governed by an N-CRM model for the mono-therapy dose cohorts and a Bayesian copula regression for the combination dose cohorts. They will be used to predict the probability of DLT at the dose levels yet to be tested to further guide these decisions. Further details of the model will be provided in the RAP

Interim analysis on Part 1 may also be conducted when all subjects enrolled in in Part 1 have had at least one post-baseline disease assessments or progressed or died or withdrawn from the study.

The goal of the interim analysis will be to further evaluate the RP2D for part 2. The totality of the data will be considered when making this evaluation.

Additionally, safety, PK, PD/biomarker data may be examined during Part 1. Prior to determining GSK2879552 dose for the next monotherapy cohort, exploratory analysis maybe conducted to assess the relationship of GSK2879552 dose levels with safety, PK and PD parameters using all data from available cohorts.

13.7.2. Part 2: Expansion Cohort

After the initial 10 evaluable 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 13.4.2. As noted in Section 13.4 data from Part 1 at the RP2D may be combined with data from part 2 to achieve the required number of subjects for the response rate analysis.

13.8. Key Elements of Analysis Plan

Data will be listed and summarized according to the GSK reporting standards, where applicable. Data will be listed and summarized mostly by doses. Separate analyses will be provided for Part I and in Part II where applicable. In some instances, analysis may also be generated based on the dose of GSK2879552. Data from Part I and Part II may be combined for some analyses at the end of the trial, for subjects treated at the same dose level. 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.

13.8.1. 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.

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 (RR) is defined as the percentage of subjects who achieved CR, CRp, PR or morphologic leukemia-free state (MLFS) among subjects who received at least one dose of treatment. Response rate and the associated 2-sided 95% exact confidence limits will be provided. A waterfall plot of percent change from baseline in bone marrow blasts and peripheral blasts will be provided.

As a secondary analysis, if data warrant, PFS, OS, DOR, and TTR will be evaluated using the Kaplain-Meier method. Summaries of median time to event, quartiles and 95% CIs will be presented.

For the analysis of PFS, if the subject received subsequent anti-cancer therapy prior to the date of documented events, PFS will be censored at the last adequate assessment (e.g. assessment where visit level response is CR, CRp, PR, MLFS, or SD) prior to the

initiation of therapy. Otherwise, if the subject does not have a documented date of events, PFS will be censored at the date of the last adequate assessment. For the analysis of overall survival (OS), the last date of known contact will be used for those subjects who have not died at the time of analysis; such subjects will be considered censored. Further details on rules for censoring will be provided in the RAP. Sensitivity analyses of PFS and further details on censoring rules will be provided in the RAP. Progression free survival (PFS) and overall survival (OS) will be summarized using Kaplan-Meier method.

The duration of response is defined for the subject or subjects with a CR, CRp, MLFS, or PR, as the time from the first documented evidence of a CR, CRp,MLFS, or PR until the first documented disease progression or death due to any cause. Censoring rules for duration of response will be outlined in detail in the RAP.

Time to Response is defined, for subjects with a CR, CRp, MLFS, or PR, as the time from first dose to the first documented evidence of responses (PR or better).

If the data warrant, duration of response and time to response will be summarized descriptively using Kaplan-Meier medians and quartiles. Only the subset of subjects who show a confirmed complete or partial tumor response will be included. Censoring rules for duration of response will follow the rules for PFS outlined in detail in the RAP.

13.8.2. Safety Analyses

The All Treated Subjects 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. Complete details of the safety analyses will be provided in the Reporting and Analysis Plan (RAP).

Safety endpoints are described in Section 2. Complete details of the safety analyses will be provided in the RAP.

A listing by subject including treatment administered, and compliance, will be generated with dates and times of treatment administered. The number of subjects exposed to study drug will be tabulated for Part 1 (for each dose cohort) and Part 2.

All relevant safety data will be listed and summarized according to IDSL standards. The reporting and analysis plan will list the IDSL templates for the displays. Adverse events will be coded and grouped by system organ class (SOC) and preferred (coded) term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA) system for adverse event coding. AEs will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 4.03. Adverse events will be summarized by maximum toxicity grade for each initial dose level. All AEs will be listed. A summary of the number and percent of subjects reporting each AE at least once will be produced for all AEs, for drug-related AEs and for SAEs for Part 1 (for each dose cohort) and Part 2. A listing of those AEs identified as dose-limiting toxicities will also be produced for each dose cohort for Part 1. A listing showing the relationship of AE

verbatim text to group terms and body systems will also be produced. A listing of withdrawals due to AEs will be provided. Deaths and SAEs will be listed should they occur.

Clinical laboratory evaluations will be performed on the days specified in the Time and Events Table. Clinical chemistry, coagulation, hematology and urinalysis values and change from baseline values will be listed for each subject and flagged high or low relative to their normal ranges, where applicable. The toxicity grade for laboratory data will be calculated using NCI CTCAE Version 4.03. The lab data will then be summarized according to the subject's baseline grade and maximum grade for each cycle of therapy. A listing of subjects with potentially clinically important lab abnormalities will also be produced. A summary of lab values and change from (baseline) may be done for Part 1 (for each dose cohort) and Part 2.

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

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

13.8.3. Pharmacokinetic Analyses

13.8.3.1. 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 and ATRA, as appropriate, 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)

GSK2879552 trough concentration (Cτ) samples collected on the specified days will be used to assess attainment of steady state. To estimate the extent of accumulation for GSK2879552 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 for GSK2879552.

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 may be pooled and analyzed qualitatively for circulating metabolites; 0-24 hour urine samples may also be analyzed for GSK2879552 and compound related metabolites. These results will be performed under a separate protocol and reported separately.

Population Pharmacokinetics

Plasma concentration-time data from Part 2 (Expansion Cohort) will be combined with data from Part 1 and possibly with data from other studies 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). Results may be reported separately.

13.8.3.2. Statistical Analysis of Pharmacokinetic Data

Statistical analyses of the PK parameters data will be the responsibility of Clinical Statistics, GSK.

Plasma concentration-time data for GSK2879552 and ATRA 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) for GSK2879552 and ATRA, if appropriate, 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).

13.8.4. 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 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.

13.8.4.1. 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.

13.8.4.2. 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 any novel biomarkers.

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:

- Institutional review board (IRB)/ethics committee (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 Institutional review board (IRB)/ethics committee (EC) is notified.

14.4. Quality Control (Study Monitoring)

In accordance with applicable regulations, Good Clinical Practice (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 electronic case report form (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 International Conference on Harmonization Good Clinical Practice (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, International Conference on Harmonization Good Clinical Practice (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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16. APPENDICES

16.1. Appendix 1: 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 below. Doses are the projected doses.

The specified prior probabilities discussed in Section 3.2 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= -1.6278(1.3652), ln(β)= -0.0116 (0.4136), and ρ=0.2429 where α and ln(β) are distributed as bivariate normal with correlation ρ.

Dose level	S1: Steep Dose-tox curve		S2: Moderate dose-tox curve		S3: Shallow dose-tox curve	
	True DLT rate	% of trials selecting dose as MTD (%)	True DLT rate	% of trials selecting dose as MTD (%)	True DLT rate	% of trials selecting dose as MTD (%)
0.25 mg	0.02	0	0.02	0	0.01	0
0.5 mg	0.05	0.1	0.05	0.3	0.02	0
1 mg	0.07	0.9	0.07	0.3	0.03	0
1.5 mg	0.12	5	0.1	1.3	0.04	0.1
2 mg	0.16	13.8	0.11	1.7	0.05	0.2
2.5 mg	0.23	21.7	0.12	3.9	0.06	0.4
3 mg	0.25	34.9	0.15	9	0.07	0.6
4 mg	0.35	21.1	0.18	18	0.08	3.4
5 mg	0.6	2.5	0.22	18.3	0.1	4.5
6 mg	0.8	0	0.25	23.3	0.13	10.8
8 mg	0.9	0	0.3	16.9	0.16	18.1
10 mg	0.95	0	0.4	5.6	0.2	17.8
12 mg	0.95	0	0.5	1.1	0.24	15.6
15 mg	1	0	0.6	0.3	0.28	15.1
20 mg	1	0	0.66	0	0.35	5.8
25 mg	1	0	0.72	0	0.42	7.6

The average sample size over the 1000 clinical trials simulated under Scenarios 1-3 was 23, 27, and 30 respectively.

16.2. Appendix 2: 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.

16.3. Appendix 3: 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:

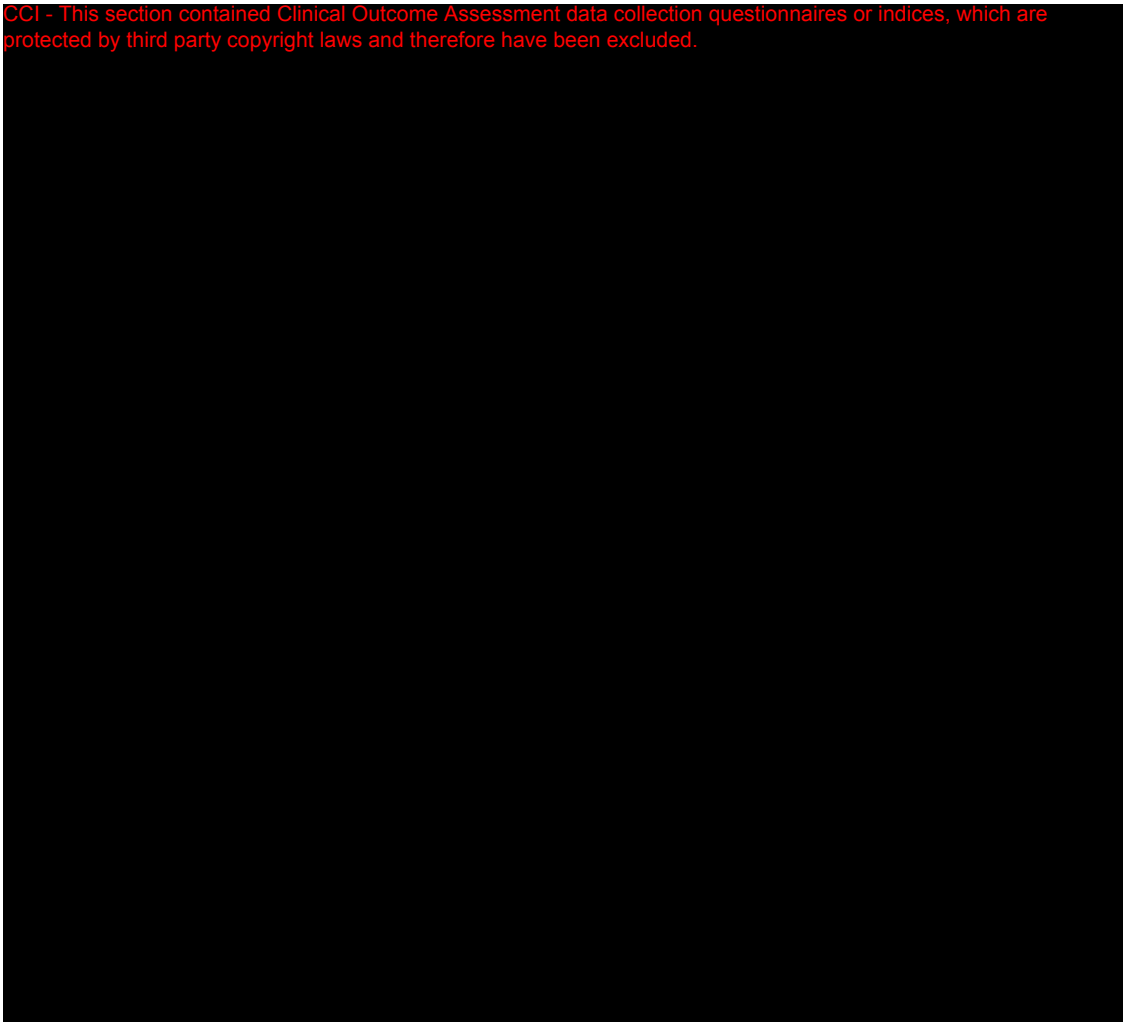
Race	Sex	Serum Creatinine, S_{cr} (µmol/L)	Equation (age in years for ≥ 18)
Black	Female	≤ 61.9	$GFR = 166 \times (S_{cr}/61.9)^{-0.329} \times (0.993)^{Age}$
Black	Female	> 61.9	$GFR = 166 \times (S_{cr}/61.9)^{-1.209} \times (0.993)^{Age}$
Black	Male	≤ 79.6	$GFR = 163 \times (S_{cr}/79.6)^{-0.411}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

$GFR = 141 \times \min(S_{cr}/\kappa, 1)\kappa \times \max(S_{cr}/\kappa, 1)$-1.209 × 0.993Age × 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.

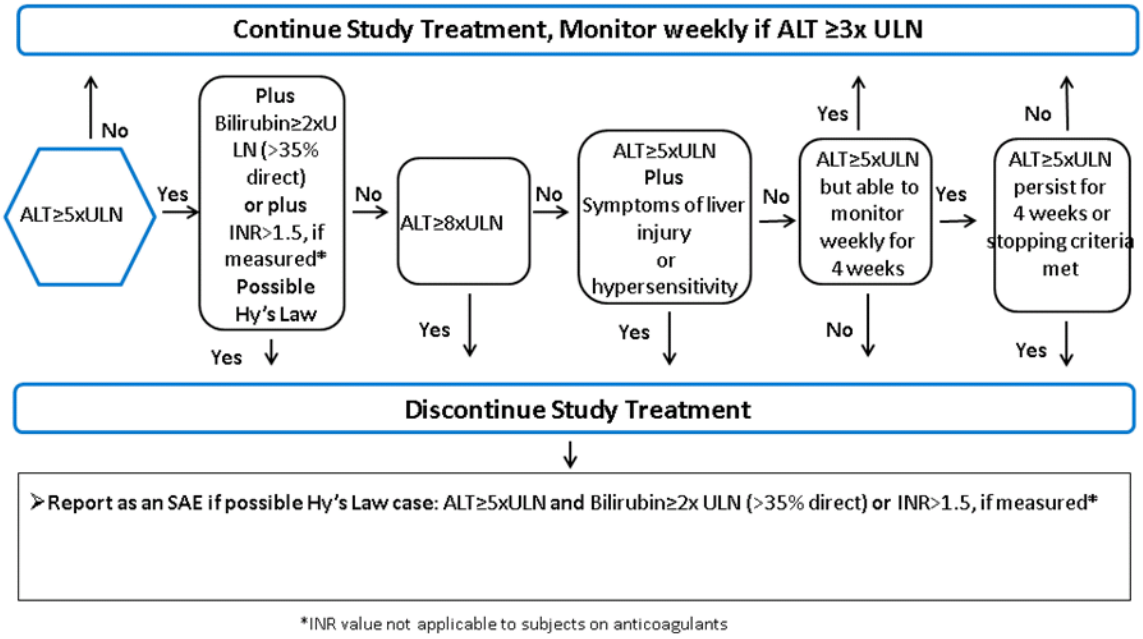
16.4. Appendix 4: ECOG Performance Status[1]



Reference:

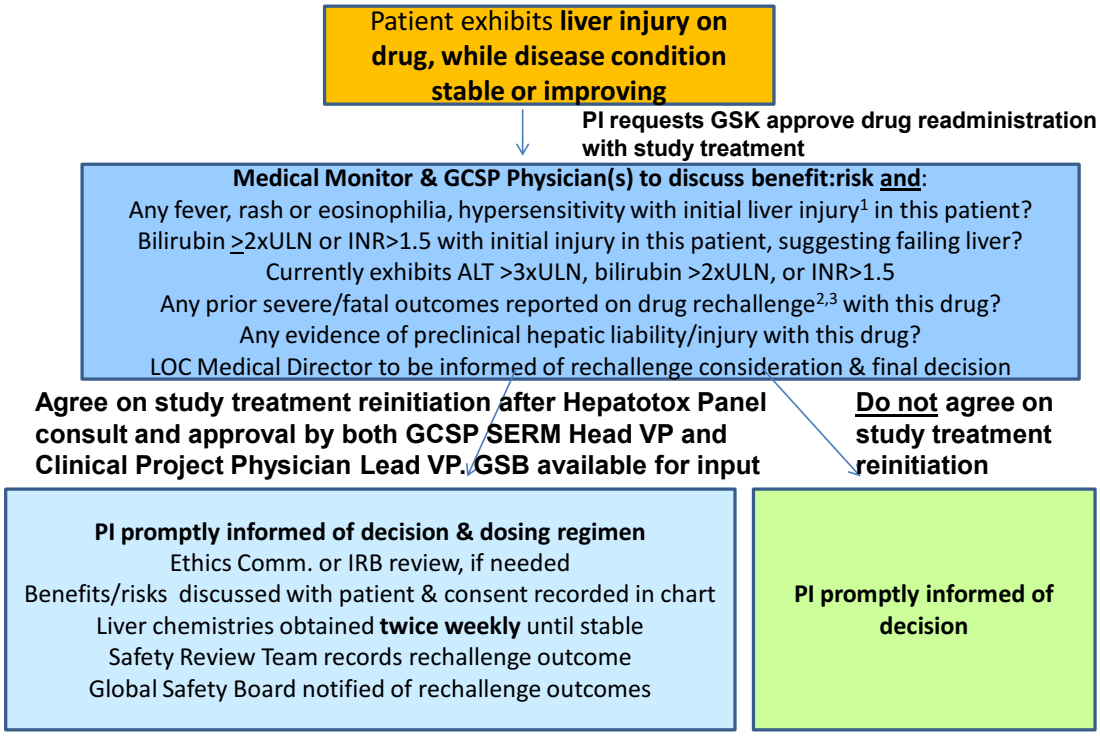
Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.

16.5. Appendix 5: Liver Chemistry Monitoring, Interruption Stopping and Follow-up Criteria



*INR value not applicable to subjects on anticoagulants

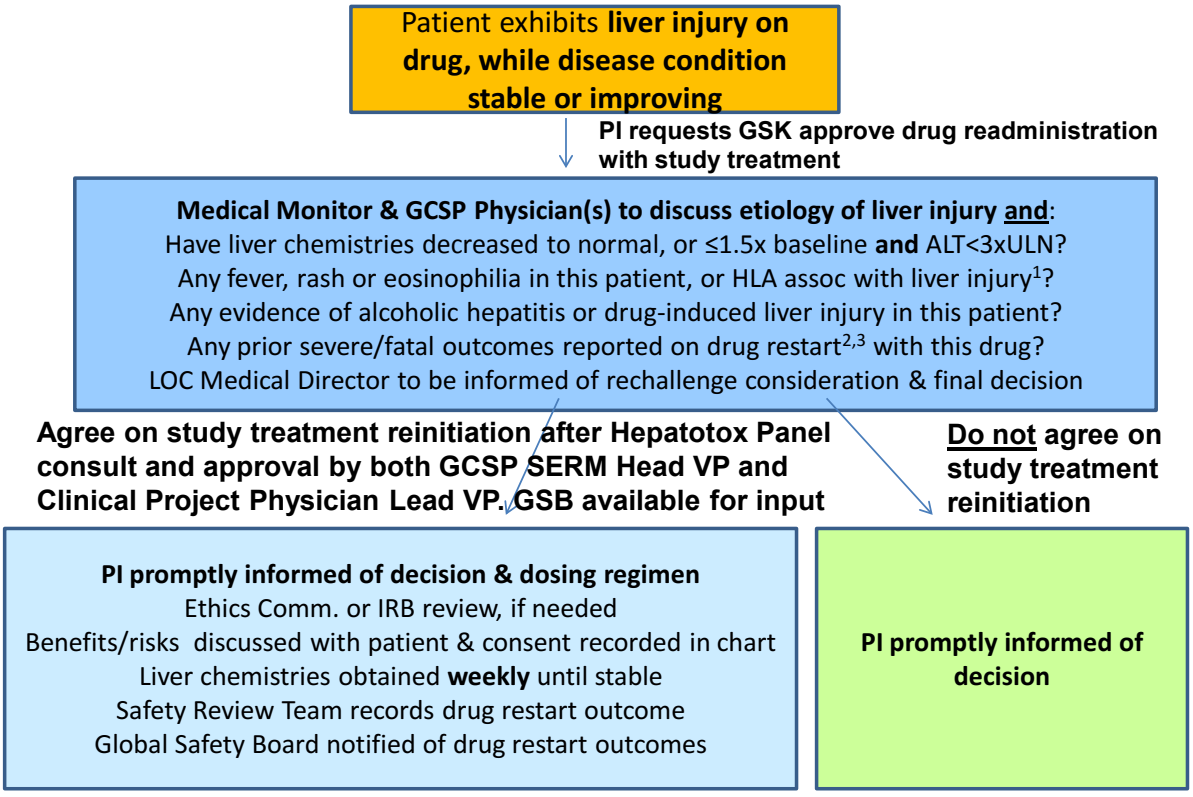
GSK process for drug rechallenge approvals



1

[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.

