TITLE PAGE

Division: Worldwide Development
Information Type: Protocol Amendment

Title:	A phase I/II, open-label, 2 arm study to investigate the safety, clinical activity, pharmacokinetics and pharmacodynamics of GSK2879552 administered alone or in combination with azacitidine, in adult subjects with IPSS-R high and very high risk myelodysplastic syndromes (MDS) previously treated with hypomethylating agents (HMA)

Compound Number: GSK2879552

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Author (s):

PPD

Oncology Epigenetics Clinical, PA, USA
Oncology Epigenetics Clinical, PA, USA
Clinical Pharmacology Modeling & Simulation, PA, USA
Clinical Biomarkers and Translational Research, PA, USA
Biology, Epigenetics DPU, PA, USA
Discovery Biometrics, PA, USA
Biology, Epigenetics DPU, PA, USA
Global Clinical Safety & Pharmacovigilance, PA, USA
In Vivo In Vitro Translation, PA, USA
Oncology Epigenetics Clinical, PA, USA

Revision Chronology

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2016N275425_01	2017-MAY-08	Amendment No. 1
Addition of 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. Minor clarifications, correction of typographical errors, reformatting of tables, administrative and grammatical changes to text and Time and Events tables/footnotes.		

SPONSOR SIGNATORY

PPD

8 May 2017

Christopher Carpenter, MD, Ph.D
Senior Vice President, Epigenetics DPU Head

Date

PPD

MEDICAL MONITOR/SPONSOR INFORMATION PAGE

Medical Monitor/SAE Contact Information:

Role	Name	Day Time Phone Number and email address	After-hours Phone/Cell/ Pager Number	Site Address
Primary Medical Monitor	PPD MD, MPH	PPD		GlaxoSmithKline 1250 South Collegeville Road, UP4410 Collegeville, PA 19426, USA PPD
Secondary Medical Monitor	PPD MD, PhD			GlaxoSmithKline 1250 South Collegeville Road, UP4410 Collegeville, PA 19426, USA PPD

Sponsor Legal Registered Address:

GlaxoSmithKline Research & Development Limited
980 Great West Road
Brentford
Middlesex, TW8 9GS
UK

In some countries, the clinical trial sponsor may be the local GlaxoSmithKline Affiliate Company (or designee). If applicable, the details of the alternative Sponsor and contact person in the territory will be provided to the relevant regulatory authority as part of the clinical trial application.

Regulatory Agency Identifying Number(s): IND number 121577

INVESTIGATOR PROTOCOL AGREEMENT PAGE

For protocol number 205744

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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1. PROTOCOL SYNOPSIS FOR STUDY 205744

Rationale

Induction of differentiation may provide a new opportunity in Myelodysplastic syndromes (MDS) treatment. Preclinical studies have shown that GSK2879552 induces the expression of putative Lysine Specific Demethylase 1 (LSD1) target genes and has potent, predominantly cytostatic, anti-proliferative activity in Acute Myeloid Leukemia (AML) cell lines. While there are no cell lines that represent MDS, the activity of GSK2879552 in myeloid cell lines suggests that myeloblasts may also be sensitive to growth inhibitory effects of GSK2879552.

Changes in the expression of cell surface markers and genes associated with myeloid differentiation suggest that GSK2879552 treatment results in a pro-differentiation effect in preclinical studies. In the ongoing AML study (200200), increases in CD11b and CD86 expression were observed with GSK2879552 monotherapy at 2-4 mg. Hypomethlating Agent (HMA) and GSK2879552 are similar in that both can promote derepression of gene expression. This mechanistic overlap leads to the hypothesis that MDS patients may respond better to a HMA when combined with GSK2879552. The proposed Phase I/II study will evaluate the safety (Part 1) and clinical activity (Part 2) of GSK2879552 administered alone or in combination with azacitidine, in adult subjects with the Revised International Prognostic Scoring System (IPSS-R) high or very high risk MDS after failure of a HMA.

Objective(s)/Endpoint(s)

Part 1

Objectives	Endpoints
Primary	
1. To determine the recommended phase 2 dose (RP2D) of GSK2879552 administered alone and in combination with azacitidine in adult subjects with HR MDS previously treated with HMA.	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 evaluate clinical activity after treatment with GSK2879552, alone or in combination with azacitidine, in adult subjects with HR MDS previously treated with HMA.	1. Clinical benefit rate (CBR) defined as % of subjects achieving CR, mCR, PR, cytogenetic response, hematologic improvement (HI) or SD. Objective response rate (ORR) defined as % of subjects achieving CR, mCR, PR, cytogenetic response, or HI [as per 2006 IWG criteria]).

Objectives	Endpoints
2. To measure the exposure to GSK2879552 alone and to GSK2879552 and azacitidine in combination, in patients with HR MDS previously treated with HMA.	2. GSK2879552 and azacitidine concentrations pre-dose and post-dose.
3. To evaluate duration of response, duration of clinical benefit, progression-free survival and overall survival.	3. Duration of response (DOR) defined as the time from first documented response to disease progression. Progression-free survival (PFS) defined as the time from first dosing day to disease progression or death from any cause. Overall survival (OS) defined as the time from first dosing day until death from any cause.
4. To evaluate frequency and time to progression to AML (per 2006 IWG criteria).	4. Proportion of subjects with disease progression to AML. Time to AML progression.
5. To evaluate platelet and RBC transfusion dependence.	5. Number of documented platelet and RBC transfusions per month prior to study entry and on study.
Exploratory	
1. To investigate the mechanism of action and indicators of sensitivity and resistance to GSK2879552 alone and in combination with azacitidine.	1. Gene and/or protein expression studies of peripheral blood and/or bone marrow aspirates; correlation of baseline epigenetic and genomic profiles with response.

Part 2

Objectives	Endpoints
Primary	
1. To evaluate clinical activity after treatment with GSK2879552, alone or in combination with azacitidine, in adult subjects with HR MDS previously treated with HMA.	1. Clinical benefit rate (CBR) defined as % of subjects achieving CR, mCR, PR, cytogenetic response, HI or SD. Objective response rate (ORR) defined as % of subjects achieving CR, mCR, PR, cytogenetic response, or HI [as per 2006 IWG criteria]).

Objectives	Endpoints
Secondary	
1. To further evaluate the safety and tolerability of GSK2879552 administered alone or in combination with azacitidine.	1. Changes in safety parameters: e.g. AEs and SAEs, changes in laboratory values, vital signs, electrocardiograms [ECGs], and physical examinations.
2. To characterize the population PK of GSK2879552, alone or in combination with azacitidine in patients with HR MDS previously treated with HMA.	2. Population PK parameters for GSK2879552 such as clearance (CL/F).
3. To evaluate duration of response, duration of clinical benefit, progression-free survival, and overall survival.	3. Duration of response (DOR) defined as the time from first documented response to disease progression. Progression free survival (PFS) defined as the time from first dosing day to disease progression or death from any cause. Overall survival (OS) defined as the time from first dosing day until death from any cause.
4. To evaluate frequency and time to progression to AML (per 2006 IWG criteria)	4. Proportion of subjects with disease progression to AML. Time to AML progression.
5. To evaluate platelet and RBC transfusion dependence.	5. Number of documented platelet and RBC transfusions per month within 3 months prior to study entry and while on study.
Exploratory	
1. To investigate the mechanism of action and indicators of sensitivity and resistance to GSK2879552 administered alone or in combination with azacitidine to patients with HR MDS previously treated with HMA.	1. Gene and/or protein expression studies of peripheral blood and/or bone marrow aspirates; correlation of baseline epigenetic and genomic profiles with response.
2. To evaluate the relationship of exposure of GSK2879552, administered alone or in combination with azacitidine, and safety/efficacy parameters, based on Part 1 and 2 data combined.	2. Relationship between GSK2879552 exposure markers (e.g. dose, concentration, Cmax or AUC (0-tau)) and safety/clinical activity.

Objectives	Endpoints
3. To investigate the relationship between genetic variants in host DNA and the safety, tolerability, and efficacy of GSK2879552 alone or in combination with azacitidine based on Part 1 and 2 data combined.	3. Pharmacogenomic (PGx) analysis using saliva samples.

Overall Design

This is a Phase I/II, open-label, 2 arm study to evaluate the safety and clinical activity of GSK2879552 alone, or in combination with azacitidine in adult subjects with MDS. Eligible subjects with IPSS-R high or very high risk MDS by World Health Organization (WHO) classification, who have failed a HMA will be enrolled into the study.

This study consists of 2 Arms, i.e., monotherapy with GSK2879552 (Arm A) and combination therapy with GSK2879552 and azacitidine (Arm B). Each Arm has Part 1 for safety evaluation followed by Part 2 to evaluate clinical activity. Both Arms will proceed in parallel and subjects will be randomized in Part 2 to receive either GSK2879552 alone or GSK2879552 in combination with azacitidine. In Arm A, approximately 3-6 subjects will receive during Part 1 the Recommended Phase 2 Dose (RP2D) of GSK2879552 determined in First Time In Humans (FTIH) study (200858), i.e., 2 mg once daily, to confirm the RP2D for MDS. In Arm B, a traditional 3+3 dose escalation procedure will be followed in Part 1 to determine the RP2D of GSK2879552 in combination with azacitidine. Bayesian Logistic Regression Model (BLRM) prediction on Dose-Limiting Toxicity (DLT) rate may also be provided at dose escalation meetings as the supplementary analysis to 3+3 design. Once the RP2D of GSK2879552 for MDS is confirmed in both Arms, Part 2 enrolment will open. Each treatment cycle is 28 days and subjects experiencing disease progression on monotherapy (Arm A) will be allowed to cross over (to Arm B) to be treated with the combination at the RP2D.