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

16.6. Appendix 6: Response Criteria

Overall efficacy will be assigned according to a criteria slightly modified from the standard response criteria for Acute Myeloid Leukemia [Cheson, 2003].

AML International Working Group Response Assessment

Response Criteria	Time of Assessment	Neutrophils (uL)	Platelets (uL)	Bone Marrow Blasts (%)	Other
Early Treatment Assessment	7-10 days after therapy				
Morphologic leukemia-free state	Varies by protocol	NA	NA	<5	Flow Cytometry EMD
Morphologic CR	Varies by protocol	>1,000	>100,000	<5	Transfusion EMD
Cytogenetic CR	Varies by protocol	>1,000	>100,000	<5	Cytogenetics – normal, EMD
Molecular CR	Varies by protocol	>1,000	>100,000	<5	Molecular – negative, EMD
Partial remission	Varies by protocol	>1,000	>100,000	>50 or decrease to 5-25	Blasts < 5% if Auer rod positive

Abbreviations: EMD, extramedullary disease; CR, complete remission.

Morphologic Complete Remission (CR) requires that the subject is independent of transfusions and that the following be present:

Peripheral blood counts

- Absolute neutrophil count >1.0 Gi/L
- Platelet count >100 Gi/L
- Note: Reduced hemoglobin concentration or hematocrit has no bearing on remission status
- Leukemic blasts must not be present in the peripheral blood

Bone Marrow Aspirate and Biopsy

- Maturation of all cell lines must be present
- <5% blasts in an aspirate with marrow spicules
- Auer rods must not be detectable
- Extramedullary leukemia, such as CNS or soft tissue involvement must not be present

If there is a question of residual leukemia in the bone marrow, another bone marrow aspirate should be repeated in approximately one week.

Partial Remission (PR) requires that all of the criteria for complete remission be satisfied except that:

- Decrease of at least 50% in bone marrow blasts to 5% to 25% in bone marrow aspirate and normalization of blood counts as described for CR

- If all other criteria for CR are met, then a value of <5% blasts with Auer rods present or abnormal morphology is considered partial remission

Relapse/Recurrence

Peripheral blood counts

- Reappearance of blasts in the blood as demonstrated by doubling of peripheral blasts which should be confirmed by bone marrow examination

Bone marrow aspirate

- Presence of >5% blasts, not attributable to another cause (i.e. bone marrow regeneration)

- Molecular and/or genetic relapse is characterized by reappearance of a cytogenetic or molecular abnormality

- If there are no circulating blasts and the bone marrow contains 5% to 20% blasts, then a repeat bone marrow performed ≥1 week later documenting more than 5% blasts is necessary to meet the criteria for relapse

A subject who does not achieve PR, or better is considered primary refractory.

Progressive Disease

Presence of > 50% increase in bone marrow blasts to a level of at least 50% and/or a doubling of the percentage of peripheral blood blasts to a level of at least 50%

Stable Disease

The absence of a complete or partial response, CRp, morphologic leukemia-free state and no progressive disease

Reference:

Cheson BD et al. Revised recommendations of the International Working Group for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia. J Clin Oncol. 2003;21(24):4642-9.

16.7. Appendix 7: 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

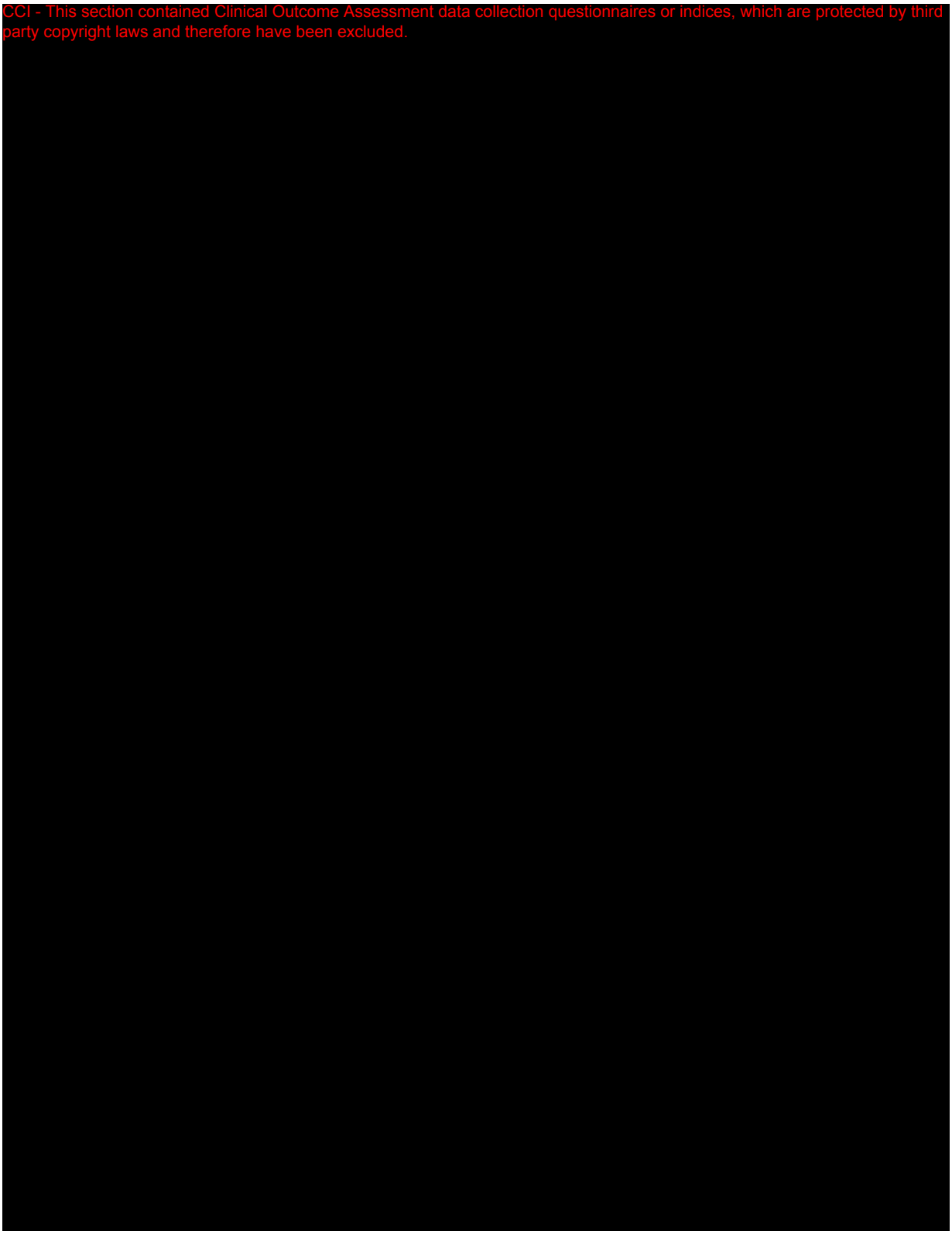
[1]Based on average corrected QT (QTc) interval value of triplicate electrocardiograms (ECGs) to include manual over-read. For example, if an ECG demonstrates a prolonged QT interval, obtain 2 more ECGs over a brief period, and then use the averaged QTc values of the 3 ECGs to determine whether the subjects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

16.8. Appendix 8: Montreal Cognitive Assessment

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



16.9. Appendix 9: Genetic Research

Genetics – Background

Naturally occurring genetic variation may contribute to inter-individual variability in response to medicines, as well as an individual's risk of developing specific diseases. Genetic factors associated with disease characteristics may also be associated with response to therapy, and could help to explain some clinical study outcomes. For example, genetic variants associated with age-related macular degeneration (AMD) are reported to account for much of the risk for the condition [Gorin, 2012] with certain variants reported to influence treatment response [Chen, 2012]. Thus, knowledge of the genetic etiology of disease may better inform understanding of disease and the development of medicines. Additionally, genetic variability may impact the pharmacokinetics (absorption, distribution, metabolism, and elimination), or pharmacodynamics (relationship between concentration and pharmacologic effects or the time course of pharmacologic effects) of a specific medicine and/or clinical outcomes (efficacy and/or safety) observed in a clinical study.

Genetic Research Objectives and Analyses

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

- Response to medicine, including GSK2879552 or any concomitant medicines;
- AML disease susceptibility, severity, and progression and related conditions

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

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

Study Population

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

Study Assessments and Procedures

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

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

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

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

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

Informed Consent

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

Subject Withdrawal from Study

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

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

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

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

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

Screen and Baseline Failures

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

Provision of Study Results and Confidentiality of Subject's Genetic Data

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

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

References

Chen H, Yu KD, Xu GZ. Association between Variant Y402H in Age-Related Macular Degeneration (AMD) Susceptibility Gene CFH and Treatment Response of AMD: A Meta-Analysis. PloS ONE 2012; 7: e42464

Gorin MB. Genetic insights into age-related macular degeneration: Controversies addressing risk, causality, and therapeutics. Mol. Asp. Med. 2012; 33: 467-486.

16.10. Appendix 10: Protocol Amendment Changes

AMENDMENT 5

Where the Amendment Applies

Protocol Amendment 5 applies to all sites participating in the conduct of the study

Summary of Amendment

Move PD secondary objective and endpoint to exploratory. Modify renal entrance criteria to align with Canadian regulatory agency. Add de-escalation language for both GSK2879552 and ATRA. Add additional dose adjustment language for hematologic toxicities. Optimize DLT criteria and safety management for retinoic acid syndrome. Update and clarify inconsistencies within protocol: update dose escalation committee language to align with new standard language, define the "baseline" MOCA, define time window for informed consent, clarify urine metabolite and PK sample collections, add morphology to analysis of bone marrow aspirates, and other administrative updates.

Section wise amendment is shown under '**Revised text**'. The deletion of the previous text is shown by '**Strike Off**' and addition of text by '**Underline**'. To minimize the size of the section, location of the change is mentioned with paragraph number and line number.

List of Specific Changes

Section: Authors:

Rationale for change:

Sponsor contact information has been updated with changes in GSK staff.

REVISED TEXT:

PPD

~~Biomarker discovery, Epigenetics DPU, PA, USA~~
Cancer Research Epigenetics Management, USA
Clinical Pharmacology, Science and Study Operations, USA

PPD

Cancer Research Epigenetics Management, USA
Clinical Pharmacology Modeling & Simulation, USA
~~Global Clinical Safety & Pharmacovigilance, UP, PA, USA~~
Biomarker discovery, Epigenetics DPU, USA
Biology, Epigenetics DPU, USA
Discovery Biometrics, USA
Biology, Epigenetics DPU, USA
~~Global Clinical Operational Sciences, RTP, NC, USA~~
~~Drug Metabolism and Pharmacokinetics, PA~~ In Vitro/In Vivo Translation, USA

PPD

~~Discovery Biometrics, PA, USA~~

Section: Sponsor/Medical Monitor Information Page

Rationale for change:

Sponsor medical monitor contact information has been updated with changes in GSK staff.

REVISED TEXT:

Role	Name	Day Time Phone Number	After-hours Phone/Cell/ Pager Number	GSK Address
Primary Medical Monitor	PPD PPD ~~MD, PhD~~ PPD PPD MD	PPD		GlaxoSmithKline 1250 South Collegeville Rd ~~Mailstop UP 4310~~ Collegeville, PA 19426, USA PPD

Section: Protocol Synopsis/ Study Objectives, Endpoints and Hypotheses

Changes made to both Part 1 Dose Escalation and Part 2 Dose Expansion

Rationale for change:

Secondary PD endpoints were moved to exploratory to ….

REVISED TEXT:

Secondary Objective #3

~~To evaluate the relationship between GSK2879552 exposure, alone or in combination with ATRA, and safety/efficacy/PD parameters~~

Secondary Endpoint #3

~~Relationship between GSK2879552 exposure markers (e.g. dose, concentration, Cmax, Cmin or AUC (0-tau)) and safety/efficacy/PD parameters. PD parameters assessed by change from baseline in select biomarkers, e.g. CD86 and CD11b~~

Exploratory Objective #1

To explore markers of differentiation (including morphology assessment) in response to GSK2879552, alone or in combination with ATRA.

Exploratory Objective #3

To evaluate the relationship between GSK2879552 exposure, alone or in combination with ATRA, and safety/efficacy/ PD parameters

Exploratory Endpoint #2

Analysis of morphology, DNA, RNA and/or protein markers in blasts cells in bone marrow aspirates and/or peripheral blood.

Exploratory Endpoint #3

Relationship between GSK2879552 exposure markers (e.g. dose, concentration, Cmax, Cmin or AUC (0-tau)) and safety/efficacy/PD parameters. PD parameters assessed by change from baseline in select biomarkers, e.g. CD86 and CD11b

Section: Protocol Synopsis/ Inclusion/ Exclusion

Rationale for change: Creatinine was removed from renal criteria and the criteria for CKD-EPI reduced as per Canadian regulatory request.

REVISED TEXT:

Criteria #10 under Subjects eligible for enrolment in the study must meet all of the following criteria:

Renal	
~~Creatinine~~ ~~OR~~ Calculated creatinine clearance by Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (**Appendix 3**) or measured from 24hr urine	~~≤1.5XULN~~ ≥ ~~50~~ 40 mL/min

Section: Protocol Synopsis/ Inclusion/ Exclusion

Rationale for change: Clarify the definition of "baseline".

Criteria #7 under Subjects meeting any of the following criteria must not be enrolled in the study:

7. ~~Baseline~~ Screening Montreal Cognitive Assessment (MOCA) score of 22 or lower

Section: Protocol Synopsis/ Clinical Activity Assessment

Rationale for change: Provide the option of performing a bone marrow biopsy if an aspirate was unevaluable at a prior timepoint.

REVISED TEXT:

Second sentence

Bone marrow aspiration/biopsy will be performed as stated in the Time and Event Table (Section 7.1).

Section 1.3.5: Clinical Safety of GSK2879552

Rationale for change: Updated version 3 of the IB available at time of publication.

REVISED TEXT:

First paragraph, first sentence:

[GlaxoSmithKline Document Number ~~2013N168888_02~~ 2013N168888_03].

Section 1.4.5: Benefit Risk Assessment

Rationale for change: Updated version 3 of the IB available at time of publication.

REVISED TEXT:

First paragraph, first sentence:

[GlaxoSmithKline Document Number ~~2013N168888_02~~ 2013N168888_03].

Section 2. Objectives, Endpoints and Hypothesis

Changes made to both Part 1 Dose Escalation and Part 2 Dose Expansion

Rationale for change:

REVISED TEXT: Secondary PD endpoints were moved to exploratory to ….

Secondary Objective #3

~~To evaluate the relationship between GSK2879552 exposure, alone or in combination with ATRA, and safety/efficacy/PD parameters~~

Secondary Endpoint #3

~~Relationship between GSK2879552 exposure markers (e.g. dose, concentration, Cmax, Cmin or AUC (0-tau)) and safety/efficacy/PD parameters. PD parameters assessed by change from baseline in select biomarkers, e.g. CD86 and CD11b~~

Exploratory Objective #1

To explore markers of differentiation (including morphology assessment) in response to GSK2879552, alone or in combination with ATRA.

Exploratory Objective #3

To evaluate the relationship between GSK2879552 exposure, alone or in combination with ATRA, and safety/efficacy/ PD parameters

Exploratory Endpoint #2

Analysis of morphology, DNA, RNA and/or protein markers in blasts cells in bone marrow aspirates and/or peripheral blood.

Exploratory Endpoint #3

Relationship between GSK2879552 exposure markers (e.g. dose, concentration, Cmax, Cmin or AUC (0-tau)) and safety/efficacy/PD parameters. PD parameters assessed by change from baseline in select biomarkers, e.g. CD86 and CD11b

Section 3.2.1: Inclusion Criteria

Rationale for change: Updated version 3 of the IB available at time of publication.

REVISED TEXT:

First paragraph, first sentence:

[GlaxoSmithKline Document Number 2013N168888_03].

Section 3.2.1: Inclusion Criteria

Rationale for change: Creatinine was removed from renal criteria and the criteria for CKD-EPI reduced as per Canadian regulatory request.

REVISED TEXT:

Inclusion criteria #10 Adequate baseline organ function as defined by:

Renal	
~~Creatinine~~ ~~OR~~ Calculated creatinine clearance by Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (Appendix 3) or measured from 24hr urine	~~≤1.5X ULN~~ ≥ ~~50~~ 40 mL/min

Section 3.2.2: Exclusion Criteria

Rationale for change: Clarify the definition of "baseline".

REVISED TEXT:

Exclusion criteria #78

8. ~~Baseline~~ Screening Montreal Cognitive Assessment (MOCA) score of 22 or lower

Section 4.2.1: GSK2879552 Monotherapy

Rationale for change: The text was updated to align with new written standards for assurance of increased data integrity during dose escalation decisions.

REVISED TEXT:

Dose Escalation Committee

First paragraph, third sentence

Quality control of critical safety data will be described in the Dose Escalation Plan, which includes ongoing study monitoring visits, Sponsor review of the clinical database, and confirmation by site investigators and/or delegate that the data is accurate and complete.

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/de-escalation should continue as recommended by the N-CRM. The dose-escalation decision and rationale for each cohort will be discussed with investigators during teleconference(s) and documented in writing, with copies maintained at each study site and in the study master file.

Section 4.2.2: GSK2879552 and ATRA combination

Rationale for change: Language was added for reduced dose levels for both GSK2879552 or ATRA for situations where dose level 1 is not tolerated.

REVISED TEXT:

Second paragraph, first sentence

Starting at dose level 1, the following GSK2879552 dose levels are planned for evaluation in combination with ATRA ~~45 mg/m^2/day~~.

Dose level	GSK2879552	ATRA
1	2 mg/day	45 mg/m^2/day
2	4 mg/day	45 mg/m^2/day
3	8 mg/day	45 mg/m^2/day
4	12 mg/day	45 mg/m^2/day
5	20 mg/day	45 mg/m^2/day

A reduced dose of GSK2879552 or ATRA may be considered if the combination is not well tolerated at dose level 1. The initial dose level reductions allow for either drug to be reduced. Subsequent dose levels are based on the totality of data and upon discussion with the investigators.

Dose level	GSK2879552 ATRA fixed at 45mg/m2
-1	1 mg/day
-2	0.5 mg/day

Dose level	GSK2879552 ATRA <30mg/m^2
1a	2 mg/day
-1a	1 mg/day
-2a	0.5 mg/day

~~Dose level 1: GSK2879552 2 mg/day~~

~~Dose level 2: GSK2879552 4 mg/day~~

~~Dose level 3: GSK2879552 8 mg/day~~

~~Dose level 4: GSK2879552 16 mg/day~~

~~Dose level 5: GSK2879552 32 mg/day~~

Section 4.2.5: Dose-Limiting Toxicity

Rationale for change: The text was updated to clarify criteria for a DLT.

REVISED TEXT:

Second paragraph, first sentence:

An event will be considered a DLT if it occurs within the first ~~4 weeks~~ 28 days of treatment (with exception of myelosuppression as stated below), and meets one of the following criteria unless it can be clearly established that the event is unrelated to treatment.

Subjects unable to receive at least 75% of scheduled doses within the DLT period for reasons other than toxicity (e.g., acute illness, disease progression) will not be evaluable

Hematologic DLT:

- Myelosuppression (as defined by absolute neutrophil count (ANC) <500/µl AND platelets ≤25,000/µl) with bone marrow hypoplasia (cellularity ≤ 5%) without evidence of leukemia (<5% blasts) for ≥ ~~28~~ 42 days after drug cessation. ~~If a subject meets above criteria at the time of drug cessation within the DLT observation period, the dose escalation decision will be delayed until 28 days have elapsed post drug cessation.~~

- Grade ≥3 ~~or 4~~ non-hematologic toxicity that is considered clinically significant and lasts >72 hours. Fatigue, asthenia, or nausea that respond to standard medical care within 72 hours and new electrolyte disturbance that respond within 24 hours are exceptions. In addition, electrolyte disturbances associated with underlying malignancy are not considered DLT.
- 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 ≥42 ~~28~~ days ~~or greater~~ due to unresolved toxicity.

Section 4.7.3: Mental Status Stopping Criteria

Rationale for change: Clarify the definition of «baseline» MOCA.

REVISED TEXT:

Second paragraph, second bullet:

- A decrease of 3 points or more from baseline (Pre-dose Day 1) MOCA score

Third paragraph, first bullet:

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

Section 4.8.3: Dose Adjustment for Hematologic Toxicity

Rationale for change: Previous protocol did not define management guidelines for thrombocytopenia with >5% blasts. Text also added for fall precautions resulting from INDSRs on the study.

REVISED TEXT:

Toxicity	**Dose Adjustment/ Stopping Criteria**	**Management Guidelines**
At all thrombocytopenia grades, implement fall precautions to avoid bleeding due to trauma, e.g. trauma to head can cause a subdural hematoma. This risk increases with higher grades of thrombocytopenia		
Thrombocytopenia regardless of blast count	Grade 1, 2 & 3 (platelets ≥25,000/mm^3)	Continue dosing at same dose level with more frequent monitoring as necessary.
Thrombocytopenia if blasts >5%	Grade 4 (platelets <25,000/mm^3) and/or any grade accompanied by severe bleeding related to thrombocytopenia	If platelet count <25,000/mm^3 but ≥10,000/mm^3: 3. Use clinical judgement to institute more frequent monitoring as necessary 4. Institute platelet transfusion as appropriate. If platelet count <10,000/mm^3: 6. Continue treatment and start platelet transfusion as per institutional guidelines. 7. If repeat platelet transfusions are not able to rescue platelet count, then consider irradiated, leuko-pherised or HLA-matched platelets as clinically appropriate 8. If still unable to rescue platelet count, investigator may consider treatment interruption in discussion with medical monitor. 9. Use of concomitant therapies (tranexamic acid) is permitted. Please note tranexamic acid is prohibited for subjects receiving GSK2879552 in combination with ATRA. 10. Use of hydroxyurea in the setting of increased blast counts in conjunction with decreased platelet counts is permitted. 1.
Thrombocytopenia if blasts <5%	Grade 4 (platelets <25,000/mm^3) and/or any grade accompanied by severe bleeding related to thrombocytopenia	If platelet count <25,000/mm^3 but ≥10,000/mm^3: 3. Use clinical judgement to institute more frequent monitoring as necessary 4. Institute platelet transfusion as appropriate. If platelet count <10,000/mm^3 (or ≤25,000/mm^3 with accompanying fever, sepsis, or minor bleeding): 5. Treatment may be held for up to 4 weeks and resume* as soon as count recovery has occurred (i.e., neutrophils ≥0.5 and platelets ≥25 x 10^9/L). Use clinical judgement to institute more frequent monitoring as necessary. 6. The treatment may be held for additional 1-2 weeks if the neutrophil and platelet counts do not recover after the initial 2 weeks. 7. After a total of 5-6 consecutive weeks, if there is no evidence of recovering blood counts, a repeat bone marrow examination should be performed during that period (approximately -35-42 days after drug cessation) to evaluate for the possibility

Toxicity	Dose Adjustment/ Stopping Criteria	Management Guidelines
		of hematologic DLT. 8. If persistent for 6 weeks and not attributed to disease or requires platelet transfusions for bleeding in the absence of the disease, the subject will be withdrawn from the study. *If treatment resumes, the dose and schedule may be adjusted based on platelet count, i.e., dose can be reduced by at least 25% increments up to two times.

~~The treatment may be held for 2 weeks if~~

- ~~≤5% myeloblasts in bone marrow AND~~
- ~~neutrophil and platelet count did not recover to neutrophils ≥0.5 x 10^9/L and platelets ≥25 x 10^9/L~~

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

~~The treatment may be held for additional 1-2 weeks if the neutrophil and platelet count did not recover after 2 weeks. If there is no evidence of recovering blood counts, a repeat bone marrow examination should be performed during that period (approximately 14-28 days after drug cessation) to evaluate for the possibility of hematologic DLT.~~

~~When the treatment resumes post remission, the dose may be adjusted based on platelet count, i.e., dose can be reduced by at least 25% increments up to twice when the platelet count <25 x 10^9/L (G4 thrombocytopenia) and it is not attributed to the disease. If a subject has persistent G4 thrombocytopenia for 4 weeks not attributed to disease or requires platelet transfusions for bleeding in the absence of the disease, the subject will be withdrawn from the study.~~

Section 4.8.4.1: Retinoic Acid-~~APL~~ Syndrome

Rationale for change: The text was updated with detailed management guidelines and signs and symptoms of differentiation syndrome which has been shown to occur in patients with APL treated with ATRA.

REVISED TEXT:

About 25% of patients with APL treated with ATRA have experienced the retinoic acid-~~APL~~ (RA ~~APL~~) syndrome characterized by fever, dyspnea, acute respiratory distress, weight gain, radiographic pulmonary infiltrates, pleural and pericardial effusions, edema,

and hepatic, renal, and multi-organ failure [ATRA Prescribing Information, 2004]. This syndrome has occasionally been accompanied by impaired myocardial contractility and episodic hypotension. The syndrome generally occurs during the first month of treatment, with some cases reported following the first dose of ATRA.

Retinoic Acid Syndrome should be strongly suspected if the following signs or symptoms (without any other clear or established etiology) emerge during treatment with GSK2879552:

- New or worsening progressive dyspnea or hypoxemia, with increasing demands for supplemental oxygen; respiratory distress refractory to treatment for the initially suspected cause
- Radiologic evidence of new or worsened bilateral pulmonary involvement (infiltrates or opacities) with or without presence of infection, refractory to treatment with anti-infectives (antibiotics, antivirals, antifungals)
- Radiologic evidence of new or worsened pleural or pericardial effusion that is refractory to treatment for an initially suspected cause
- New or worsened peripheral edema, with rapid weight gain (e.g., >5 kg/11 pounds over 7 days)
- Increase in serum creatinine (e.g., >2-fold from baseline)
- The following symptoms or signs may be features of retinoic acid syndrome but if isolated and not accompanied by pulmonary or renal manifestations, may not require rapid initiation of retinoic acid syndrome treatment (unless sufficiently severe and prolonged):
    - Unexplained fever $\geq 38^{o}C$ ($100.4^{o}F$)
    - Rash of unknown origin
    - Bone pain
    - Lymphadenopathy

The measures below are recommended to be taken at the earliest manifestations of suspected retinoic acid syndrome:

- Patients with severe or rapidly progressing retinoic acid syndrome should be hospitalized for continued observation
- In case of uncertainty with the diagnosis, e.g., presence of less specific symptoms of moderate severity, patients should be closely monitored, as the condition may rapidly worsen
- Corticosteroids should be promptly initiated (e.g., 10 mg of dexamethasone every 12 hours until resolution of retinoic acid syndrome). Once resolved the corticosteroid dose can be progressively reduced over 1-2 weeks
- GSK2879552 and/or ATRA may be withheld at the physician's discretion. Due to the long half-life of GSK2879552 (about 16 hours), treatment interruption may not immediately reverse the symptoms of retinoic acid syndrome. If interrupted, GSK2879552 treatment may be reinitiated at the original or a reduced dose, once the signs and symptoms resolve and the patient's clinical condition improves
- In patients with elevated WBC counts, prompt initiation of hydroxyurea is suggested, or treated as per standard local practice (e.g., dose of 2 to 3g PO 2- or 3-times daily for WBC $>30x10^{9}/L$)

- In cases of severe leukocytosis, use of leukapheresis may be appropriate
- For substantial fluid accumulation, initiation of furosemide may be appropriate, as per local standard practice
- Patients with pericardial effusion (a less common manifestation of retinoic acid syndrome) can require urgent cardiac intervention due to it being a life-threatening condition
- Patients with increasing serum creatinine levels should be evaluated for tumor lysis syndrome
- Patients experiencing a rapid increase in peripheral blood cells should be monitored for disseminated intravascular coagulopathy and hemorrhage
- Imaging techniques such as standard or high-resolution computerized tomography (CT) scan and chest X-ray are useful for establishing a diagnosis of retinoic acid syndrome by identifying pulmonary infiltrates or effusions; noting that a CT scan is more sensitive in detecting early radiological signs of retinoic acid syndrome-associated changes

~~High dose steroids should be immediately initiated at the first suspicion of the RA-APL syndrome irrespective of the leukocyte count, e.g., dexamethasone 10 mg intravenously administered every 12 hours for 3 days or until the resolution of symptom. . The first signs of the syndrome include:~~

~~unexplained fever~~

~~dyspnea and/or weight gain~~

~~abnormal chest auscultatory findings or radiographic abnormalities~~

~~Prophylactic treatment with steroid may be considered per institutional guideline when leukocyte counts double in number to >10,000/uL from baseline leukocyte <10,000/uL.~~

~~Prophylactic treatment with hydroxyurea and steroid may be considered per institutional guideline when leukocyte counts double in number from baseline leukocyte 10,000-30,000 /uL.~~

~~In cases of moderate and severe RA-APL syndrome, temporary interruption of ATRA treatment should be considered.~~

Section 6.1: Screen and Baseline Failures

Rationale for change: Text was updated to allow for rescreening of potential subjects.

REVISED TEXT:

Second paragraph:

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. Rescreened participants should be assigned the same

participant number as for the initial screening if rescreening for same arm of study (monotherapy to monotherapy or ATRA combination to ATRA combination.) If rescreening for a different arm of the study, (monotherapy to ATRA combination or ATRA combination to monotherapy) participants will need a new screening number. Please refer to the Study Procedures Manual for more details.

Section 7: Study Assessments and Procedures

Rationale for change: Text was updated to widen the window for signing of the informed consent.

REVISED TEXT:

Seventh paragraph:

Visit Window

Informed consent should be signed within 35 days prior to dosing.

Section 7.1: Time and Events Table (Table 3 – Time and Events, Part 1 Dose Escalation)

Rationale for change: The Time and Events Tables were updated to clarify vitamin B12, TSH, free T3 or free T4 requirement at screening, addition of allowance for bone marrow biopsies when bone marrow aspirate is inevaluable, urine metabolite collection.

REVISED TEXT:

Modified rows:

		First Treatment Phase (28 days)										Continuation Phase	EOT
	SCR	D 1	D 2	D 4	D 8	D 11	D 15	D 16	D 18	D22	D25		
Vitamin B12, TSH, Free T4 or Free T3[23]	X												
Blood samples for PD[6, 21] (peripheral blood)	X		X	X	X	bone marrow day[6]						Wk 4, between Wk 6- 8[19], Wk 12 and then every 12 wks.	X
Bone marrow aspirate for PD[21]	X[7]					X[18]						Wk 4, between Wk 6- 8[19], Wk 12 and then every 12 wks	X[17]
Bone marrow	X[7]					X[18]						Wk 4,	X[17]

	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	D22	D25		
aspirate for exploratory studies [21]												between Wk 6- 8[19], Wk 12 and then every 12 wks.	
Bone marrow aspirate/biopsy for disease assessment[24, 25]	X[20]						X[18]					Wk 4, between Wk 6- 8[19], Wk 12 and then every 12 wks.	
Highest Dose in PK/PD expansion cohort ONLY													
Urine for PK		X[5, 12]	X[5]				X[5]	X[5]					

Modified footnotes #6, 9, 20, 23, 24, 25:

6. Blood samples for PD and exploratory ~~biomarkers~~ studies should be collected pre-dose.
9. Additional samples will be collected for metabolite evaluation in the highest dose cohort in PK/PD expansion cohorts, in at least ~~6~~ 3 subjects. The plasma samples will be collected at following time points on Days 1 and 15: pre-dose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, and 24 hrs post dose
20. Baseline disease assessment should be completed within 21 days prior to dosing start. Cytogenetics testing should be performed as part of disease assessment at baseline. Cytomorphology is the preferred method to determine bone marrow blast counts. However, if a bone marrow aspirate cannot be obtained for cytomorphology review, a bone marrow biopsy is ~~allowed~~ strongly recommended to determine the bone marrow blast count.
23. Free T3 to be tested only when clinically indicated
24. At any time point in the study, if a bone marrow aspirate is found to be hemodilute (no spicules), then a bone marrow biopsy is strongly recommended to be collected at the next disease assessment time point in addition to the aspirate to ensure the conduct of a disease assessment.
25. BM slides may be evaluated for changes in morphology.

Section 7.1: Time and Events Table (Table 4 – Time and Events, Part 2 Dose Expansion)

REVISED TEXT:

Modified rows:

	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	D22	D25		
Vitamin B12, TSH, Free T4 or Free T3[20]	X												
Bone marrow aspirate/biopsy for disease	X[16]					X[14]						Wk 4, between Wk 6- 8[13], Wk 12	

	SCR	First Treatment Phase (28 days)									Continuation Phase	EOT
		D1	D2	D4	D8	D11	D15	D16	D18	D22	D25	
assessment[21, 22]											and then every 12 wks.	

Modified footnotes:#3,16; Added:#20,21 & 22

3. Blood samples for PD, exploratory ~~biomarkers~~ studies should be collected pre-dose.
16. Baseline disease assessment should be completed within 21 days prior to dosing start. Cytogenetics testing should be performed as part of disease assessment at baseline. Cytomorphology is the preferred method to determine bone marrow blast counts. However, if a bone marrow aspirate cannot be obtained for cytomorphology review, a bone marrow biopsy is ~~allowed~~ strongly recommended to determine the bone marrow blast count.
20. Free T3 to be tested only when clinically indicated
21. At any time point in the study, if a bone marrow aspirate is found to be hemodilute (no spicules), then a bone marrow biopsy is strongly recommended to be collected at the next disease assessment time point in addition to the aspirate to ensure the conduct of a disease assessment.
22. BM slides may be evaluated for changes in morphology.

Section 7.2: Demographic/Medical History and Baseline Assessments

REVISED TEXT:

Baseline (Screening) assessments obtained will include:

Fifth paragraph, fourth bullet:

- Clinical laboratory tests: hematology, clinical chemistry, coagulation parameters, vitamin B12, TSH, free T3 or free T4 (see Table 5 for full list of laboratory tests required at screening). Patients should have baseline thyroid function, vitamin B12, and metabolic panel within acceptable limits (FDA request May 2015).

Fifth paragraph, last bullet:

- Montreal Cognitive Assessment (MOCA)

Section 7.3.7: Laboratory Assessments

REVISED TEXT:

Added to Table 5: List of Clinical Laboratory Tests, under Clinical Chemistry

Free T4 or Free T3 and Vit B12

Section 7.6: Translational Research

REVISED TEXT:

Last sentence:

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

Section 7.7: Evaluation of Anti-cancer therapy

REVISED TEXT:

Last sentence:

BM slides may be evaluated for morphological changes indicative of differentiation or other potential cellular changes due to the drug.

Section 8.3: Laboratory and Other Safety Assessment Abnormalities Reported as AEs or SAEs

REVISED TEXT:

First paragraph, first sentence:

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.

Section 10.1: Permitted Medication(s)

REVISED TEXT:

Second paragraph added:

Some azoles are well known to interact with ATRA; please follow your local institutional guidelines for choosing the best anti-fungal agent while the subject is on ATRA to minimize drug-drug interactions.

Section 10.2: Prohibited Medication(s)

REVISED TEXT:

First paragraph, first sentence:

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.

Section 10.2.2: Drugs that may have their PK altered by GSK2879552

REVISED TEXT:

Second paragraph:

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 organic cation transporters (OCT2) and multidrug and toxin extrusion transporters (MATE1 and MATE2-K) should be used with caution. ~~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.~~

Section 16.6: Appendix 6: Response Criteria

REVISED TEXT:

~~Overall efficacy will be assigned according to a criteria slightly modified from the standard response criteria for Acute Myeloid Leukemia [Cheson, 2003].~~

~~**AML International Working Group Response Assessment**~~

Response Criteria	**Time of Assessment**	**Neutrophils (uL)**	**Platelets (uL)**	**Bone Marrow Blasts (%)**	**Other**
Early Treatment Assessment	7-10 days after therapy				
Morphologic leukemia-free state	Varies by protocol	NA	NA	<5	Flow Cytometry EMD
Morphologic CR	Varies by protocol	>1,000	>100,000	<5	Transfusion EMD
Cytogenetic CR	Varies by protocol	>1,000	>100,000	<5	Cytogenetics – normal, EMD
Molecular CR	Varies by protocol	>1,000	>100,000	<5	Molecular – negative, EMD
Partial remission	Varies by protocol	>1,000	>100,000	>50 or decrease to 5-25	Blasts < 5% if Auer rod positive

Abbreviations: EMD, extramedullary disease; CR, complete remission.

Morphologic Complete Remission (CR) requires that the subject is independent of transfusions and that the following be present:

Peripheral blood counts

- Absolute neutrophil count >1.0 Gi/L
- Platelet count >100 Gi/L
- Note: Reduced hemoglobin concentration or hematocrit has no bearing on remission status
- Leukemic blasts must not be present in the peripheral blood

Bone Marrow Aspirate and Biopsy

- Maturation of all cell lines must be present
- <5% blasts in an aspirate with marrow spicules
- Auer rods must not be detectable
- Extramedullary leukemia, such as CNS or soft tissue involvement must not be present

If there is a question of residual leukemia in the bone marrow, another bone marrow aspirate should be repeated in approximately one week.