The statistical design and number of subjects to be enrolled in Part 2 is based on the predictive probability of success if enrollment continues until all planned subjects are recruited . The predictive probability design allows for evaluation of stopping rules after each subject once a minimum number of subjects are evaluable. The study will stop for futility, while also taking into account subject and study termination criteria as defined in the protocol. Final decisions on stopping enrolment will depend on the totality of the data collected.

Treatment Schedule and Duration

Treatment with GSK2879552 in both arms will be administered orally as continuous daily dosing until progression. Azacitidine will be administered at 75 mg/m^2 on days 1-7 of each 28 day cycle by intravenous (iv) infusion or subcutaneous (sc) injection (route of administration: by physicians choice). Subcutaneous administration will be required during the first cycle as pharmacokinetic (PK) information will be collected.

Alterations to the dose and schedule of GSK2879552 may be incorporated based on emerging safety, tolerability and PK data. The dose and schedule of azacitidine may be also altered based on emerging safety, tolerability and PK data. Azacitidine dosing on Mon-Fri (Days 1-5) and Mon-Tue (Days 8-9) may be allowed on a case by case basis.

Subjects may continue treatment in the study until disease progression, unacceptable toxicity, or withdrawal of consent. Subjects experiencing disease progression on mono therapy (Arm A) will be allowed to cross over to be treated with the combination (Arm B) once the RP2D has been established. All subjects will be followed after study treatment discontinuation until death, lost to follow-up or withdrawal of consent. The duration of the study will depend on recruitment rates, and timing of subject's duration on study. Subjects may be allowed to continue on study treatment after disease progression if the Investigator, in consultation with the sponsor's Medical Monitor, determines that continuing treatment will benefit the patient.

Type and Number of Subjects

Approximately 3-12 subjects may be enrolled in Part 1 of each Arm. Later, approximately 28 subjects will be enrolled in Part 2 of each Arm with a total of 74 (Arm A: 6+28; Arm B: 12+28) subjects in the study. The number of subjects may change depending on the dose levels in Part 1.

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

If subjects prematurely discontinue the study, additional replacement subjects may be recruited at the discretion of the Sponsor.

A subject will be eligible for inclusion in this study only if all of the following criteria apply:

AGE
1. ≥ 18 years of age and provided signed written informed consent

TYPE OF SUBJECT AND DIAGNOSIS INCLUDING DISEASE SEVERITY
2. Subjects must have IPSS-R high or very high risk myelodysplastic syndromes (MDS) by WHO classification 3. Subjects must have failed hypomethylating treatment where "failure" is defined as: a) Progression (according to 2006 International Working Group [IWG] criteria) at any time after initiation of the hypomethylating treatment OR b) Failure to achieve complete or partial response or hematological improvement (HI) (according to 2006 IWG) after at least 4 cycles treatment OR c) Relapse after initial complete or partial response or HI (according to 2006 IWG criteria). 4. Subjects are not a candidate, or have failed allogeneic stem cell transplantation.

Subjects who underwent allo-transplant in the past are eligible under following conditions:

a) transplant was ≥2 year prior to enrolment, and

b) no evidence of active Graft-versus-host disease (GVHD)

5. Eastern Cooperative Oncology Group (ECOG) performance status of 0-2.
6. Subjects have a life expectancy of at least 12 weeks, in the opinion of the investigator.
7. 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.
8. 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 enrolment (except for alopecia).

LABORATORY

9. Adequate baseline organ function defined by:

System	Laboratory Values
Coagulation	
INR and aPTT	≤1.3 X ULN
Hematologic	
PLT	≥10,000 (transfusions permitted to bring platelet count to >10,000)
Hepatic	
Total bilirubin ALT	≤ 1.5 X ULN[a] ≤2.5 × ULN
Renal	
Creatinine OR Calculated creatinine clearance by Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation or measured from 24hr urine	≤1.5 X ULN ≥ 50 mL/min
Cardiac	
Ejection fraction	≥ LLN by Echocardiogram (ECHO) or MUGA

a. 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

GENDER and REPRODUCTIVE POTENTIAL
10. 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, during the study and for 7 days following the last dose of study treatment.
11. Men with a female partner of childbearing potential must have either had a prior vasectomy or agree to use effective contraception, 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.