Partial Remission (PR) requires that all of the criteria for complete remission be satisfied except that:

- Decrease of at least 50% in bone marrow blasts to 5% to 25% in bone marrow aspirate and normalization of blood counts as described for CR

- ~~If all other criteria for CR are met, then a value of <5% blasts with Auer rods present or abnormal morphology is considered partial remission~~

~~Relapse/Recurrence~~

~~Peripheral blood counts~~

- ~~Reappearance of blasts in the blood as demonstrated by doubling of peripheral blasts which should be confirmed by bone marrow examination~~

~~Bone marrow aspirate~~

- ~~Presence of >5% blasts, not attributable to another cause (i.e. bone marrow regeneration)~~

- ~~Molecular and/or genetic relapse is characterized by reappearance of a cytogenetic or molecular abnormality~~

- ~~If there are no circulating blasts and the bone marrow contains 5% to 20% blasts, then a repeat bone marrow performed ≥1 week later documenting more than 5% blasts is necessary to meet the criteria for relapse~~

~~A subject who does not achieve PR, or better is considered primary refractory.~~

~~Progressive Disease~~

~~Presence of > 50% increase in bone marrow blasts to a level of at least 50% and/or a doubling of the percentage of peripheral blood blasts to a level of at least 50%~~

~~Stable Disease~~

~~The absence of a complete or partial response, CRp, morphologic leukemia-free state and no progressive disease~~

~~Reference:~~

~~Cheson BD et al. Revised recommendations of the International Working Group for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia. J Clin Oncol. 2003;21(24):4642-9.~~

[Modified Cheson, 2003]

Complete remission (CR): The subject must achieve a morphologic leukemia-free state (≤ 5% blasts) and have no evidence of extramedullary disease. The subject must be free of all symptoms related to leukemia, have an absolute neutrophil count ≥1 x 10^9/L and platelet count ≥100 x 10^9/L, and be transfusion independent.

CRp: Marrow response as per CR but platelet count <100 x 10^9/L.

CRi: Marrow response as per CR but platelet count <100 x 10^9/L or neutrophil count <1 x 10^9/L.

Partial remission (PR): A decrease from baseline of at least 50% in the number of bone marrow blasts, to between 5% and 25% of the bone marrow aspirate.

No response: Subject does not meet criteria for CR, CRp, CRi, or PR.

Recurrence: Morphologic relapse, defined as the reappearance of peripheral blasts or increase in bone marrow blasts ≥ 5% not attributable to any other cause (e.g., infection, growth factor support, bone marrow regeneration)

AMENDMENT 4

Where the Amendment Applies

Protocol Amendment 4 applies to all sites participating in the conduct of the study

Summary of Amendment

Add language to include a stopping rule that halts enrollment upon the occurrence of any encephalopathy, unless clearly attributable to central nervous system disease involvement or intercurrent illness.

List of Specific Changes

Section 4.7.3 Mental Stopping Criteria

REVISED TEXT: (Added)

Enrollment will be stopped upon the occurrence of any encephalopathy, unless clearly attributable to central nervous system disease involvement or intercurrent illness.

AMENDMENT 3

Where the Amendment Applies

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

Summary of Amendment

A combination arm with ATRA is added. One of the Dose Limiting Toxicities criteria has been revised according to the NCI criteria. Pharmacodynamic/exploratory sample collection and processing have been changed. Pharmacogenetic sample has been added. The criteria for Progressive Disease and Stable Disease have been added in the response criteria. Concomitant medications have been updated.

Section wise amendment is shown under '**Revised text**'. The deletion of the previous text is shown by '**Strike Off**' and addition of text by '**Underline**'. To minimize the size of the section, location of the change is mentioned with paragraph number and line number.

List of Specific Changes

Section: Medical Monitor Information Page / Sponsor Contact Information:

REVISED TEXT:

Role	Name	Day Time Phone Number	After-hours Phone/Cell/ Pager Number	GSK Address
Primary Medical Monitor	PPD MD, PhD			GlaxoSmithKline 1250 South Collegeville Rd Mailstop UP 4310 Collegeville, PA 19426, USA PPD

Section: List Of Abbreviations

REVISED TEXT: (added)

ATRA	All-Trans Retinoic Acid

Section: Protocol Synopsis
REVISED TEXT:
Last sentence: The proposed Phase I study will evaluate the safety and tolerability, pharmacokinetics, pharmacodynamics, and clinical activity to determine the recommended Phase 2 Dose (RP2D) and regimen of GSK2879552, alone or in combination with ATRA, given orally in adult subjects with relapsed/refractory AML.

Section: Protocol Synopsis- Study Objectives, Endpoints And Hypotheses and Section 2: Objectives, Endpoints And Hypotheses
REVISED TEXT:

PART 1: Escalation Cohort		
	Objectives	**Endpoints**
Primary	1. To determine the safety, tolerability, MTD and/or RP2D and regimen of GSK2879552, alone or in combination with ATRA, given orally in adult subjects with AML	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 PK of GSK2879552, alone or in combination with ATRA, after single- and repeat-dose oral administration. 2. To evaluate clinical response after treatment with GSK2879552, alone or in combination with ATRA. 3. To evaluate the relationship between GSK2879552 exposure, alone or in combination with ATRA, and safety/efficacy/ PD parameters 4. To characterize the PK of ATRA in combination with 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, tmax, t½ (terminal phase and/or effective half-life), accumulation ratio, and time invariance. 2. Objective response rate (% of subjects achieving CR, PR, CRp or morphologic leukemia-free state) per response criteria. 3. Relationship between GSK2879552 exposure markers (e.g. dose, concentration, Cmax, Cmin or AUC (0-tau)) and safety/efficacy/PD parameters. PD parameters assessed by change from baseline in select biomarkers, e.g. CD86 and CD11b 4. ATRA PK parameters following single and repeat-dose administration of ATRA and GSK2879552, including AUC, Cmax, tmax, t½ (terminal phase).
Exploratory	1. To explore markers of differentiation ~~assess feasibility of a select gene panel for use as a PD assay for~~ in response to GSK2879552, alone or in combination with ATRA.	1. Change from baseline expression in ~~select genes~~ cell surface markers in AML cells derived from bone marrow and/or peripheral blood.

	2. To investigate the mechanism of action and indicators of sensitivity and ~~relationship between tumor genomic profile, and response or~~ resistance to GSK2879552, alone or in combination with ATRA.	2. Analysis of DNA, RNA and/or protein markers in blasts cells in bone marrow aspirates and/or peripheral blood. ~~tumor samples to discover determinants of response~~
	~~3. To assess RNA expression profile in tumor cells for identifying mechanisms of rational combination and potential resistance mechanism.~~	~~3. Transcriptomic (RNA) profile of blast cells in bone marrow aspirates and peripheral blood pre- and post-treatment with GSK2879552.~~
	~~4. To discover circulating markers of response and resistance and correlation with clinical outcome~~	~~4. Analysis of circulating biomarkers (e.g. circulating cell free DNA [cfDNA], protein and RNA) and correlation with response~~
	3. To characterize the metabolite profile of GSK2879552 after oral single and repeat-dosing in some subjects	3. GSK2879552 metabolites in plasma and/or urine
	4. To determine the amount of GSK2879552 excreted in urine after oral single and repeat-dosing in some subjects treated with GSK2879552	4. Concentration of GSK2879552 in urine measured with an investigational bio-analytical method and extrapolated to total amount excreted in urine over time
	5. To investigate the relationship between genetic variants in candidate genes,PK and safety profile of GSK2879552, alone or in combination with ATRA.	5. Pharmacogenomic (PGx) study using buccal samples
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 alone or in combination with ATRA, at the respective RP2D given orally in adult subjects with AML.	1. Objective response rate (% of subjects achieving CR, PR, CRp or morphologic leukemia-free state) per response criteria.
Secondary	1. To evaluate the safety and tolerability of respective RP2D of GSK2879552, alone or in combination with ATRA. 2. To characterize the population PK of GSK2879552~~2~~, alone or in combination with ATRA. 3. To evaluate the exposure response (PK/PD) relationship between GSK2879552, alone or in combination with ATRA and safety/efficacy/PD parameters. 4. To evaluate duration of response and best overall response	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, ECGs, 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, concentration, Cmax or AUC (0-tau)) and safety/efficacy/PD parameters. PD parameters assessed by change from baseline in select biomarkers, e.g. CD86 and CD11b 4. Duration of response and best overall response
Exploratory	1. To investigate the mechanism of action and indicators of sensitivity and resistance to ~~assess the feasibility of measuring expression changes of a select gene panel for use as a PD assay for~~ GSK2879552, alone or in combination with ATRA. ~~2.~~ To investigate the relationship between genetic variants in candidate genes, PK and	~~1. Change from baseline expression in select genes in AML cells derived from bone marrow and peripheral blood~~ 2. Analysis of DNA, RNA and/or protein markers in blast cells from bone marrow aspirate and/or peripheral blood ~~tumor~~ sample~~s to discover determinants of response~~ 3. Pharmacogenomic (PGx) study using buccal samples

	safety profile of GSK2879552, alone or in combination with ATRA. ~~tumor genomic profile, and response or resistance to GSK2879552.~~ ~~3. To assess RNA expression profile in tumor cells for identifying mechanisms of rational combination and potential resistance.~~ ~~4. To discover circulating markers of response and resistance and correlation with clinical outcome..~~	~~4. Transcriptomics (RNA) profile of blast cells in bone marrow aspirates and peripheral blood pre- and post-treatment with GSK2879552.~~ ~~Analysis of circulating biomarkers (e.g. circulating cell free DNA [cfDNA], protein and RNA) and correlation with response.~~
Hypothesis	Clinical response will be defined as Objective Response Rate (% of subjects achieving CR, PR, CRp or morphologic leukemia-free state) per response criteria. The null hypothesis is: H0: RR ≤10% The alternative hypothesis is: HA: ≥30%	

Section: Protocol Synopsis- Study Design
REVISED TEXT:
This is a Phase I, open-label, multi-center, non-randomized, 2-part study. Part 1 is a dose escalation phase to determine the MTD and/or RP2D for GSK2879552, alone or in combination with ATRA 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 safety, tolerability, PK and PD.
Once MTD and/or RP2D is identified, an expansion cohort (Part 2) of up to 30 subjects will be enrolled to further evaluate the efficacy and tolerability of GSK2879552, alone or in combination with ATRA in subjects with relapsed/refractory AML.
The proposed treatment schedule of GSK2879552 is continuous daily dosing. The starting dose for GSK2879552 mono therapy arm will be 0.25 mg/day or the highest dose determined to be safe in the ongoing SCLC study, whichever is higher with a maximum of 1 mg/day (see Section 1.4.3.2 for details). The starting dose of GSK2879552 in combination with ATRA will be 1-2 dose levels below the highest dose determined to be safe in the GSK2879552 mono therapy arm in this study, i.e., 2 mg once daily.
Alterations to the dose and schedule may be incorporated based on emerging PK, PD, and tolerability data. Dose reduction and/or truncated dose scheduling may be considered for subjects with recurrent/ persistent toxicity or according to the institutional guideline.

Section: Protocol Synopsis- Number Of Subjects

Revised:
It is estimated that approximately ~~30~~55 subjects will be enrolled into Part 1 dose-escalation and additional ~~40~~25 subjects into PK/PD expansion cohorts in GSK2879552 mono therapy and combination with ATRA arm ~~the study~~. Up to ~~30~~60 subjects will be

enrolled in Part 2 (expansion cohort) of GSK2879552 alone and combination with ATRA arm. A total of approximately ~~100~~140 subjects will be enrolled in the study. Additional subjects/cohorts may be enrolled to allow for evaluation of additional dose levels.

Section: Protocol Synopsis- Inclusion/Exclusion Criteria And Protocol Section 3.2.1: Inclusion criteria
Point number 10. (Inclusion criteria)

REVISED TEXT:

~~TSH, T4~~	~~WNL~~
~~Vitamin B12~~	~~≥ LLN~~
~~BUN~~	~~≤1.5 X ULN~~
~~Na, K^2, Ca, Cl, CO_2~~	~~WNL~~
~~Glucose (fasting)~~	~~≤1.25 X ULN~~
Lipid (ATRA combination ONLY)	
Triglyceride (fasting)	≤ 300 mg/dL
Cholesterol (fasting)	≤ 300 mg/dL

2. 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~~

REVISED TEXT: Point number 11:
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 (Section 11.1), during the study and for 7 days (GSK2879552 mono therapy) or 30 days (combination with ATRA), following the last dose of study treatment.

Section: Protocol Synopsis- Inclusion/Exclusion Criteria And Protocol Section 3.2.2: Exclusion Criteria

REVISED TEXT- Point number 18, 19, 20, 21, 22 (Exclusion criteria)-Addition
18. Previous treatment with GSK2879552

For ATRA Combination arm ONLY
19. Known hypersensitivity to ATRA, parabens (preservatives in the gelatin capsule) or other retinoids.
20. ATRA capsule contains sorbitol. Subjects with rare hereditary problems of fructose intolerance are excluded.
21. History of seizure within 12 months or brain tumor (primary)
22. History of taking mega-dose vitamin A (>25,000 USP U/day) within 3 months from the dosing start.

Section: Protocol Synopsis- Pharmacokinetic/ Pharmacodynamic Assessment(S)
REVISED TEXT: (Paragraph 1, 2 And 3)
For all subjects in the dose escalation cohorts in Part 1, serial blood samples for analysis of GSK2879552 and ATRA 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 for GSK2879552 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 blood samples for PD, exploratory and biomarker will be collected at planned visits as listed in the Time and Event Table.

For subjects in the highest dose of Part 1 PK/PD expansion cohort, additional blood samples for GSK2879552 metabolite profiling will be collected on Day 1 ~~at pre-dose~~ and Day 15 at the same time points as listed in the Time and Event Table (Section 7.1). In addition, pre-dose urine sample will be collected on Day 1, and 24 hour urine sample will be collected starting from ~~pre~~post-dose on Days 1 and 15 until dosing on Days 2 and 16, respectively.

Sentence 1: For all subjects in Part 2 expansion cohorts, serial blood samples for analysis of GSK2879552 and ATRA concentrations will be collected on Days 1 and 15 at planned time points as listed in the Time and Event Table (Section 7.1).

Section: Protocol Synopsis- Clinical Activity Assessment

REVISED TEXT:
Sentence 1: Disease assessments will be made by physical examination and laboratory evaluation. Bone marrow aspiration ~~and biopsy~~ will be performed as stated in the Time and Event Table (Section 7.1).

Section: Protocol Synopsis- Translational Research
REVISED TEXT:
Blood and/or bone marrow aspriates will be collected at various times, throughout the study in order to support research aimed at understanding the biological effect of GSK2879552 alone or in combination with ATRA in AML as well as identifying indicators of sensitivity or resistance. ~~Comparative examination of baseline cancer cell 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 AML and medically related conditions. Comparative examination of post-dosing cancer cell profiles in conjunction with pre-dosing cancer cell profiles may yield known or novel candidate biomarkers/profiles and new insights which relate to the action of GSK2879552.~~

Section: Protocol Synopsis- Statistical Methods
REVISED TEXT: (Paragraph 4)
Sentence 2: A maximum of **30** subjects will be enrolled at the respective RP2D for GSK2879552 mono therapy and in combination with ATRA. All available data will be considered in making enrollment decisions.

Section 1.1: Background – LSD1
REVISED TEXT: (Paragraph 3)
GSK2879552 is a potent, selective inhibitor of LSD1/CoREST. GSK2879552 causes an increase in histone 3 lysine 4 di-methylation (H3K4me2) at promoters of putative LSD1 target genes and has predominantly cytostatic effect on small cell lung cancer (SCLC) and acute myeloid leukemia (AML) cell lines (Refer to the Investigator Brochure (IB) for GSK2879552 [GlaxoSmithKline Document Number ~~2013N168888_01~~2013N168888_0 2013N168888_02).

Section 1.3.1: GSK2879552 – Background
REVISED TEXT: (Paragraph 1-2nd line)
GSK2879552 is a potent, selective, mechanism-based inactivator of LSD1/CoREST activity (K_i = 767 nM, k_{inact} = 0.1 min^{-1} ~~K_i = 1.7 µM, k_{inact} = 0.1 min^{-1}~~)

REVISED TEXT: (Paragraph 4- Added text)

In a MLL-$AF9^+$ murine model of AML, treatment with GSK2879552 led to a significant delay in leukemia onset in treated mice relative to vehicle treated controls.

REVISED TEXT: (Paragraph 5- 3rd line)

Macroscopic and histopatholgic examination suggested that the severity of the thrombocytopenia ~~is~~ was likely due to the combined effects of irradiation, engraftment of injected AML cells into marrow and multiple other organs, and the effect of GSK2879552 on platelets.

Section 1.3.2: LSD1 inhibitor and All-Trans Retinoic Acid (added)

Revised (Added text)
Retinoic acid regulates normal embryonic cell differentiation and development of many tissues including the brain, lungs, and other organs [Niederreither, 2008]. All-*trans*-retinoic acid (ATRA) induced differentiation has been explored in cancers that appear to retain stem-like cells as well as those in which molecular features of differentiation have been characterized. Sarcoma cells including osteosarcoma and rhabdomyosarcoma display morphological changes and alterations in molecular markers consistent with osteoblast and myogenic differentiation in response to ATRA [Luo, 2010; Barlow 2006]. The presence of cancer stem cells in glioblastoma has been associated with therapeutic resistance and tumor initiating potential. Pre-clinical models have been developed to reveal this subpopulation and, in this setting, glioblastoma cells exposed to ATRA undergo reduced proliferation and self-renewal, differentiation into glial and neuronal lineages, and ultimately apoptosis [Karsy, 2010; Choschzick, 2014]. Despite the pre-clinical data suggesting ATRA treatment can promote differentiation in a number of tumor models, ATRA therapy has not proven efficacious in solid tumors clinically.

ATRA has been used successfully in hematological malignancies and is the current standard of care for acute promyelocytic lekemia (APL), a subtype of acute myeloid leukemia (AML). ATRA therapy promotes complete remission in more than 90% of patients through differentiation of leukemic blasts, however, this efficacy has not

translated to non-APL subtypes of AML. The selective response to ATRA in APL is associated with the expression of PML-RAR, the fusion protein that results from chromosomal translocation t(15,17)(q22;q21). In this setting, ATRA can induce expression changes in genes associated with myeloid differentiation through relief of repression of the myeloid expression program imposed by the PML-RAR fusion protein [Melnick, 1999; Johnson 2015]. These data suggest that targeting a differentiation mechanism may also provide an effective therapy in AML if expression of myeloid gene programs can be achieved.

Inhibition of LSD1 by GSK2879552 can promote differentiation in AML cells as evaluated by several measures including gene expression and cell surface marker changes consistent with myeloid differentiation. LSD1 has been implicated in regulation of the ATRA driven response through increases in H3K4me2 at key genes involved in the ATRA pathway [Schenck, 2012; Sakamoto, 2014]. Given the overlapping mechanism associated with each single agent, and the potentiating effect of LSD1 inhibition on the ATRA pathway, treatment of AML may demonstrate greater response to ATRA when combined with GSK2879552.

Section 1.3.3: Pre-Clinical PK and Safety of GSK2879552 (General toxicology)

REVISED TEXT: (Paragraph 1)

Sentence 4: Summaries of principal findings following single and repeat dosing of GSK2879552 and a comparison of systemic exposures achieved in these studies are presented in the IB for GSK2879552 [GlaxoSmithKline Document Number ~~2013N168888_01~~2013N168888_0 2013N168888_02].

Section 1.3.4: Pharmacokinetics of GSK2879552 in Humans

REVISED TEXT: (Paragraph 2-added and deleted previous paragraph 2)

As of 20-NOV-2015, the PK of GSK2879552 was evaluated following administration of single (N=18) and repeated (N=16) oral administration of 0.25 mg to 3 mg of GSK2879552 in subjects with SCLC in Study 200858 and following single (N=11) and repeated (N=8) oral administration of 1 mg to 8 mg in subjects with AML in Study 200200. GSK2879552 pharmacokinetics are characterized by a rapid absorption with maximum concentration occurring typically within the first hour after dosing. GSK2879552 is eliminated slowly with an average terminal phase half-life of 12 to 38 hours, leading to a moderate average increase in exposure of 72% for AUC at 2 mg daily. Following single and repeated administration of 0.25 mg to 4 mg of GSK2879552, Cmax and AUC tended to increase in a dose proportional fashion.