A subject will not be eligible for inclusion in this study if any of the following criteria apply:

DIAGNOSTIC ASSESSMENTS AND OTHER CRITERIA
1. AML according to WHO criteria (i.e. bone marrow blasts >20%)
2. Active hepatitis B or hepatitis C treatment
3. Baseline (pre-dose Day 1)Montreal Cognitive Assessment (MOCA) score of 22 or lower

CONCURRENT CONDITIONS/MEDICAL HISTORY
4. History of or concurrent malignancy of solid tumours, except for below: Exception: Subjects who have been disease-free for 2 years, or subjects with a history of completely resected non-melanoma skin cancer or successfully treated in situ carcinoma are eligible. Consult GSK Medical Monitor if unsure whether second malignancies meet requirements specified above
5. Prior treatment with temozolomide, dacarbazine or procarbazine
6. Prior treatment with poly ADP ribose polymerase (PARP) inhibitors (e.g., olaparib, ABT-888)
7. Currently receiving other anti-cancer therapy (chemotherapy, radiation therapy, immuno- therapy, biologic therapy, hormonal therapy, surgery, and/or tumour embolization)
8. Received major surgery, radiotherapy, or immunotherapy within 4 weeks of GSK2879552 administration
9. 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
10. Current active liver or biliary disease (with the exception of Gilbert's syndrome or asymptomatic gallstones or otherwise stable chronic liver disease per investigator's assessment)
11. Patients with any major bleeding within the past 4 weeks. (e.g. recent GI hemorrhage

or neurosurgery).

12. Administration of an investigational drug within 14 days or 5 half-lives, whichever is shorter, preceding the first dose of study treatment(s) in this study.
13. Cardiac abnormalities as evidenced by any of the following:
    - Clinically significant uncontrolled arrhythmias or uncontrolled hypertension.
    - History or evidence of current ≥Class II congestive heart failure as defined by New York Heart Association (NYHA)
    - History of acute coronary syndromes (including unstable angina and myocardial infarction), coronary angioplasty, or stenting within the past 3 months
    - Baseline QTc interval using 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

CONCOMITANT MEDICATIONS/OTHER RESTRICTIONS
14. Current use of a prohibited medication including anticoagulants or platelet inhibitors or expected to require any of these medications during treatment with the investigational drug
15. 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
16. Lactating female

CONTRAINDICATION
17. Have a known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to GSK2879552 or LSD1 inhibitors that contraindicates their participation
18. Known hypersensitivity to azacitidine or mannitol

Analysis

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 1 and in Part 2 where applicable. In some instances, analysis may also be generated based on the dose of GSK2879552. Data from Part 1 and Part 2 may be combined for some analyses such as safety and efficacy 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.

2. INTRODUCTION

2.1. Rationale

2.1.1. Lysine Specific Demethylase 1 (LSD1) and Haematological Malignancy

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 CoRepressor for Element-1-Silencing Transcription factor (CoREST) and HDACs (Histone Deacetylases) 1 and 2 [You, 2001; Shi, 2003]. These data suggest that LSD1 localization and activity correlates with transcriptional repression and that inhibition of LSD1 will result in increased expression of LSD1 target genes.

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

Within acute myeloid leukemia (AML), LSD1 is most highly expressed in less differentiated subtypes [Rhodes, 2007; Wouters, 2009; Radich, 2006]. Knockdown or inhibition of LSD1 has been shown to have a pro-differentiation effect [Harris, 2012] and sensitizes AML cells to all-trans retinoic acid (ATRA), a differentiation therapy used in Acute Promyelocytic Leukemia (APL) [Schenk, 2012].

2.1.2. Rationale for subject population

Myelodysplastic syndromes (MDS) are clonal disorders of the bone marrow characterized by ineffective hematopoiesis with peripheral blood-cytopenia and a propensity to transform to acute myeloid leukemia (AML). MDS may evolve into AML in up to 45% of patients [Greenberg, 1997]. Differentiation of hematopoietic stem cells is impaired in MDS. Clonal expansion of the abnormal stem cells results in the production of cells which have lost the ability to differentiate into normal blood cells [Fenaux, 2014]. In MDS patients, myeloblasts often constitute more than 5% of the cells in the bone marrow. The number of myeloblasts is one of the principal determinants of

disease severity, where the percentage of blasts of >20% constitutes a transformation to AML. MDS occurs in 3-4 individuals per 100,000 in the US population. Incidence rates increase with age. Individuals age 60 and above have a higher prevalence rate of 7-35 per 100,000 [Rollinson, 2008]. The median age at diagnosis of MDS is 73 years [Mufti, 2012].