~~As of 29-April-2014, the pharmacokinetics of GSK2879552 has been evaluated in 1 small cell lung cancer subject in GSK study 200858 following single and repeated daily oral administration of 0.25 mg of GSK2879552. GSK2879552 pharmacokinetics are characterized by a rapid absorption with maximum concentration occurring 0.5 to 1 hour after dosing followed by a bi-exponential decline. The maximum concentration was 4.55 ng/mL after a single dose and 3.61 ng/mL after repeated administration. GSK2879552~~

~~preliminary terminal phase half-life was around 20 to 23 hours but estimated over a short time interval. The area under the curve from zero to 24 hours was 13.2 ng.h/mL after a single dose and 28.5 ng.h/mL after repeated daily dosing, leading to a 2.16-fold accumulation in this subject following once daily oral administration.~~

Section 1.3.5: Clinical Safety of GSK2879552

REVISED TEXT: (Paragraph 1- deleted and Paragraph 1,2 and 3 added)

~~As of 29-April-2014, no AEs have been reported in a single subject receiving GSK2879552 0.25 mg once daily in small cell lung cancer study. A trend in slight decrease in platelet count was observed with a nadir reached on Day 11 (121 x 10^9/L vs. 163 x 10^9/L at baseline) followed by full recovery with a platelet count of 173 x 10^9/L observed on Day 28. A trend in slight decrease in ANC beyond Day 21 was observed after initial drop from the pre-treatment level. Otherwise laboratory test results and vital signs have been unremarkable.~~

Summary of findings from clinical studies conducted with GSK2879552 can be found in the Investigator Brochure for GSK2879552 [GlaxoSmithKline Document Number 2013N168888_02].

As of 20-NOV-2015, 11 subjects have been enrolled in Part 1 at once daily doses of 1 mg (n=1), 2 mg (n=2), 4 mg (n=7), and 8 mg (n=1). All 11 subjects (100%) had experienced AEs. The most frequently reported AEs (>20%) were fatigue, febrile neutropenia, nausea, anemia, decreased appetite, hypotension, rash, cellulitis, hypokalemia, and local edema. All Grade 4 AEs were hematological and included thrombocytopenia and neutropenia. Treatment-related AEs reported in at least 10% of subjects were nausea, decreased appetite, and thrombocytopenia. The treatment-related thrombocytopenia AEs were Grade 4 in both subjects; one of these subjects also had Grade 3 febrile neutropenia and Grade 3 anemia. Other treatment-related events that were Grade 3 or 4 included anemia and nausea. There were no fatal AEs.

All 11 subjects in Study 200200 have experienced SAEs. The most common SAE was febrile neutropenia. All cases of febrile neutropenia resolved. No other SAEs occurred in more than 1 subject. One subject had fatal pleural effusion secondary to disease under study, which was considered by the investigator to be not related to study treatment.

Section 1.3.6: Combination Agent (added)

Section 1.3.6.1: All-Trans Retinoic Acid (ATRA) (added)

All-trans retinoic acid (ATRA, tretinoin) is indicated for the induction of remission in patients with acute promyelocytic leukemia (APL) at 45 mg/m^2/day, or according to the French-American-British (FAB) classification the M3 subtype of acute myeloid leukemia (AML-M3).

The most frequently reported adverse events of ATRA are similar to those described in patients taking high doses of vitamin A and included headache (86%), fever (83%), skin/mucous membrane dryness (77%), bone pain (77%), nausea/vomiting (57%), rash (54%), mucositis (26%), pruritus (20%), and increased sweating (20%) [ATRA Prescribing Information, 2004].

About 25% of patients with APL treated with ATRA have experienced the retinoic acid-APL (RA-APL) syndrome. The syndrome generally occurs during the first month of

treatment, with some cases reported following the first dose of ATRA. During ATRA treatment, about 40% of patients will develop rapidly evolving leukocytosis which is associated with a higher risk of life threatening complications. Retinoids have been associated with pseudotumor cerebri (benign intracranial hypertension), especially in pediatric patients. Up to 60% of patients experienced hypercholesterolemia and/or hypertriglyceridemia, which were reversible upon completion of treatment. Elevated liver function test results occur in 50% to 60% of patients during treatment. However, the majority of these abnormalities resolve without interruption of ATRA or after completion of treatment. ATRA has teratogenic and embryotoxic effects and there is a high risk that severe fetal abnormalities may result with ATRA administration during pregnancy. Cases of thrombosis involving various sites have been reported rarely [ATRA Prescribing Information, 2004].

In a Phase I study conducted in subjects with solid tumor, ATRA was administered at doses ranging from 45 to 309 mg/m^2 per day [Conley, 1997]. Hypertriglyceridemia was dose-limiting at 269 mg/m^2 per day. Other frequent toxicities included mucocutaneous dryness and headache. The recommended once-daily ATRA dose was 215 mg/m^2. In another Phase I study conducted in subjects with solid tumor, ATRA dose ranged from 45 to 200 mg/m^2 per day [Lee, 1993]. Skin toxicities were dose limiting in this study at 175 mg/m^2 or higher dose. Headache was one of the most common toxicities and nausea/vomiting were frequent at dose levels higher than 100 mg/m^2. The recommended once daily ATRA dose was 150 mg/m^2. In a Phase I study conducted in patients with head and neck squamous cell carcinoma with prior surgical resection [Park, 2000], ATRA was administered at 45, 90, or 150 mg/m^2 either once daily or as divided doses. A similar toxicity profile was observed with headache, mucocutaneous dryness, and hypertriglyceridemia as the frequent toxicities. The maximum tolerable dose of ATRA in this population was established at 45 mg/m2/day, although the reason for the lower tolerance in this subject population is not clear.

ATRA is available in a 10 mg soft gelatin capsule for oral administration. The recommended dose in APL is 45 mg/m^2/day administered as two divided doses, as equally as feasible.

Pharmacokinetics of ATRA

ATRA (tretinoin) is rapidly absorbed following oral administration with peak concentration observed within 1 to 2 hours after dosing. ATRA is eliminated rapidly, with a terminal half-life of 0.5 to 2 hours following the first dose in patients with APL or CML. Cytochrome P450 3A4, 2C8 and 2E enzymes have been implicated in the oxidative metabolism of ATRA. There is evidence that ATRA induces its own metabolism. Plasma ATRA concentrations decrease on average to one-third of their day 1 values during 1 week of continuous therapy. Mean ± SD peak ATRA concentrations decreased from 394 ± 89 to 138 ± 139 ng/mL, while area under the curve (AUC) values decreased from 537 ± 191 ng·h/mL to 249 ± 185 ng·h/mL following 45 mg/m2 daily dosing in 7 APL patients [ATRA Prescribing Information 2004]. This reduction in exposure was reverted following a one week dose interruption [Russo, 1998].

Section 1.4.1: Rationale for Study
REVISED TEXT:

Last sentence: The proposed Phase I study will evaluate the safety and tolerability, pharmacokinetics, pharmacodynamics, and clinical activity to determine the

recommended Phase 2 Dose (RP2D) and regimen of GSK2879552, alone or in combination with ATRA, given orally in adult subjects with relapsed/refractory AML.

Section 1.4.1.1: Rationale for Combination with ATRA (added)
REVISED TEXT:
Previous studies indicated that, when combined with ATRA, knockdown of LSD1 or treatment of AML cells with a non-selective LSD1 inhibitor, tranylcypromine, resulted in a greater anti-leukemic effect *in vitro* and *in vivo*. The addition of LSD1 inhibitor potentiatied ATRA induced cell surface marker changes, myeloid differentiation gene expression, and *in vivo* engraftment of AML cells. These effects were observed in both ATRA sensitive and insensitive cells [Schenk, 2012].

Several approaches were undertaken to evaluate the combination effects of GSK2879552 with ATRA. As described, growth inhibition by GSK2879552 alone is cytostatic and does not invoke cell death mediated by apoptosis. Evaluation of proliferation in AML cell lines showed that ATRA alone has growth inhibitory effects. Co-treatment of AML cell lines with fixed concentrations of ATRA (0, 1, 10, 100, or 1000 nM) with GSK2879552A (3000 nM-0.152 nM) decreased the EC_{50} associated with GSK2879552 growth inhibition and resulted in cytotoxicity at earlier timepoints than ATRA alone in MOLM-13 cells and OCI-AML3 cells. Overall, percent maximum inhibition increased in combination relative to GSK2879552 alone in 5 of 6 cell lines tested. Using a similar study paradigm, caspase activation, a hallmark of apoptotic cell death was measured to further evaluate the mechanism of cytotoxicity invoked by the combination. GSK2879552 in combination with ATRA resulted in increased caspase activation when compared to activity of either single agent and supra -additive effects were observed in 5 of 6 AML cell lines tested. Five of 6 cell lines tested reached a supra-additive effect at 100 nM and 1000 nM ATRA while 3 cell lines, HL-60, MV-4-11 and SIG-M5, reached a supra-additive effect at 10 nM ATRA. Supra-additive effects occurred at GSK2879552A concentrations ≥ 37 nM except in SIG M5 cells where the supra-additive were only evident at lower doses of GSK2879552A (0.46 nM to 37 nM).

In a separate study using samples derived from bone marrow of AML patients, AML blast colony forming ability was evaluated with the combination of GSK2879552 with fixed concentrations of ATRA (0-1000nM). While each single agent did inhibit AML blast colony number to varying degrees in a 6 of 9 samples, co-treatment with 0.1 µM or 1 µM ATRA in combination with GSK2879552 resulted in a greater anti-leukemic effect as revealed by a lower GSK2879552 IC_{50} or greater maximal inhibition of AML blast colony forming ability than either single agent alone. Supra-additive effects were observed in 2 of 6 evaluable samples.

Finally, flow cytometric evaluation of cell surface markers of 2 AML cell lines (KG-1 and KG-1a) revealed increased CD11b and CD86 expression above single agent activity in 1 of the 2 cell lines. Taken together, these studies indicate that the combination of LSD1 inhibition with ATRA can enhance in vitro growth inhibition of AML cells beyond that achievable by either agent alone.
In this study, a combination arm will be included to evaluate safety, tolerability, PK, PD and clinical activity of GSK2879552 in combination with ATRA.

Section 1.4.3: Rationale for Dose - GSK2879552 Monotherapy (addition in title)

Section 1.4.4: Rationale for Dose – GSK2879552 and ATRA combination (added as new title)

Section 1.4.4.1: Predicted Effective Dose (added)
REVISED TEXT: (added)
Effective doses for GSK2879552 in combination with ATRA are anticipated to be at or below the predicted single agent effective doses of 10 to 40 mg daily.

ATRA dose of 45 mg/m2/day as two divided doses (as equally as feasible) would provide maximum concentrations around 500 nM, average steady-state concentrations around 80 nM and concentrations above 100 nM for around 6 hours. ATRA concentrations at 100 to 1000 nM ranges in combination with up to 2 µM GSK2879552 resulted in a greater anti-leukemic effect in *in vitro* studies.

Section 1.4.4.2: Starting dose (added)
REVISED TEXT: (added)
ATRA dose will be fixed at 45 mg/m^2/day as two divided doses, as equally as feasible. The starting dose for GSK2879552 will be 2 mg. These starting doses were chosen based on the following considerations:

- GSK2879552 and ATRA do not have overlapping toxicity profiles based on the nonclinical toxicology and clinical safety profile of GSK2879552 at doses up to 4 mg daily.
- GSK2879552 mono-therapy has been well tolerated in this study at up to 4 mg daily dose. 2 mg daily dose of GSK2879552 represents a 50% reduction from the highest cleared dose of 4 mg daily as of 20-NOV-2015.
- A dose of 45 mg/m^2/day for ATRA represents the recommended dose in APL as a single agent, well below the MTD of 150-215 mg/m^2/day.
- The risk of GSK2879552 altering ATRA PK is low. In-vitro data suggests that GSK2879552 has a very low potential to inhibit or induce CYP enzymes, and to inhibit Pgp, BCRP, OATP1B1 or OATP1B3 transporters.
- The risk for ATRA to increase GSK2879552 exposure is very low. ATRA has only been reported to be an enzyme inducer.

Section 1.4.5: Benefit Risk assessment
REVISED TEXT:
Summaries of findings from non-clinical and clinical studies conducted with GSK2879552 can be found in the Investigator Brochure (IB) for GSK2879552 [GlaxoSmithKline Document Number ~~2013N168888_01~~2013N168888_0 2013N168888_02]. The following section outlines the risk assessment and mitigation strategy for this protocol.

Section 1.4.5.1: Risk Assessment

REVISED TEXT: (in row 2 and addition after row 2)

Potential Risk of Clinical Significance	**Data/Rationale for Risk**	**4. Mitigation Strategy**
~~Mental status change~~ Encephalopathy	~~Two~~Three (out of ~~16~~ 18) subjects enrolled in 200858 study experienced encephalopathy.	- No change from the previous version
ATRA Combination ONLY		
RA-APL syndrome or respiratory compromise	About 25% of patients with APL treated with ATRA have experienced the retinoic acid-APL (RA-APL) syndrome.	Protocol provides the guideline for RA-APL syndrome management.
Leukocytosis	About 40% of patients may develop rapidly evolving leukocytosis during ATRA treatment	Subjects with an increased risk of a further rapid increase in WBC counts, i.e., WBC >30,000/uL, are excluded.
Pseudotumor cerebri/ intracranial hypertension.	ATRA may cause pseudotumor cerebri/intracranial hypertension.	Concomitant administration of ATRA and agents known to cause pseudotumor cerebri/intracranial hypertension (e.g., tetracycline) will be prohibited.
5. Hypercholesterolemia/ hypertriglyceridemia	Up to 60% of patients experienced hypercholesterolemia and/or hypertriglyceridemia with ATRA treatment.	Subjects with hypertriglyceridemia or hypercholesterolemia >300 mg/dL are excluded. Lipid panel will be checked weekly for the first 4 weeks and then q 4 weeks thereafter.
Liver function test elevation	Elevated liver function test results occur in 50% to 60% of patients during ATRA treatment.	LFT is monitored twice weekly for the first 2 weeks, weekly for the next 2 weeks and then q 4 weeks thereafter. Treatment stopping criteria based on elevation in LFT is in place and the safety management guideline is also provided.
Hypervitaminosis A	Chemically, ATRA is all-trans retinoic acid and is related to retinol (Vitamin A).	Vitamin A or multivitamins including vitamin A are prohibited.
Teratogenic effect	There is a high risk that a severely deformed infant will result if ATRA is administered during pregnancy.	Female subjects with child bearing potential will be required to use 2 reliable forms of contraception methods simultaneously during the treatment and until 30 days after the last dose of ATRA or 7 days after the last dose of GSK2879552, whichever is later.

		Contraception counselling will be repeated monthly throughout ATRA treatment. Serum pregnancy test will be performed at screening and end of treatment visit, and urine pregnancy test at week 4 and every 4 weeks thereafter.
6. Thrombosis	7. Cases of fatal thrombotic complications have been reported rarely in patients concomitantly treated with ATRA and anti-fibrinolytic agents.	CBC and coagulation panel are monitored weekly for the first 4 weeks and then every 4 weeks thereafter. Concomitant administration of antifibrinolytic agents (such as tranexamic acid, aminocaproic acid, or aprotinin) will be prohibited.

Section 1.4.5.2.: Benefit Assessment

REVISED TEXT: (addition of Paragraph 2)

ATRA is indicated for acute promyelocytic leukemia (APL). While there has been significant success in the utility of ATRA as a differentiation therapy in APL, ATRA has not been found to invoke a similar mechanism in other AML subtypes. GSK2879552 promotes differentiation in AML cell lines leading to the hypothesis that, through an overlapping mechanism, treatment of AML may demonstrate a greater response to ATRA when combined with GSK2879552. Any potential beneficial effect for an individual subject attributable to the combination of ATRA with GSK2879552 in non-APL type AML is unknown.

Section 1.4.5.3.: Overall Risk Benefit Conclusion

REVISED TEXT:

Current data from GSK2879552 preclinical studies, alone or in combination with ATRA, indicate a potential for clinical activity by induction of differentiation in AML. Taking into account the measures taken to minimise risks to subjects participating in this Phase I clinical trial, the potential risks identified in association with GSK2879552, alone or in combination with ATRA, are justified by the anticipated benefits that may be afforded to subjects with relapsed/refractory AML, for whom there are currently no effective available therapies.

Section 3.1: Number of subjects

REVISED TEXT (Paragraph 1)

Sentence 3: It is estimated that approximately ~~30~~ 55 subjects will be enrolled into Part 1 dose-escalation and additional ~~40~~ 25 subjects will be enrolled into PK/PD expansion cohorts in GSK2879552 mono therapy and combination with ATRA arm. Up to ~~30~~ 60 subjects will be enrolled in Part 2 (expansion cohort) of GSK2879552 alone and combination with ATRA arm~~the study~~. A total of approximately ~~100~~140 subjects will be

enrolled in the study. Additional subjects/cohorts may be enrolled to allow for evaluation of additional dose levels.

Section 3.2.1 Inclusion criteria

REVISED TEXT: (Paragraph 1)

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) for GSK2879552 [GlaxoSmithKline Document Number ~~2013N168888_01~~2013N168888_0 2013N168888_02.

Section 4.1: Discussion of study design

REVISED TEXT (In paragraph 1, 2, 3 and addition of paragraph 4)

Sentence 1: This is a Phase I, open-label, multi-center, non-randomized, 2-part study. Part 1 is a dose escalation phase to determine the MTD and/or RP2D for GSK2879552, alone or in combination with ATRA, based on the safety, tolerability, pharmacokinetic, and pharmacodynamic…..
Once MTD and/or RP2D is identified, an expansion cohort (Part 2) of up to 30 subjects each will be enrolled to further evaluate the efficacy and tolerability of GSK2879552, alone or in combination with ATRA, in subjects with relapsed/refractory AML.
The proposed treatment schedule of GSK2879552 is continuous daily dosing. The starting dose for GSK2879552 mono therapy arm will be 0.25 mg/day or the highest dose determined to be safe in the ongoing SCLC study, whichever is higher with a maximum of 1 mg/day (see Section1.4.3.2 for details). The starting dose of GSK2879552 in combination with ATRA will be 1-2 dose levels below the highest dose determined to be safe in the GSK2879552 mono therapy arm in this study, i.e., 2 mg once daily.
Alterations to the dose and schedule may be incorporated based on emerging PK, PD, and tolerability data.
Dose reduction and/or truncated dose scheduling may be considered for subjects with recurrent/ persistent toxicity or according to the institutional guideline. For example, once the disease control (CR, CRp, PR or a morphologic leukemia-free state) is attained, ATRA may be given in an intermittent schedule, e.g., 2 week on/2 weeks off.

Section 4.2: Part 1: Dose-Escalation Phase (given the section number)

Section 4.2.1: GSK2879552 Mono-therapy

Revised section

Sentence 2: If the first subject becomes ~~inevaluable~~ unevaluable for reasons other than toxicity, another subject will be recruited.

Under: Completion of Dose Escalation:

REVISED TEXT:

Sentence 5 (added): Up to 12 additional subjects will be enrolled at the dose to further define the safety and tolerability of the dose and schedule. If necessary, alternate schedules can be explored to determine additional biologically active doses even after a RP2D is defined.