Using the Revised International Prognostic Scoring System (IPSS-R), patients with MDS are grouped into 5 risk groups: very low, low, intermediate, high and very high risk. Patients with high and very high risk MDS have a median survival of 1.6 and 0.8 years respectively [Greenberg, 1997]. Allogeneic stem cell transplantation is the only curative treatment modality for patients with MDS, but due to advanced age, frequent co-morbidities, and limited allogeneic graft sources, only a minority of high risk-MDS patients undergo allogeneic stem cell transplantation [Zeidan, 2014]. Remaining high and very high risk MDS patients can be treated with AML-like regimens, or with HMAs. There are two Hypomethlating Agent (HMA) drugs currently approved in the USA for treatment of MDS patients: azacitidine and decitabine. While both drugs have demonstrated superior response rates and a longer time to AML transformation when compared with supportive care alone, they have not been directly compared with each other in a randomized trial. So far, a survival advantage has been only demonstrated for azacitadine. Only 30-40% of patients with high risk MDS respond to treatment with HMA [Zeidan, 2014]. In addition, half of responders lost response within 20 months [Fenaux, 2009]. Patients failing azacitidine or decitabine have a poor outcome, with an estimated 1-year survival probability of 28% and 21-24 month survival probability of 15% [Prebet, 2011; Duong, 2013]. The median overall survival after azacitidine or decitabine failure in patients with MDS is 5.6 and 4.3 months, respectively. Alternative treatments (including best supportive care, low dose chemotherapy, intensive AML-like chemotherapy) are of little benefit in this setting [Prebet, 2011; Jabbour, 2010]. Therefore, there is an urgent need for new treatment options in MDS patients who have been previously treated with a HMA.

2.1.3. Study Rationale

Induction of differentiation may provide a new opportunity in MDS treatment. 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. While there are no cell lines that represent MDS, the activity of GSK2879552 in myeloid cell lines suggests that myeloblasts may also be sensitive to growth inhibitory effects of GSK2879552.

Changes in the expression of cell surface markers and genes associated with myeloid differentiation suggest that GSK2879552 treatment results in a pro-differentiation effect in preclinical studies. In the ongoing AML study (200200), an increase of expression of differentiation markers CD11b and CD86 was observed with GSK2879552 monotherapy at 2-4 mg. HMA and GSK2879552 are similar in that both can promote de-repression of gene expression. This mechanistic overlap leads to the hypothesis that MDS patients may respond better to HMA when combined with GSK2879552. The proposed Phase I/II study will evaluate the safety (Part 1) and clinical activity (Part 2) of GSK2879552

administered alone or in combination with azacitidine, to adult subjects with IPSS-R high or very high risk MDS after failure of a HMA.

2.2. Background

2.2.1. GSK2879552

GSK2879552 is a potent, selective, mechanism-based, irreversible inhibitor of lysine-specific demethylase-1 (LSD1)/RE1 silencing transcription factor co-repressor (CoREST). GSK2879552 had potent anti-proliferative activity in small cell lung carcinoma (SCLC) and acute myelogenous leukemia (AML) cell lines in vitro. The anti-proliferative effect was predominantly cytostatic, although there was evidence of cytotoxic effects in certain contexts.

GSK2879552 treatment resulted in an increase in H3K4me2 at regions surrounding transcriptional start sites of putative LSD1 target genes and increased their expression in vitro in AML and SCLC cell lines.Gene expression analysis in vitro as well as in tumors from mice bearing human SCLC xenograft tumors suggests that while the onset of gene expression changes in response to treatment may be relatively rapid, multiple days of dosing may be required in order to achieve the maximal effect.

In AML cell lines, treatment with GSK2879552 resulted in increased expression of cell surface markers, CD86 and CD11b. Decreased expression of CD71 as well as an increase in superoxide production in a subset of cell lines was also observed. Together, these findings suggest that treatment of AML cells with GSK2879552 may lead to a more differentiated phenotype. CD86 and CD11b expression also increased in a dose-dependent manner upon treatment with GSK2879552 in mice engrafted with MV-4-11 cells, although there was no effect on survival for this model under the conditions of the study. In a MLL-$AF9^{+}$ retroviral murine model of AML, treatment with GSK2879552 led to a significant delay in leukemia onset in treated mice relative to vehicle treated controls.

2.2.2. LSD1 inhibitor and azacitidine

Given that there were no cell line models of MDS available, the activity of GSK2879552A in combination with 5-Aza-2'-deoxycytidine (DAC) was investigated in a panel of AML cell lines. To evaluate the effect of combining DAC with GSK2879552 on the inhibition of AML cell growth, 12 AML cell lines were pre-treated with up to 100 nM DAC for 72 hours then exposed to a 20-point dose response of GSK2879552 for 6 days. DAC pre-treatment resulted in increased sensitivity to GSK2879552 in four AML cell lines in a 6-day Growth/Death assay. Greater than 5-fold potency shifts (EC_{50} or gIC_{50}) and/or increased percent growth inhibition by greater than 30% were observed in comparison to LSD1 single agent activity. These data suggest that there is a potential combination benefit to the use of HMA with an LSD1 inhibitor.