Section 4.2.2: GSK2879552 and ATRA combination (new addition)

REVISED TEXT: (addition)

In Cohort 1, three subjects will receive GSK2879552 2 mg once daily dose with ATRA 45 mg/m^2/day as two divided doses. After all three subjects complete the first 4 weeks of treatment, the safety data will be reviewed for DLT. Available PK and PD data will be also reviewed prior to a dose escalation decision and starting Cohort 2. Each cohort will enroll 3 or more subjects to obtain sufficient data. If any subject becomes unevaluable for reasons other than toxicity, a replacement subject will be enrolled. In addition, subjects who fail to take at least 75% of their scheduled doses of each drug in the first 4 weeks for reasons other than toxicity will be replaced. Starting with Cohort1, the dose escalation will use the N-CRM with prior DLT information of GSK2879552 and ATRA mono-therapies and follow the same rule with regards to the number of subjects, maximum dose increment, and the completion of dose escalation as described in Section 4.2.1. The details of priors used in N-CRM model is described in Section 13.2
Following GSK2879552 dose levels are planned for evaluation in combination with ATRA 45 mg/m^2/day. A reduced dose of ATRA may be considered if the combination is not well tolerated at dose level 1.

- Dose level 1: GSK2879552 2 mg/day
- Dose level 2: GSK2879552 4 mg/day
- Dose level 3: GSK2879552 8 mg/day
- Dose level 4: GSK2879552 16 mg/day

Dose level 5: GSK2879552 32 mg/day

Section 4.2.4: Alternative Dosing and PK/PD Sampling Schedules

REVISED TEXT (Paragraph 2 and 3)

Further alterations may be made to the dosing schedule and/or PK/PD sampling schedule of GSK2879552 or ATRA based on the results of emerging PK, PD, efficacy and safety data, and documented in the SPM. These changes will be communicated to IRB/EC, but would not constitute a protocol amendment.
Sentence 1: Schedules that incorporate a recovery period may be explored (e.g., 4 days on/3 days off). Alternatively, a drug holiday after continuous dosing may be explored for GSK2879552 and/or ATRA.

Section 4.2.5: Dose-Limiting Toxicity

REVISED TEXT: (paragraph 1 and point 1)

An event will be considered a DLT if it occurs within the first 4 weeks of treatment (with exception ~~as below~~of myelosuppression), and meets one of the following criteria unless it can be clearly established that the event is unrelated to treatment:

- ~~Prolonged grade 4 neutropenia (≤0.5 x 10^9/L) or thrombocytopenia (≤25 x 10^9/L)~~Myelosuppression with bone marrow hypoplasia (cellularity < 5%) ~~, 28 days after ceasing study treatment~~ without evidence of leukemia ~~(<5% blasts at the time of drug cessation and bone marrow biopsy confirmed absence of leukemia 21-28 days later)~~ for > 28 days. If a subject meets above criteria at the time of drug cessation within DLT observation period, the dose escalation decision will be delayed until 28 days have elapsed post drug cessation.

Section 4.2.6: Maximum Tolerated Dose and Recommended Phase 2 Dose

REVISED TEXT: (paragraph 2)

Sentence 3 added: The RP2D may be different for mono-therapy and for the combination therapy with ATRA.

Section 4.3: Part 2: Expansion Cohort

REVISED TEXT: (paragraph 1 and addition of paragraph 3)
Once the respective RP2D has~~ve~~ been determined, an expansion cohort of up to 30 subjects each, GSK2879552 mono-therapy or in combination with ATRA, will be enrolled in order to better characterize the clinical activity and safety profile of the RP2D.

The statistical design and number of subjects to be enrolled in the dose expansion cohort is based on the predictive probability of success if enrollment continues until all planned subjects are recruited [Lee, 2008]. The predictive probability design allows for evaluation of stopping rules after each subject once a minimum number of subjects are evaluable. In this particular study, we will stop only for futility. Final decisions on stopping enrolment will depend on the totality of the data collected.

Section 4.6: Dosage and Administration of Study Treatment(s)

REVISED TEXT:
See Section5.1 for the dosage and administration of GSK2879552 and ATRA.

Section 4.6.1 Meals and Dietary Restrictions

REVISED TEXT: (paragraph 2)
GSK2879552 ~~Study treatment(s)~~ will be administered under fasting conditions, either 1 hour before or 2 hours after a meal. Subjects should take their morning ATRA dose fasted, at the same time as GSK2879552. If ATRA concentrations are lower than

anticipated following fasted administration, subjects may be asked to take their morning ATRA dose with food. Subject should take their evening ATRA dose with food.

Section 4.8.2: Dose Adjustment for Non-Hematologic Toxicity

REVISED TEXT: (Addition at the footer of the table for G2 and G3 and G4)
[†]In combination cohort, consider holding ATRA dosing first for skin related toxicity (dryness, rash), nausea, vomiting, pain, headache, and mucositis. With fever, consider holding LSD1 first to allow neutrophil count to recover.

REVISED TEXT: (paragraph 2)
Sentence 1: If the non-hematologic toxicity or event resolves to baseline or ≤ Grade 1 within 14 days of stopping therapy, treatment with GSK2879552 and/or ATRA may be restarted with at least **25%** dose reduction.

Section 4.8.4: Safety Management for ATRA Combination (addition of new section and sub sections)

REVISED TEXT: (addition of subsection 4.8.4.1)
Retinoic Acid-APL syndrome
About 25% of patients with APL treated with ATRA have experienced the retinoic acid-APL (RA-APL) syndrome characterized by fever, dyspnea, acute respiratory distress, weight gain, radiographic pulmonary infiltrates, pleural and pericardial effusions, edema, and hepatic, renal, and multi-organ failure [ATRA Prescribing Information, 2004]. This syndrome has occasionally been accompanied by impaired myocardial contractility and episodic hypotension. The syndrome generally occurs during the first month of treatment, with some cases reported following the first dose of ATRA.
High dose steroids should be immediately initiated at the first suspicion of the RA-APL syndrome irrespective of the leukocyte count, e.g., dexamethasone 10 mg intravenously administered every 12 hours for 3 days or until the resolution of symptom. The first signs of the syndrome include:

- unexplained fever
- dyspnea and/or weight gain
- abnormal chest auscultatory findings or radiographic abnormalities

Prophylactic treatment with steroid may be considered per institutional guideline when leukocyte counts double in number to >10,000/uL from baseline leukocyte <10,000/uL.
Prophylactic treatment with hydroxyurea and steroid may be considered per institutional guideline when leukocyte counts double in number from baseline leukocyte 10,000-30,000 /uL.
In cases of moderate and severe RA-APL syndrome, temporary interruption of ATRA treatment should be considered.

REVISED TEXT: (addition of subsection 4.8.4.2)

Liver Function Test Elevation
If ALT ≥5 X ULN, ATRA dose should be held while GSK2879552 dosing continues

- If resolved in 14 days, ATRA dose should resume at full dose
- If not resolved in 14 days, GSK2879552 dose should be also held.
    - If resolved in another 14 days, resume GSK2879552 at a reduced dose by minimum 25% and ATRA at full dose
    - If not resolved in another 14 days, withdraw the subject from the study.

REVISED TEXT: (addition of subsection 4.8.4.3)
Pseudotumor Cerebri (benign intracranial hypertension)
Early signs and symptoms include papilledema, headache, nausea, vomiting, and visual disturbances. Subjects with these symptoms should be evaluated for pseudotumor cerebri, and, if present, appropriate care should be instituted including high dose steroid. ATRA dose should be held for moderate to severe pseudotumor cerebri.

Section 5: Investigational Product(S)

REVISED TEXT: (paragraph 1)
The term 'study treatment' is used throughout the protocol to describe investigational product(s) (IP) received by the subject as per the protocol design. Study treatment may therefore refer to the individual study treatments or the combination of those study treatments.

REVISED TEXT: (Section 5.1: Description of Investigational Product(s))

Product name:	**GSK2879552 Capsule**
Formulation description*:	GSK2879552 capsules contain ~~0.25 mg,~~ 0.5 mg, 2 mg or 5 mg of GSK2879552 as parent.
Unit dose strength(s)	~~0.25 mg,~~ 0.5 mg, 2 mg and 5 mg
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.~~

NOTE: 0.25 mg strength of GSK2879552 capsule is no longer being used and is removed from the table.

GSK2879552 will be provided to sites by GSK, whereas ATRA will be locally supplied and prepared according to local standards. The contents of the label will be in accordance with all applicable regulatory requirements.

Product name:	**Tretinoin (ATRA) Capsule**
Formulation description:	ATRA is supplied as a 10 mg capsule for oral administration.
Dosage form:	Capsule
Unit dose strength(s)	10 mg
Route/Regimen	Oral/The initial dosing regimen will be continuous oral twice daily dosing, i.e., morning and evening. ATRA dose may be divided evenly 2-4 times a day, as needed. Subjects should take their morning dose fasted, at the same time as GSK2879552. If ATRA concentrations are lower than anticipated following fasted administration, subjects may be asked to take their morning ATRA dose with food. Subject can take their evening ATRA dose with food.

Section 5.2: Preparation/Handling/Storage of ~~GSK2879552, GSK~~ Investigational Product

REVISED TEXT: (below storage, paragraph 2)
GSK2879552 is to be stored at a temperature range of 2-8°C (36-46°F), protected from moisture. See package insert for ATRA storage conditions.

Section 5.4: Treatment Compliance

REVISED TEXT: (paragraph 1 and 2)
1st sentence of paragraph 1: On clinic days, GSK2879552 and ATRA should be taken in the clinic after safety procedures including blood sampling for CBC and PK/PD samplings, if applicable, are completed.

1st sentence of paragraph 2: Compliance with ~~GSK2879552~~ IP 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.

Section 5.5: Treatment of Investigational Product Overdose

REVISED TEXT (addition of paragraph 2)
The MTD of ATRA in patients with myelodysplastic syndrome or solid tumors was 195 mg/m2/day. Overdosage with other retinoids has been associated with transient headache, facial flushing, cheilosis, abdominal pain, dizziness and ataxia. These symptoms have quickly resolved without apparent residual effects. There is no specific treatment in the case of an overdose, however, it is important that the patient be treated in a special hematological unit [ATRA Prescribing Information, 2004].

Section 6.2: Subject Completion Criteria

REVISED TEXT: (full section)
~~A subject will be considered to have completed the study if they have received at least one dose of the study drug and completed at least one post-treatment follow-up visit.~~

In Part 1, a subject will be considered to have completed the study if:

- they complete screening assessments, the 28-day DLT observation period, and taking a minimum of 75% of planned doses,
- they progress or die while receiving study treatment, or
- they are receiving ongoing study treatment at the time of the Sponsor's decision to close the study.

In Part 2, a subject will be considered to have completed the study if:

- they die while receiving study treatment,
- they progress while receiving study treatment and are followed until death, or
- they are receiving ongoing study treatment at the time of the Sponsor's decision to close the study.

Subjects who have not died, and are no longer being followed for survival are considered to have discontinued the study. The End of Study eCRF should only be completed when a subject is no longer being followed.

Section 6.3: Permanent Discontinuation from Study Treatment (5th point – 5th line)
REVISED TEST: (5th point – 5th line)
If the investigator and GSK Medical Monitor conclude that the benefit: risk ~~rupports~~ supports continued

Section 6.4: Study Completion

REVISED TEXT: (paragraph 1)
First sentence: The study will be considered completed, having met the study objectives, ~~approximately 2 years from the last subject's first dosing or~~ when 80% or more ~~all~~ subjects in Part 2 have withdrawn from the study~~, whichever occurs first~~.

Section 7: STUDY ASSESSMENTS AND PROCEDURES

REVISED TEXT: (below 'Visit Window-4 paragraph)
Visits in the first 4 weeks will be allowed ± **1** day window. Bone marrow on Day 15 can be done between Day 8 and Day 21.

Section 7.1: Time and Events Table(s)

REVISED TEXT: (Table 3)

	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	D22	D25		
Chemistry Panel including liver function tests	X			X[22]	X	X[22]	X			X		every 4 wks	X
~~**Vitamin B12, TSH, T4**~~	~~X~~												
Fasting Lipid panel (triglyceride, cholesterol)[22]	X				X		X			X		every 4 wks	
Blood samples for PD[6, 21] **(peripheral blood)**	X		X	X	X	bone marrow day[6]						Wk 4, between Wk 6- 8[19], Wk 12 and then every 12 wks.	X
Blood samples for exploratory studies[6, 21] **(peripheral blood)**	X		~~X~~	X	~~X~~	~~bone marrow day~~[21]						~~Wk 4 and Wk 24~~	~~X~~
~~**Blood samples for circulating biomarkers and DNA**[6]~~ ~~**(plasma and cell pellet)**~~		~~X~~				~~bone marrow day~~[21]							~~X~~
Bone marrow aspirate for PD[21,22]	X[7]					X[18]						Wk 4, between Wk 6- 8[19], Wk 12 and then every 12 wks	X[17]
Bone marrow aspirate for exploratory studies [21] ~~**DNA, and RNA)**~~	X[7]					X[18]						Wk 4, between Wk 6- 8[19], Wk 12 and then every 12 wks. ~~Wk 4 and 24~~	X[17]
PGX sample (buccal swab)	X												
Blood for metabolite evaluation		X[9]	X[9]				X[9]	X[9]					
Urine for metabolite evaluation		X[5, 12]	X[5]				X[5]	X[5]					

REVISED TEXT: (footer of table)

Point 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, 10, and 24 hrs post dose. In the combination cohort, a blood sample for ATRA PK analysis will be also collected at the same time points except for the 0.25, 10 and 24 hour sample. Additional samples may be collected at 48 and 72 hrs post dose in subjects not receiving a dose on Days 2 and 3 to better characterize the terminal half-life of GSK2879552, if needed.

Point 2: A blood sample will be collected for PK analysis on D8 at following time points: pre-dose, 0.5, 3 hrs post dose. In the combination cohort, a blood sample for ATRA PK analysis will be also collected at the same time points.

Point 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, 10, and 24 hrs post dose. In the combination cohort, a blood sample for ATRA PK analysis will be also collected at the same time points except for the 0.25, 10 and 24 hour sample.

Point 5: On Days 1 and 15, 24hr urine will be collected in the highest dose cohort in PK/PD expansion cohorts starting from ~~pre~~post-dose on Day 1 and 15, and for 24 hours, i.e., until dosing on Days 2 and 16, respectively. The 24hr urine will be measured and samples collected for PK and metabolite evaluation.

Point 6: Blood samples for PD and exploratory ~~and circulating~~ biomarkers should be collected pre-dose

Point 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 pre-dose on Day 1 and~~ at following time points on Days 1 and 15: pre-dose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, and 24 hrs post dose

Height will be measured at screening only

Point 19: ~~Sample should be collected at pre-dose on the day of bone marrow aspirate collection.~~

Point 20: Baseline disease assessment should be completed within 21 days prior to dosing start. Cytogenetics testing should be performed as part of disease assessment at baseline. Cytomorphology is the preferred method to determine bone marrow blast counts. However, if a bone marrow aspirate cannot be obtained for cytomorphology review, a bone marrow biopsy is allowed to determine the bone marrow blast count

Point 21: In PK/PD expansion cohorts, PD and/or exploratory sample (peripheral blood and BMA) collection may be stopped earlier at the sponsor's discretion.

Point 22: ATRA combination arm only.

Table 4: Time and Events Table: Part 2 – Expansion Cohort

-	SCR	First Treatment Phase (28 days)								Continuation Phase	EOT
		D 1	D4	D 8	D11	D 15	D18	D22	D25		
~~Vitamin B12, TSH, T4~~	~~X~~										
Fasting Lipid panel (triglyceride, cholesterol)[18]	X			X		X		X		Every 4 wks	
Blood samples for PD (peripheral blood)[3, 19]	X		X	X	~~bone marrow day~~[14]					Wk 4, between Wk 6-8, Wk 12, then every 12 wks	X
Blood samples for exploratory ~~markers~~ studies[3, 19] (peripheral blood)	X		X	~~X~~	~~bone marrow day~~[14]					~~Wk 4, between Wk 6- 8, Wk 12, then every 12 wks. (on bone marrow day)~~	
~~Blood samples for circulating biomarkers[3] and DNA (plasma and cell pellet)~~					~~bone marrow day~~[14]						~~X~~
Bone marrow aspirate for PD[19]	X				X[14]					Wk 4, between Wk 6-8, Wk 12, then every 12 wks	X[5]
Bone marrow aspirate for exploratory studies ~~DNA, and RNA)~~ [19]	X[11]				X[14]					Wk 4, between Wk 6-8, Wk 12, then every 12 wks	X[5]
PGX samples (buccal swab)	X										

REVISED TEXT: (footer of table)
Point 1: A blood sample will be collected for PK analysis on D1 at pre-dose, 0.5, and 3 hrs post dose. . In the combination cohort, a blood sample for ATRA PK analysis will be collected at the same time points.
Point 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. In the combination cohort, a blood sample for ATRA PK analysis will be collected at the same time points
Point 3: Blood samples for PD, exploratory ~~and circulating~~ biomarkers should be collected pre-dose

Point 16: Baseline disease assessment should be completed within 21 days prior to dosing start. Cytogenetics testing should be performed as part of disease assessment at baseline. Cytomorphology is the preferred method to determine bone marrow blast counts. However, if a bone marrow aspirate cannot be obtained for cytomorphology review, a bone marrow biopsy is allowed to determine the bone marrow blast count.

Point 18 (addition): ATRA combination only

Point 19 (addition): PD and/or exploratory sample (peripheral blood and BMA) collection may be stopped earlier at the sponsor's discretion

Section 7.2: Demographic/Medical History and Baseline Assessments

REVISED TEXT:
Point 4: Clinical laboratory tests: hematology, clinical chemistry, coagulation parameters ~~vitamin B12, thyroid (TSH, T4)~~
Point 5 (addition): Lipid panel (ATRA combination only): triglyceride and cholesterol

Section 7.3.7: Laboratory Assessments

REVISED TEXT: (addition under clinical chemistry panel)]

Lipid			
Triglyceride	cholesterol		

Section 7.4.1: Blood Sample Collection for Pharmacokinetics
REVISED TEXT: (first paragraph)
First sentence: Blood samples for pharmacokinetic (PK) analysis of GSK2879552 and ATRA will be collected at the time points indicated in the Time and Events Schedule (Section 7.1).

Section 7.4.3: Pharmacokinetic Sample Analysis
Plasma sample analysis will be performed under the management of ~~Bioanalytical Science and ToxicokineticsBioanalysis~~, Immunogenicity & Biomarkers (BIB), ~~Drug Metabolism and Pharmacokinetics (DMPK)~~. In Vitro/In Vivo Translation (IVIVT), Platform Technology and Science (PTS), GlaxoSmithKline for GSK2879552 and InVentiv Health Clinical for ATRA. Concentrations of GSK2879552 and ATRA 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 and InVentiv Health Clinical. 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 Bioanalysis, Immunogenicity & Biomarkers (BIB), In Vitro/In Vivo Translation (IVIVT)~~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.

Section 7.5: Pharmacodynamic:
REVISED TEXT:
In Part 1 and Part 2 of the study, blast cell cell-surface markers such as CD11b and CD86 that are indicative of AML sub-population will be assessed in peripheral blood and bone marrow aspirates when possible to determine the effects of GSK2879552 alone or in combination with ATRA. Change from baseline levels will be measured. ~~In addition, the above samples may be utilized for the development of a gene signature panel indicative of AML modulation in response to GSK2879552 as a potential PD marker. Changes in~~

~~the gene levels from baseline will be assessed. The PD outcome may be correlated to clinical outcome.~~

Section 7.6: Translational Research
REVISED TEXT:

~~Comparative examination of baseline cancer cell 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 AML and medically related conditions. Comparative examination of post-dosing cancer cell profiles in conjunction with pre-dosing cancer cell profiles may yield known or novel candidate biomarkers/profiles and new insights which relate to the action of GSK2879552.~~

Blood and/or bone marrow aspirates will be collected at various times, throughout the study in order to support research aimed at understanding the biological effect of GSK2879552 alone or in combination with ATRA in AML as well as identifying indicators of sensitivity or resistance.