2.2.3. Pre-Clinical PK and Safety of GSK2879552

2.2.3.1. Pharmacokinetics and Product Metabolism in Animals

The nonclinical intravenous (IV) pharmacokinetics of GSK2879552 was similar across species. GSK2879552 had moderate to high blood clearance and volume of distribution in the mouse, rat and dog. The oral bioavailability in the mouse, rat and dog was moderate to high following single oral administration of GSK2879552 in solution. In the safety species (i.e. rat and dog), systemic exposure to GSK2879552 generally was similar between males and females, increased dose-proportionally and there was no evidence for accumulation after repeat dosing. The renal clearance of GSK2879552 in the rat was similar to glomerular filtration rate (GFR). Renal elimination was the primary route of excretion from both the intact and bile duct-cannulated rats following oral administration of [^{14}C] GSK2879552. In vitro plasma protein binding of GSK2879552 was low to moderate and GSK2879552 partitioned into blood cells (blood to plasma ratio was ~1 across nonclinical species and humans) which is consistent with its high permeability. GSK2879552 had low in vitro intrinsic clearance, suggesting limited oxidative metabolism in any species tested.

Consistent with its high permeability and moderate to high volume of distribution, following oral administration, [^{14}C] GSK2879552-related material was rapidly and widely distributed into tissues and concentrations declined steadily over time. GSK2879552 is not a Pgp substrate and was distributed into central nervous system (CNS) tissues. It also demonstrated strong but reversible affinity for melanin-containing tissues.

Preliminary in vitro assessments of metabolism, cytochrome P450 (CYP) inhibition and pregnane X receptor (PXR) activation potential indicated that GSK2879552 is unlikely to have the potential of being a perpetrator or victim of drug-drug interactions through the CYP enzymes. The in vitro assessments indicated that GSK2879552 is unlikely to have the potential of being a perpetrator in drug-drug interactions through P-gp, BCRP, OATP1B1, OATP1B3, OCT2 (organic cation transporter 2) or MATE2-K (multidrug and toxin extrusion transporter 2-K) inhibition or being a victim in drug-drug interactions through P-gp, BCRP, OCT2, MATE1 (multidrug and toxin extrusion transporter 1), MATE2-K, OAT1, or OAT3 transporters.

2.2.3.2. General Toxicology

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 (greater the suppression, the greater the rebound off-dose) peaking in approximately 10 days. By 4 weeks after dosing, platelet counts returned to or near pre-treatment 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 pre-treatment 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 pre-treatment 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 pre-treatment values after cessation of dosing and returned to pre-treatment values by 4 weeks after dosing.

The decreases in circulating platelets, neutrophils and reticulocytes result from the pharmacologic activity of GSK2879552 on hematopoietic lineages in the bone marrow as evidenced by a shift to immaturity of progenitor cells in the megakaryocytic, granulocytic and erythroid lineages, while the increase in monocytes results from stimulation of monopoiesis. Myelofibrosis and hyperostosis in rat (but not dog) was secondary to the marked regenerative response in the bone marrow in response to the peripheral blood cytopenias and likely represents a rodent-specific response. Generally mild to moderate, reversible effects (reduced weight, cellularity or necrosis/hemorrhage) were observed in lymphoid tissues of rats or dogs without an effect on circulating lymphocytes, of which the relationship to the pharmacology of GSK2879552 is uncertain.

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

Based on the morbidity secondary to thrombocytopenia at 0.4 mg/kg/day, the no observed adverse effect level (NOAEL) in rats was 0.2 mg/kg/day. Gender averaged systemic exposure on Day 30 at the NOAEL was 367 ng.h/mL (mean AUC_{0-t}) and 81.3 ng/mL (mean C_{max}). In rats, the STD10 was considered to be 0.4 mg/kg/day. Given the intercurrent deaths of dogs at 0.3 and 0.1 mg/kg/day, the NOAEL and the 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)].

2.2.4. Pharmacokinetics and Pharmacodynamics of GSK2879552 in Human

GSK2879552 pharmacokinetics (PK) 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 accumulation following once daily oral administration.

Following single and repeated once daily administration of 0.25 mg to 4 mg of GSK2879552, C_{max} and AUC tended to increase in a dose proportional fashion.

As LSD1 inhibition results in a blockage of platelet maturation, platelet count changes can be viewed as a PD effect and was evaluated in subjects with small cell lung cancer (study 200858). Following daily administration of 3 mg in 3 subjects, the median lowest platelet count was 10 G/L (range: 9 to 15), observed between Day 15 and Day 18. The median platelet nadir was 29 G/L (range: 22 to 93) in the 5 subjects who received 2 mg of GSK2879552 once daily. There is a steep relationship between platelet nadir and GSK2879552 dose, Cmax, or AUC. Following GSK2879552 dose interruption, platelet count started to recover within days with full recovery seen after a week interruption. But platelet count decreased once again, with a delay, following treatment restart.

Based on preclinical data, it is predicted that an increase in CD11b- and CD86-positive AML blasts will be consistent with a pro-differentiation mechanism and/or target engagement in subjects with AML (study 200200). Using 10% additional CD11b or CD86 positive blasts in treatment samples compared with baseline as a threshold, CD11b and CD86 positive blasts increased in bone marrow aspirates at 1 or more time points in 8 of 8 subjects and 2 of 8 subjects, respectively. Using these same criteria CD11b and CD86 positive blasts increased in peripheral blood of 7 of 9 subjects and 3 of 9 subjects, respectively. An increase in CD11b and/or CD86 occurs as early as 2 days of treatment, and as late as the last assessment at 4 weeks. A dose responsive increase could not be assessed with the 2 doses evaluated (2 mg and 4 mg).

2.2.5. 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_02].

In ongoing study 200858, 18 subjects with small cell lung cancer (SCLC) have been enrolled at 5 dose levels of daily doses (0.25 mg, 0.50 mg, 1 mg, 2 mg, and 3 mg) and 2 intermittent dosing regimens (3 mg for 4 days on then either 3 days off or 10 days off). Thirteen subjects have completed the study. Three subjects have prematurely discontinued; 2 subjects discontinued due to AEs (encephalopathy and asthenia) and 1 subject withdrew consent. The most frequently reported AEs (>20%) were thrombocytopenia, fatigue, anemia, constipation, decreased appetite, nausea, and back pain. The most frequently reported (>20%) treatment-related AEs were thrombocytopenia, anemia, fatigue, decreased appetite and nausea. Grade 4 AEs included thrombocytopenia/platelet count decreased (n=6), neutropenia (n=1), and increased gamma glutamyl transferase (n=1). Four subjects (22%) have had serious adverse events (SAEs), including encephalopathy (n=3), asthenia (n=1), malaise (n=1), and pericardial effusion (n=1). One event of encephalopathy was fatal. The other 2 subjects with SAEs of encephalopathy died due to disease progression. Dose-limiting toxicities (DLTs) included thrombocytopenia/platelet count decreased (n=3) and encephalopathy (n=2). In addition to the 1 death due to AE, 4 subjects have died due to disease under study. In the ongoing study 200200, 11 subjects with acute myeloblastic leukemia (AML) have been enrolled at 4 dose levels of daily doses (1 mg, 2 mg, 4 mg, or

8 mg of GSK2879552). All subjects have completed the study. The most frequently reported AEs (>20%) were fatigue, febrile neutropenia, nausea, anemia, decreased appetite, hypotension, rash, cellulitis, hypokalemia, and localized edema. Treatment-related AEs reported in at least 10% of subjects were nausea (n=4), decreased appetite (n=2), and thrombocytopenia (n=2). All Grade 4 AEs were hematological, including thrombocytopenia (n=2) and neutropenia (n=1). Treatment-related events that were Grade 3 or 4 included thrombocytopenia (n=2, Grade 4), anemia and nausea (1 subject each, Grade 3). There have been no DLTs reported in Study 200200. All 11 subjects in Study 200200 have experienced SAEs. Febrile neutropenia was the most frequently reported SAE (n=6). All cases of febrile neutropenia resolved. No other SAE has been reported in more than 1 subject. No cases of encephalopathy were reported in the AML study. Two subjects have died due to disease under study, including the subject with fatal pleural effusion.

2.2.6. Azacitidine

Azacitidine (5-azacitidine, 5-aza, Vidaza) is a pyrimidine nucleoside analog of cytidine, which causes hypomethylation (demethylation) of DNA and has direct cytotoxicity on abnormal bone marrow hematopoietic cells. It is approved for the treatment of patients with MDS in the US. Available studies indicate overall response rates in patients with low or intermediate-1 risk MDS of approximately 50 percent, with survival benefits observed in responders versus nonresponders. In most centers azacitidine is administered in an outpatient setting at a dose of 75mg/m^2 per day subcutaneously for 7 consecutive days every 28 days. Best responses may not occur until six cycles have been given. In the combined the Cancer and Leukemia Group B (CALGB) experience, the median number of cycles to first response was three, with 90 percent of responses seen by cycle six. More convenient dosing regimens, in which the agent is given for only five consecutive days, or with a "drug holiday" over the weekend, or as a 10-day cycle have also been adopted by clinicians. Dose adjustment and growth factor support are necessary for some patients during treatment with azacitidine.

Most common adverse reactions (>30%) by SC route are: nausea, anemia, thrombocytopenia, vomiting, pyrexia, leukopenia, diarrhea, injection site erythema, constipation, neutropenia and ecchymosis. Most common adverse reactions by IV route also included petechiae, rigors, weakness and hypokalemia. Azacitidine is available in lyophilized powder in 100 mg single-use vials.