The successful collection of quality tumor specimens will be critical to furthering our understanding the mechanism of action of GSK2879552 alone or in combination with ATRA, and identifying the best way to treat patients with GSK2879552. Specifically, the evaluation of responders, responders at relapse, and non-responders for DNA methylation, gene alteration status, cell surface marker expression and/or pathway activation may lead to the discovery of potential new diagnostic markers or novel combinations. Similarly, pre- and post-dose tumor specimens will be evaluated for markers of target engagement, tumor response, and/or evaluated for changes in gene expression; thus supporting identification of a biologically effective dose and furthering our mechanistic understanding of LSD1 inhibition in these settings.~~The candidate biomarkers may be identified by application of:~~

- ~~DNA/gene, RNA and protein analysis of tumor cells.~~
- ~~Circulating cell free DNA analysis of blood/plasma and other circulating markers like cytokines in blood.~~

~~RNA transcriptome analysis of blast cells in peripheral blood or bone marrow aspirates pre and post treatment~~

Section 7.6.1: Tumor Biomarker Analysis
REVISED TEXT:

All subjects will be asked to submit peripheral blood and fresh bone marrow aspirate at baseline, during the study and at the end of treatment in order to conduct retrospective tests for the identification of potential markers of sensitivity or resistance through the assessment of DNA, RNA and/or protein.

Section 7.6.2: ~~Circulating Cell Free DNA (cfDNA) and Additional Circulating Biomarker Analysis~~ (full section deleted)
REVISED TEXT:

~~Tumor-specific circulating nucleic acid (cfDNA) found in the plasma or serum of cancer subjects can harbor many genetic alterations (mutations, microsatellite alterations, aberrant methylation), which are generally consistent with the tumor. Thus, correlation of clinical outcome with molecular aberrations identified in the cfDNA may serve as a useful tool for the identification of sensitive and resistance markers. Proteins including~~

~~cytokines and angiogenic factors circulating in the plasma may also be explored as markers of sensitivity and resistance.~~
~~Blood samples pre-treatment, on study and at the end of study will be collected from all subjects.~~

Section 7.6.2: RNA Expression Changes Pre and Post Treatment (according to current document)
REVISED TEXT:
First sentence: Transcriptomic analysis may be performed for RNA isolated from peripheral blast cells or bone marrow aspirates pre and post treatment of GSK2879552 alone or in combination with ATRA.

Section 7.8: Pharmacogenetics (added new section)

REVISED TEXT:
An important objective of the clinical study is pharmacogenetics (PGx) research. Participation in PGx is optional, but all subjects who are eligible for the clinical study will be given the opportunity to participate. Subjects may decline participation without effect on their medical care or care during the clinical study. A separate consent signature is required for PGx research.

Subjects who provide consent will have a buccal swab sample taken for analysis. The presence/absence of genetic variations in selected candidate genes in DNA from saliva will be analysed to determine their relationship with response (safety, tolerability, PK, and efficacy) to treatment with GSK2879552, alone or in combination with ATRA.

Information regarding PGx research is included in Appendix 9. The IRB/ EC and, where required, the applicable regulatory agency must approve the PGx assessments before these can be conducted at the site. The approval(s) must be in writing and will clearly specify approval of the PGx assessments (i.e., approval of Appendix 9). In some cases, approval of the PGx assessments can occur after approval is obtained for the rest of the study. If so, then the written approval will clearly indicate approval of the PGx assessments is being deferred and the study, except for PGx assessments, can be initiated. When PGx assessments will not be approved, then the approval for the rest of the study will clearly indicate this and therefore, PGx assessments will not be conducted

Section 10.2: Prohibited Medications

REVISED TEXT: (addition of paragraph 3)
In the combination arm with ATRA, antifibrinolytic agents (such as tranexamic Acid, aminocaproic acid, or aprotinin), agents known to cause pseudotumor cerebri/intracranial hypertension (e.g., tetracycline) and vitamin A or multivitamin including vitamin A will be prohibited while receiving ATRA.

Section 10.2.2: Drugs that may have their PK altered by GSK2879552

REVISED TEXT: (paragraph 2)
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 ~~OATP, BCRP~~ OCT and MATE should be avoided when possible or monitored carefully. Examples of such drugs are dofetillide, pilsicainide and procainamide. ~~shown in Table 6~~.

~~Table6 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, pitavastatin,pravastatin, rosuvastatin,simvastatin*~~	~~HMG-CoA Reductase Inhibitors~~
~~*glyburide, repaglinide*~~	~~Antidiabetics~~
~~*bosentan, ambrisentan*~~	~~Pulmonary hypertension~~
~~*dofetillide, pilsicainide, procainamide*~~	~~Antiarrythmic~~

Section 11.1.1: Female Subjects
REVISED TEXT: (addition of 2 paragraphs from the last sentence)
Female subjects of childbearing potential receiving ATRA combination treatment must use two reliable forms of contraception simultaneously during treatment and 30 days after the last dose of ATRA or 7 days after the last dose of GSK2879552, whichever is later. Contraceptive counselling should be repeated monthly while receiving ATRA and documented in the site source file.

Hormonal contraceptives are NOT considered acceptable form of contraception for female subjects of childbearing potential receiving ATRA combination treatment. Intrauterine device or intrauterine system, male partner sterilization and double-barrier method as described below are acceptable forms of contraception for female subjects of childbearing potential receiving ATRA combination treatment.

REVISED TEXT: (under-Contraceptive Methods with a Failure Rate of ≤1%) (Point 1 to 5)

- Oral contraceptives (either combined or progesterone only) if not contraindicated for this subject population or per local practice. – GSK2879552 monotherapy ONLY
- Estrogenic vaginal ring if not contraindicated for this subject population or per local practice. – GSK2879552 monotherapy ONLY
- Percutaneous contraceptive patches if not contraindicated for this subject population or per local practice. – GSK2879552 monotherapy ONLY
- Implants of levonorgestrel if not contraindicated for this subject population or per local practice. – GSK2879552 monotherapy ONLY
- Injectable progesterone if not contraindicated for this subject population or per local practice. – GSK2879552 monotherapy ONLY

Section 13.2: Part 1: Dose-Escalation Phase

REVISED TEXT: (addition of text after paragraph 1)

Bayesian Prior for Combination Therapy Cohorts

The underlying Bayesian model requires that a Bayesian prior for the DLT rates for the combination be pre-specified. The monotherapy DLT rates on observed data from 200200 study and a prior Phase I ATRA study [Lee, 1993] were incorporated in the DLT prior distribution calculation. Table 6 shows the prior DLT data at a given dose.

Table 6 Prior Monotherapy DLT Data

GSK2879552 Dose level (mg)	# of DLTs / # Subjects	ATRA Dose Level (mg)	# of DLTs / # Subjects
1 mg	0/1	45 mg/m2	1/6
2 mg	0/2	60 mg/m2	0/3
4 mg	0/4	80 mg/m2	0/3
8 mg	0/1		

Additional detail on the model will be provided in the RAP.

Section 13.4.1: Part 1: Dose-Escalation Phase

REVISED TEXT:

The total number of subjects to be enrolled into Part 1 will depend on the number of dose escalations required to establish the maximum tolerated dose of GSK2879552 alone or in combination with ATRA; they are not driven by statistical considerations. To complete dose escalation, it is estimated that approximately 55 evaluable subjects will be enrolled .

Monotherapy doses to be studied in Part 1 will be guided by calculating the posterior probability that the DLT rate falls within an acceptable range for each subsequent dose after each dose cohort observation period. The N-CRM method will be used to calculate posterior probabilities utilizing a pre-specified prior distribution.

Combination doses to be studied in Part 1 will be guided by calculating the posterior probability that the DLT rate is as close to, but below the target toxicity rate of 33% at adjacent dose combinations. The Bayesian logistic regression method will be used to calculate posterior probabilities utilizing the pre-specified prior distribution of the toxicity rates on combinations.~~No formal statistical hypothesis will be tested in Part I. The sample size depends on the actual number of cohorts of subjects treated.~~

Section 13.4.2: Part 2: Expansion Cohort

REVISED TEXT (after paragraph 1)

Bayesian statistics will be employed to calculate the predictive probability that the response rate is greater than the historic response rate at interim analyses using a weak/non-informative prior. A Bayesian analysis expresses uncertainty about a parameter in terms of probability. A prior distribution is defined to characterize the level of knowledge about a parameter before the data are collected. Once the data are collected, a posterior distribution is formed using the prior distribution and the observed data. A very

weak prior Beta distribution with a mean response rate equal to the target response rate is assumed. Thus, the posterior distribution for the response rate will be primarily driven by the data and can be derived as follows:
Let p denote the response rate, the number of responses in the current n subjects, x, follows a binomial distribution, Binomial (n, p). Taking the Bayesian method and combining the prior distribution and the observed data x, the posterior distribution of the response rate follows a beta distribution, i.e.
In the following case, 30% is the target response rate.

$p \sim \text{Beta}(0.03 + x, 0.07 + n-x)$ with the posterior mean $(0.03+ x)/(0.07 + n)$.

For each cohort, to test hypotheses:
H_0: RR≤10%
H_A: RR≥30%
When maximum sample size is 30, the design will have a Type I error (α) of 0.064 and 89% power with the probability of early termination is 0.88 when the treatment is futile and probability of early termination 0.084 when the treatment is effective (true RR=0.3).Futility analysis for each dose expansion cohort will begin when response data is available for at least 10 evaluable subjects. The dose expansion cohort may be stopped early for futility if the predictive probability of success (response rate ≥ historical response rate) is less than 5%. Futility stopping rules are described below.
After 10 evaluable subjects have been enrolled to examine safety and efficacy, the number of observed ~~confirmed~~ objective responses will guide further enrolment according to the rules summarized in Figure 3. A maximum of **30** subjects will be enrolled at the RP2Ds for GSK2879552 and GSK2879552 2 in combination with ATRA, respectively. All available data will be considered in making enrollment decisions. If both cohorts enroll the maximum number of subjects, this will result in 60 subjects total.

Section 13.7.1: Part 1: Dose-Escalation

REVISED TEXT:

In Part 1, interim analyses to inform dose escalation will be performed following the completion of each monotherapy and combination dose cohort in part 1. The primary driver for dose escalation decisions in Part 1 will be governed by an N-CRM model for the mono-therapy dose cohorts and a Bayesian copula regression for the combination dose cohorts. They will be used to predict the probability of DLT at the dose levels yet to be tested to further guide these decisions. Further details of the model will be provided in the RAP
~~No formal interim analysis will be performed for Part 1 of the study~~.
Interim analysis on Part 1 may be conducted when

- Part1 is completed or
- All subjects enrolled in in Part 1 have had at least one post-baseline disease assessment s or progressed or died or withdrawn from the study

Additionally, s~~S~~afety, PK, PD/biomarker data may ~~will~~ be examined during Part 1. Prior to determining GSK2879552 dose for the next monotherapy cohort, exploratory analysis may~~will~~ be conducted to assess the relationship of GSK2879552 dose levels with safety, PK and PD parameters using all data from available cohorts

Section 13.7.2: Part 2: Expansion Cohort

REVISED TEXT:

After the initial 10 evaluable subjects have enrolled…

Section 13.8.1: Anti-Cancer Activity Analyses

REVISED TEXT:

Response rate (RR) is defined as the percentage of subjects who achieved CR, CRp, PR ~~and~~ or ~~a~~ morphologic leukemia-free state (MLFS) among subjects who received at least one dose of treatment.

Addition of text after paragraph 3:

As a secondary analysis, if data warrant, PFS, OS, DOR, and TTR will be evaluated using the Kaplain-Meier method. Summaries of median time to event, quartiles and 95% CIs will be presented.

For the analysis of PFS, if the subject received subsequent anti-cancer therapy prior to the date of documented events, PFS will be censored at the last adequate assessment (e.g. assessment where visit level response is CR, CRp, PR, MLFS, or SD) prior to the initiation of therapy. Otherwise, if the subject does not have a documented date of events, PFS will be censored at the date of the last adequate assessment. For the analysis of overall survival (OS), the last date of known contact will be used for those subjects who have not died at the time of analysis; such subjects will be considered censored. Further details on rules for censoring will be provided in the RAP. Sensitivity analyses of PFS and further details on censoring rules will be provided in the RAP. Progression free survival (PFS) and overall survival (OS) will be summarized using Kaplan-Meier method.

The duration of response is defined for the subject or subjects with a CR, CRp, MLFS, or PR, as the time from the first documented evidence of a CR, CRp, ,MLFS, or PR until the first documented disease progression or death due to any cause. Censoring rules for duration of response will be outlined in detail in the RAP.

Time to Response is defined, for subjects with a CR, CRp, MLFS, or PR, as the time from first dose to the first documented evidence of responses.

If the data warrant, duration of response and time to response will be summarized descriptively using Kaplan-Meier medians and quartiles. Only the subset of subjects who show a confirmed complete or partial tumor response will be included. Censoring rules for duration of response will follow the rules for PFS outlined in detail in the RAP.

Section 13.8.2.1: ~~Extent of Exposure~~

REVISED TEXT:

~~The number of subjects administered study treatment will be summarized according to the duration of therapy.~~
~~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.~~

Section 13.8.2.2: ~~Adverse Events~~

REVISED TEXT:

~~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 National Cancer Institute- Common Toxicity Criteria for Adverse Events (NCI-CTCAE), (version 4.03).~~
~~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, serious adverse events (SAEs) and AEs leading to discontinuation of study treatment. Adverse events (AEs), if listed in the NCI-CTCAE (version 4.03) will be summarized by the maximum grade. Otherwise, the AEs will be summarized by maximum intensity.~~
~~AEs of special interest will be outlined in the RAP.~~
~~The incidence of deaths and the primary cause of death will be summarized.~~

Section 13.8.2.3: ~~Clinical Laboratory Evaluations~~

REVISED TEXT:

~~Hematology and clinical chemistry data will be summarized using frequencies and proportions according to National Cancer Institute-Common Toxicity Criteria for Adverse Events (NCI-CTCAE) (version 4.03). Laboratory test results outside the reference ranges that do not have an associated NCI-CTCAE criteria will be summarized using proportions. Further details will be provided in the Reporting and Analysis Plan (RAP)~~

Section 13.8.2.4: ~~Other Safety Measures~~

REVISED TEXT

~~Data for vital signs and electrocardiograms (ECGs) will be summarized based on predetermined criteria identified to be of potential clinical concern (PCI). Further details will be provided in the Reporting and Analysis Plan (RAP).~~

Section 13.8.3.1: Pharmacokinetic Parameters

REVISED TEXT: (Under Non-compartmental Pharmacokinetic Analyses)

Paragraph 1, first sentence- Pharmacokinetic analysis of GSK2879552 and ATRA, as appropriate, in Part 1 will be conducted by non-compartmental methods.

Paragraph 2- GSK2879552 t~~T~~rough concentration (Cτ) samples collected on the specified days will be used to assess attainment of steady state. To estimate the extent of accumulation for GSK2879552 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 for GSK2879552**.**

REVISED TEXT: (under Metabolic Profiling)

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

REVISED TEXT: (under Population Pharmacokinetics)

First line: Plasma concentration-time data from Part 2 (Expansion Cohort) will be combined with data from Part 1 and possibly with data from other studies and analyzed using a population approach.

Section 13.8.3.2: Statistical Analysis of Pharmacokinetic Data

REVISED TEXT:

Paragraph 1: Statistical analyses of the PK parameters data will be the responsibility of Clinical Statistics ~~Discovery Biometrics~~, GSK.

Paragraph 2, first sentence: Plasma concentration-time data for GSK2879552 and ATRA will be listed by dose and…

Paragraph 3, first sentence: Cmax and AUC (AUC[0-∞], single dose, and AUC[0-τ], steady state) for GSK2879552 and ATRA, if appropriate, will be plotted…

Section 13.8.4.2: Novel Biomarker(s) Analyses

Revised section: paragraph 2

Additional exploratory analyses may be performed to further characterize ~~the~~ any novel biomarkers

Section 15: Reference:

REVISED TEXT

Changes in one reference:

GlaxoSmithKline Document Number 2013N168888_0~~1~~2. GSK2879552 Investigator's Brochure. Report Date: 29-FEB-2016~~01-MAR-2015~~

Addition of new references:

Vesanoid (ATRA) Prescribing Information, July 2004

Barlow JW et al. Differentiation of rhabdomyosarcoma cell lines using retinoic acid. Pediatr Blood Cancer. 2006;47(6):773-84

Conley BA et al. Phase I clinical trial of all-trans-retinoic acid with correlation of its pharmacokinetics and pharmacodynamics. Cancer Chemother Pharmacol. 1997;39(4):291-9

Choschzick I et al. Phase I clinical trial of all-trans-retinoic acid with correlation of its pharmacokinetics and pharmacodynamics. Neuroscience, 2014, 279; 44–64

Johnson DE and Redner RL. An ATRActive future for differentiation therapy in AML. Blood Rev. 2015 Jul;29(4):263-8

Karsy M et al. All-trans retinoic acid modulates cancer stem cells of glioblastoma multiforme in an MAPK-dependent manner. Anticancer Res, 2010 Dec;30(12):4915-20

Lee SH et al. Phase I Trial of All-Trans Retinoic Acid in Patients with Treated Head and Neck Squamous Carcinoma. Clin Cancer Res. 2000;6(3):847-54.

Luo P et al, Retinoid-suppressed phosphorylation of RARalpha mediates the differentiation pathway of osteosarcoma cells. Oncogene. 2010;13;29(19):2772-83.

Melnick A and Licht JD. Deconstructing a disease: RARalpha, its fusion partners, and their roles in the pathogenesis of acute promyelocytic leukemia. Blood. 1999 May 15;93(10):3167-215

Park SH et al. Phase I trial of all-trans retinoic acid in patients with treated head and neck squamous carcinoma. Clin Cancer Res. 2000 Mar;6(3):847-54.

Russo D et al. All-trans retinoic acid (ATRA) in patients with chronic myeloid leukemia in the chronic phase. Leukemia 1998; 12: 449-454

Sakamoto K et al. Sensitivity of MLL-rearranged AML cells to all-trans retinoic acid is associated with the level of H3K4me2 in the RARa promoter region. Blood Cancer Journal 2014; 4: 1-8.

Schenk T et al. Inhibition of the LSD1 (KDM1A) demethylase reactivates the all-trans-retinoic acid differentiation pathway in acute myeloid leukemia. Nature Medicine 2012; 18 (4): 605-611.

Section 16.6: Appendix 6: Response Criteria

REVISED TEXT:

Paragraph 1: Overall efficacy will be assigned according to a criteria slightly modified from the standard response criteria for Acute Myeloid Leukemia [Cheson, 2003].

Addition:

Progressive Disease
Presence of > 50% increase in bone marrow blasts to a level of at least 50% and/or a doubling of the percentage of peripheral blood blasts to a level of at least 50%
Stable Disease
The absence of a complete or partial response, CRp, morphologic leukemia-free state and no progressive disease.

Section 16.9: Appendix 9: Genetic Research (Addition of new appendix)

Genetics – Background

Naturally occurring genetic variation may contribute to inter-individual variability in response to medicines, as well as an individual's risk of developing specific diseases. Genetic factors associated with disease characteristics may also be associated with response to therapy, and could help to explain some clinical study outcomes. For example, genetic variants associated with age-related macular degeneration (AMD) are reported to account for much of the risk for the condition [Gorin, 2012] with certain variants reported to influence treatment response [Chen, 2012]. Thus, knowledge of the genetic etiology of disease may better inform understanding of disease and the development of medicines. Additionally, genetic variability may impact the pharmacokinetics (absorption, distribution, metabolism, and elimination), or pharmacodynamics (relationship between concentration and pharmacologic effects or the time course of pharmacologic effects) of a specific medicine and/or clinical outcomes (efficacy and/or safety) observed in a clinical study.

Genetic Research Objectives and Analyses

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

- Response to medicine, including GSK2879552 or any concomitant medicines;
- AML disease susceptibility, severity, and progression and related conditions

Genetic data may be generated while the study is underway or following completion of the study. Genetic evaluations may include focused candidate gene approaches and/or examination of a large number of genetic variants throughout the genome (whole genome analyses). Genetic analyses will utilize data collected in the study and will be limited to understanding the objectives highlighted above. Analyses may be performed using data from multiple clinical studies to investigate these research objectives.
Appropriate descriptive and/or statistical analysis methods will be used. A detailed description of any planned analyses will be documented in a Reporting and Analysis Plan (RAP) prior to initiation of the analysis. Planned analyses and results of genetic investigations will be reported either as part of the clinical RAP and study report, or in a separate genetics RAP and report, as appropriate.

Study Population

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

Study Assessments and Procedures

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

A saliva swab sample will be taken for Deoxyribonucleic acid (DNA) extraction. A saliva sample is collected at the baseline visit, after the subject has been randomized and provided informed consent for genetic research. Instructions for collection and shipping of the genetic sample are described in the laboratory manual. The DNA from the saliva sample may undergo quality control analyses to confirm the integrity of the sample. If there are concerns regarding the quality of the sample, then the sample may be destroyed. The saliva sample is taken on a single occasion unless a duplicate sample is required due to an inability to utilize the original sample.

The genetic sample is labelled (or "coded") with the same study specific number used to label other samples and data in the study. This number can be traced or linked back to the subject by the investigator or site staff. Coded samples do not carry personal identifiers (such as name or social security number).
Samples will be stored securely and may be kept for up to 15 years after the last subject completes the study, or GSK may destroy the samples sooner. GSK or those working with GSK (for example, other researchers) will only use samples collected from the study for the purpose stated in this protocol and in the informed consent form. Samples may be used as part of the development of a companion diagnostic to support the GSK medicinal product.
Subjects can request their sample to be destroyed at any time.

Informed Consent

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

Subject Withdrawal from Study

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

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

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

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

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

Screen and Baseline Failures

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

Provision of Study Results and Confidentiality of Subject's Genetic Data

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

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

validity of the results are undetermined. Further, data generated in a research laboratory may not meet regulatory requirements for inclusion in clinical care.

References:

Chen H, Yu KD, Xu GZ. Association between Variant Y402H in Age-Related Macular Degeneration (AMD) Susceptibility Gene CFH and Treatment Response of AMD: A Meta-Analysis. PloS ONE 2012; 7: e42464

Gorin MB. Genetic insights into age-related macular degeneration: Controversies addressing risk, causality, and therapeutics. Mol. Asp. Med. 2012; 33: 467-486.

AMENDMENT 2

Where the Amendment Applies

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

Summary of Amendment

This amendment is initiated to modify eligibility criteria and add additional safety monitoring measures in response to recent safety findings.

List of Specific Changes

Section 1.3.1 GSK2879552 – Background, 1st paragraph

PREVIOUS TEXT

GSK2879552 is a potent, selective, mechanism-based inactivator of LSD1/CoREST activity (K_i = 767 nM, k_{inact} = 0.1 min^{-1}).

REVISED TEXT

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}).

Section 1.4.4 Benefit Risk Assessment, 1st paragraph

PREVIOUS TEXT

Summaries of findings from non-clinical studies conducted with GSK2879552 can be found in the Investigator Brochure (IB) and supplement for GSK2879552 [GlaxoSmithKline Document Number 2013N168888_00; GlaxoSmithKline Document Number 2014N197022_00].

REVISED TEXT

Summaries of findings from non-clinical studies conducted with GSK2879552 can be found in the Investigator Brochure (IB) ~~and supplement~~ for GSK2879552 [GlaxoSmithKline Document Number **2013N16888_01**~~2013N168888_00~~; ~~GlaxoSmithKline Document Number 2014N197022_00~~].

Section 1.4.4.1 Risk Assessment

PREVIOUS TEXT

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. Reduced platelet aggregation has been observed in rats following repeat dosing at a time when there was significant thrombocytopenia. 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, hypocellularity was not observed in the bone marrow of these animals.	Informed Consent Form includes the risk of hematologic toxicity. Protocol specifies: - Exclusion criteria for non-AML related major bleeding (e.g. recent GI hemorrhage or neurosurgery) - Laboratory assessments (complete blood count [CBC]) - Dose stopping/modification criteria Signs and symptoms of bleeding or infection will be closely monitored during the study.

REVISED TEXT

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. Reduced platelet aggregation has been observed in rats following repeat dosing at a time when there was significant thrombocytopenia. 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, hypocellularity was not observed in the bone marrow of these animals.	Informed Consent Form includes the risk of hematologic toxicity. Protocol specifies: - Exclusion criteria for non-AML related major bleeding (e.g. recent GI hemorrhage or neurosurgery) - Laboratory assessments (complete blood count [CBC]) - Dose stopping/modification criteria Signs and symptoms of bleeding or infection will be closely monitored during the study.
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 3.2.1 Inclusion Criteria

PREVIOUS TEXT

10. Adequate baseline organ function defined by:

System	Laboratory Values
Hematologic	
White blood cell count (absolute) Coagulation assays (PT/INR and aPTT)	≤30,000/uL ≤1.3 X ULN
Hepatic	
Total bilirubin ALT and AST	≤ 1.5 X ULN[1] ≤2.5 × ULN
Renal	
Creatinine OR Calculated creatinine clearance by Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (Appendix 3) or measured from 24hr urine	≤1.5 X ULN ≥ 50 mL/min
Cardiac	
Ejection fraction	≥ LLN by Echocardiogram (ECHO) or MUGA

2. 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

10. Adequate baseline organ function defined by:

System	Laboratory Values
Hematologic	
White blood cell count (absolute) Coagulation assays (PT/INR and aPTT)	≤30,000/uL ≤1.3 X ULN
Hepatic	
Total bilirubin ALT and AST	≤ 1.5 X ULN[1] ≤2.5 × ULN
Renal	
Creatinine OR Calculated creatinine clearance by Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (Appendix 3) or measured from 24hr urine	≤1.5 X ULN ≥ 50 mL/min
Cardiac	
Ejection fraction	≥ LLN by Echocardiogram (ECHO) or MUGA
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 3.2.2 Exclusion Criteria

NEW TEXT added

23. Prior treatment with temozolomide, dacarbazine or procarbazine

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

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

Section 4.7 Safety Management Guideline

NEW SECTION added

Section 4.7.3 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.

Section 7 Study Assessments and Procedures

PREVIOUS TEXT

Visit Window

Baseline disease assessment should be completed within **21 days** prior to dosing start.

REVISED TEXT

Visit Window

Baseline disease assessment should be completed within **21 days** prior to dosing start.

ECHO/MUGA should be completed within 35 days prior to dosing start.

Section 7.1 Time and Events Tables, Table 3 and Table 4

NEW TEXT added

Table 3 Time and Events, 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	D22	D25		
Montreal Cognitive Assessment	**X**	**X**			**X**		**X**			**X**		**Wk 4 and every 4 wks**	
Vitamin B12, TSH, T4	**X**												

Table 4 Time and Events, Part 2 Expansion Cohort

	SCR	First Treatment Phase (28 days)								Continuation Phase	EOT
		D 1	D4	D 8	D11	D 15	D18	D22	D25		
Montreal Cognitive Assessment	**X**	**X**		**X**		**X**		**X**		**Wk 4 and every 4 wks**	
Vitamin B12, TSH, T4	**X**										

Section 7.2 Demographic/Medical History and Baseline Assessments, 4th paragraph

PREVIOUS TEXT

Baseline (Screening) assessments obtained 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 electrocardiogram (ECG)
- Echocardiogram (ECHO) or multi-gated acquisition (MUGA) scan
- Baseline disease assessment and bone marrow aspirates
- Review of concomitant medications

REVISED TEXT

Fasting will be required for screening clinical laboratory tests.

Baseline (Screening) assessments obtained 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 electrocardiogram (ECG)
- Echocardiogram (ECHO) or multi-gated acquisition (MUGA) scan
- Baseline disease assessment and bone marrow aspirates
- Review of concomitant medications
- **Montreal Cognitive Assessment**

Section 7.3 Safety Evaluations

NEW SECTION added

Section 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 8.

Section 7.3.7 Laboratory Assessments, Table 5

PREVIOUS TEXT

Table 5 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)			
Blast count			
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
Phosphate	Lactate Dehydrogenase (LDH)		
Other tests			
Coagulation Panel including PT, PTT, INR, fibrinogen			
Fetal hemoglobin (Hgb F)			
Other screening tests			
Follicle stimulating hormone (FSH) and estradiol (as needed in women of non-child bearing potential only)			
HIV, Hepatitis B surface antigen (HBsAg) and Hepatitis C antibody (HCV Ab) testing			

REVISED TEXT

Table 5 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)~~			
Blast count			
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
Phosphate	Lactate Dehydrogenase (LDH)	**Thyroid Stimulating Hormone**	**T4**
Vitamin B12			
Other tests			
Coagulation Panel including PT, PTT, INR, fibrinogen			
Fetal hemoglobin (Hgb F)			
Other screening tests			
Follicle stimulating hormone (FSH) and estradiol (as needed in women of non-child bearing potential only)			
HIV, Hepatitis B surface antigen (HBsAg) and Hepatitis C antibody (HCV Ab) testing			

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 DLT criteria following the regulatory review. PD sampling requirements and subject populations are also clarified.

List of Specific Changes

SPONSOR/MEDICAL MONITOR INFORMATION PAGE

PREVIOUS TEXT

Medical Monitor and Sponsor Contact Information:

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

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

Section 4.2.1 PK/PD Expansion Cohorts

PREVIOUS TEXT

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. Subjects may be enrolled at previously completed dose levels for the purpose of obtaining additional data. 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.

REVISED TEXT

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. However, PD sample (peripheral blood and bone marrow aspirate) collection may be stopped early at the sponsor's discretion. Subjects may be enrolled at previously completed dose levels for the purpose of obtaining additional data. 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.

Section 4.2.3 Dose Limiting Toxicity

PREVIOUS TEXT

An event will be considered a DLT if it occurs within the first 4 weeks of treatment (with exception as below), and meets one of the following criteria unless it can be clearly established that the event is unrelated to treatment:

- Prolonged grade 4 neutropenia ($\leq 0.5 \times 10^9$/L) or thrombocytopenia ($\leq 25 \times 10^9$/L), 28-days after ceasing study treatment without evidence of leukemia (<5% blasts at the time of drug cessation and bone-marrow biopsy confirmed absence of leukemia 21-28 days later). If a subject meets above criteria at the time of drug cessation within DLT observation period, the dose escalation decision will be delayed until 28 days have elapsed post drug cessation.
- Drug related Grade 3 or 4 non-hematologic toxicity. Fatigue, asthenia, or nausea that respond to standard medical care within 72 hours and new electrolyte disturbance that

respond within 24 hours are exceptions. In addition, electrolyte disturbances associated with underlying malignancy are not considered DLT.

- 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 28 days or greater due to unresolved drug-related toxicity.

REVISED TEXT

An event will be considered a DLT if it occurs within the first 4 weeks of treatment (with exception as below), and meets one of the following criteria unless it can be clearly established that the event is unrelated to treatment:

- Prolonged grade 4 neutropenia ($\leq 0.5 \times 10^9$/L) or thrombocytopenia ($\leq 25 \times 10^9$/L), 28-days after ceasing study treatment without evidence of leukemia (<5% blasts at the time of drug cessation and bone-marrow biopsy confirmed absence of leukemia 21-28 days later). If a subject meets above criteria at the time of drug cessation within DLT observation period, the dose escalation decision will be delayed until 28 days have elapsed post drug cessation.
- ~~Drug related~~ Grade 3 or 4 non-hematologic toxicity. Fatigue, asthenia, or nausea that respond to standard medical care within 72 hours and new electrolyte disturbance that respond within 24 hours are exceptions. In addition, electrolyte disturbances associated with underlying malignancy are not considered DLT.
- ~~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 28 days or greater due to unresolved ~~drug-related~~ toxicity.

Section 7 STUDY ASSESSMENTS AND PROCEDURES

PREVIOUS TEXT

Visit Window

Baseline disease assessment should be completed within **21 days** prior to dosing start. Baseline fresh bone marrow aspirates can be collected up to **28 days** prior to dosing.

REVISED TEXT

Visit Window

Baseline disease assessment should be completed within **21 days** prior to dosing start. ~~Baseline fresh bone marrow aspirates can be collected up to **28 days** prior to dosing.~~

Section 7.1 Time and Events Table

PREVIOUS TEXT

Table 7 Time and Events, Part 1 Dose Escalation

		First Treatment Phase (28 days)										Continuation Phase	EOT
	SCR	D 1	D 2	D 4	D 8	D 11	D 15	D 16	D 18	D22	D25		
Blood samples for PD[6] (peripheral blood)	X		X	X	X	bone marrow day[21]						Wk 4	
Blood samples for exploratory[6] (peripheral blood)	X		X	X	X	bone marrow day[21]						Wk 4, between Wk 6- 8, Wk 12, then every 12 wks (on bone marrow days)	
Blood samples for circulating biomarkers and DNA[6] (plasma and cell pellet)		X				bone marrow day[21]							X
Bone marrow aspirate for PD	X[7]					X[18]						Wk 4	X[17]
Bone marrow aspirate for Exploratory (DNA and RNA)	X[7]					X[18]						Wk 4, between Wk 6- 8, Wk 12 and then every 12 wks.	X[17]

7. Archival bone marrow aspirates are requested from all subjects. If archival specimen is not available, a fresh bone marrow aspirate may be performed. Subjects enrolled in multi-subject cohorts during dose escalation and select PK/PD expansion cohorts must submit fresh bone marrow aspirates at screening. Samples collected up to 4 weeks prior to dosing are acceptable.

Table 8 Time and Events Table: Part 2 – Expansion Cohort

	SCR	First Treatment Phase (28 days)								Continuation Phase	EOT
		D 1	D4	D 8	D11	D 15	D18	D22	D 25		
Blood samples for PD[3] (peripheral blood)	X		X	X	bone marrow day[17]					Wk 4	
Blood samples for exploratory markers[3] (peripheral blood)	X		X	X	bone marrow day[17]					Wk 4, between Wk 6- 8, Wk 12, then every 12 wks. (on bone marrow day)	
Blood samples for circulating biomarkers[3] and DNA (plasma and cell pellet)		X			bone marrow day[17]						X
Bone marrow aspirate for PD	X[11]				X[14]					Wk 4	X[5]
Bone marrow aspirate for Exploratory (DNA and RNA)	X[11]				X[14]					Wk 4, between Wk 6-8, Wk 12, then every 12 wks	X[5]

REVISED TEXT

Table 9 Time and Events, Part 1 Dose Escalation

	SCR	First Treatment Phase (28 days)										Continuation Phase	EOT
		D1	D2	D4	D8	D11	D15	D16	D18	D22	D25		
Blood samples for PD[6, 22] (peripheral blood)	X		X	X	X	bone marrow day[21]						Wk 4	
Blood samples for exploratory[6,](peripheral blood)	X		X	X	X	bone marrow day[21]						Wk 4~~,~~ ~~between Wk 6- 8, Wk 12, then every 12 wks (on bone marrow days)~~ and Wk 24	X
Blood samples for circulating biomarkers and DNA[6] (plasma and cell pellet)		X				bone marrow day[21]							X
Bone marrow aspirate for PD[22]	X[7]					X[18]						Wk 4	X[17]
Bone marrow aspirate for Exploratory (DNA and RNA)	X[7]					X[18]						Wk 4~~,~~ ~~between Wk 6- 8, Wk 12 and then every 12 wks.~~ and wk 24	X[17]

7. A fresh bone marrow aspirate is requested from all subjects. This requirement is mandatory for all subjects participating in the PK-PD cohorts. ~~Archival bone marrow aspirates are requested from all subjects. If archival specimen is not available, a fresh bone marrow aspirate may be performed. Subjects enrolled in multi-subject cohorts during dose escalation and select PK/PD expansion cohorts must submit fresh bone marrow aspirates at screening. Samples collected up to 4 weeks prior to dosing are acceptable.~~
22. In PK/PD expansion cohorts, PD sample (peripheral blood and BMA) collection may be stopped earlier at the sponsor's discretion.

Table 10 Time and Events Table: Part 2 – Expansion Cohort

	SCR	First Treatment Phase (28 days)							Continuation Phase	EOT
		D 1	D4	D 8	D 11	D 15	D18	D22	D25	
~~**Blood samples for PD[3] (peripheral blood)**~~	~~X~~		~~X~~	~~X~~	~~bone marrow day[17]~~					~~Wk 4~~	
Blood samples for exploratory markers[3] (peripheral blood)	X		X	X	bone marrow day[17]					Wk 4, between Wk 6- 8, Wk 12, then every 12 wks. (on bone marrow day)	
Blood samples for circulating biomarkers[3] and DNA (plasma and cell pellet)		X			bone marrow day[17]						X
~~**Bone marrow aspirate for PD**~~	~~X[11]~~				~~X[14]~~					~~Wk 4~~	~~X[5]~~
Bone marrow aspirate for Exploratory (DNA and RNA)	X[11]				X[14]					Wk 4, between Wk 6-8, Wk 12, then every 12 wks	X[5]

Section 7.6.1 Tumor Biomarker Analysis

PREVIOUS TEXT

All subjects will be asked to submit a most recent bone marrow aspirate specimen at baseline in order to conduct retrospective tests for the identification of potential markers of sensitivity or resistance. If archival specimen is not available, a fresh biopsy may be performed. Subjects enrolled in multi-subject cohorts during dose escalation, select PK/PD expansion cohorts and Part 2 expansion cohort must submit fresh bone marrow aspirates at screening. Samples collected up to 4 weeks prior to dosing are acceptable.

This exploratory work may include protein measurements, mRNA measurements as well as DNA (mutation, DNA copy number, translocation) and epigenetic (DNA methylation, microRNA) measurements. Results of previous cytogenetic work performed on the subject will also be collected. Similar studies will also be performed on cancer specimen collected at progression or end of treatment when feasible to identify mechanisms of resistance.

REVISED TEXT

All subjects will be asked to submit peripheral blood and fresh bone marrow aspirate at baseline, during the study and at the end of treatment ~~a most recent bone marrow aspirate specimen at baseline~~ in order to conduct retrospective tests for the identification of potential markers of sensitivity or resistance through the assessment of DNA, RNA and protein. If archival specimen is not available, a fresh biopsy may be performed. Subjects enrolled in multi-subject cohorts during dose escalation, select PK/PD expansion cohorts and Part 2 expansion cohort must submit fresh bone marrow aspirates at screening. Samples collected up to 4 weeks prior to dosing are acceptable.

~~This exploratory work may include protein measurements, mRNA measurements as well as DNA (mutation, DNA copy number, translocation) and epigenetic (DNA methylation, microRNA) measurements. Results of previous cytogenetic work performed on the subject will also be collected. Similar studies will also be performed on cancer specimen collected at progression or end of treatment when feasible to identify mechanisms of resistance.~~

Section 13.6.1 Analysis Populations

PREVIOUS TEXT

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.

REVISED TEXT

All Treated 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 Treated Subjects Population and for whom a PK sample is obtained and analyzed.

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

Section 13.8.2 Safety Analysis

PREVIOUS TEXT

The All Subjects Population will be used for the analysis of safety data.

REVISED TEXT

The All Treated Subjects Population will be used for the analysis of safety data.