Azacitidine is rapidly absorbed and eliminated after SC administration with the peak plasma azacitidine concentration occurring in 0.5 hour and a mean half-life of 41 minutes. The bioavailability of SC azacitidine relative to IV azacitidine is approximately 89%, based on AUC. AUC and Cmax of SC administration of azacitidine were approximately dose proportional within the 25 to 100 mg/m2 dose range. Multiple dosing at the recommended dose-regimen does not result in drug accumulation. Urinary excretion is the primary route of elimination of azacitidine and its metabolites [Vidaza Prescribing Information 2015].

3. OBJECTIVE(S) AND ENDPOINT(S)

3.1. Part 1

Objectives	Endpoints
Primary	
1. To determine the recommended phase 2 dose (RP2D) of GSK2879552 administered alone and in combination with azacitidine in adult subjects with HR MDS previously treated with HMA.	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 evaluate clinical activity after treatment with GSK2879552, alone or in combination with azacitidine, in adult subjects with HR MDS previously treated with HMA.	1. Clinical benefit rate (CBR) defined as % of subjects achieving CR, mCR, PR, cytogenetic response, hematologic improvement (HI) or SD. Objective response rate (ORR) defined as % of subjects achieving CR, mCR, PR, cytogenetic response, or HI [as per 2006 IWG criteria]).
2. To measure the exposure to GSK2879552 alone and to GSK2879552 and azacitidine in combination, in patients with HR MDS previously treated with HMA.	2. GSK2879552 and azacitidine concentrations pre-dose and post-dose.
3. To evaluate duration of response, duration of clinical benefit, progression-free survival and overall survival.	3. Duration of response (DOR) defined as the time from first documented response to disease progression. Progression-free survival (PFS) defined as the time from first dosing day to disease progression or death from any cause. Overall survival (OS) defined as the time from first dosing day until death from any cause.
4. To evaluate frequency and time to progression to AML (per 2006 IWG criteria).	4. Proportion of subjects with disease progression to AML. Time to AML progression.
5. To evaluate platelet and RBC transfusion dependence.	5. Number of documented platelet and RBC transfusions per month prior to study entry and on study.
Exploratory	
1. To investigate the mechanism of action and indicators of sensitivity and resistance to GSK2879552 alone and in combination with azacitidine.	1. Gene and/or protein expression studies of peripheral blood and/or bone marrow aspirates; correlation of baseline epigenetic and genomic profiles with

Objectives	Endpoints
	response.

3.2. Part 2

Objectives	Endpoints
Primary	
1. To evaluate clinical activity after treatment with GSK2879552, alone or in combination with azacitidine, in adult subjects with HR MDS previously treated with HMA.	1. Clinical benefit rate (CBR) defined as % of subjects achieving CR, mCR, PR, cytogenetic response, HI or SD. Objective response rate (ORR) defined as % of subjects achieving CR, mCR, PR, cytogenetic response, or HI [as per 2006 IWG criteria]).
Secondary	
1. To further evaluate the safety and tolerability of GSK2879552 administered alone or in combination with azacitidine.	1. Changes in safety parameters: e.g. AEs and SAEs, changes in laboratory values, vital signs, electrocardiograms [ECGs], and physical examinations.
2. To characterize the population PK of GSK2879552, alone or in combination with azacitidine in patients with HR MDS previously treated with HMA.	2. Population PK parameters for GSK2879552 such as clearance (CL/F).
3. To evaluate duration of response, duration of clinical benefit, progression-free survival, and overall survival.	3. Duration of response (DOR) defined as the time from first documented response to disease progression. Progression free survival (PFS) defined as the time from first dosing day to disease progression or death from any cause. Overall survival (OS) defined as the time from first dosing day until death from any cause.
4. To evaluate frequency and time to progression to AML (per 2006 IWG criteria)	4. Proportion of subjects with disease progression to AML. Time to AML progression.
5. To evaluate platelet and RBC transfusion dependence.	5. Number of documented platelet and RBC transfusions per month within 3 months prior to study entry and while on study.

Objectives	Endpoints
Exploratory	
1. To investigate the mechanism of action and indicators of sensitivity and resistance to GSK2879552 administered alone or in combination with azacitidine to patients with HR MDS previously treated with HMA.	1. Gene and/or protein expression studies of peripheral blood and/or bone marrow aspirates; correlation of baseline epigenetic and genomic profiles with response.
2. To evaluate the relationship of exposure of GSK2879552, administered alone or in combination with azacitidine, and safety/efficacy parameters, based on Part 1 and 2 data combined.	2. Relationship between GSK2879552 exposure markers (e.g. dose, concentration, Cmax or AUC (0-tau)) and safety/clinical activity.
3. To investigate the relationship between genetic variants in host DNA and the safety, tolerability, and efficacy of GSK2879552 alone or in combination with azacitidine based on Part 1 and 2 data combined.	3. Pharmacogenomic (PGx) analysis using saliva samples.

4. STUDY DESIGN

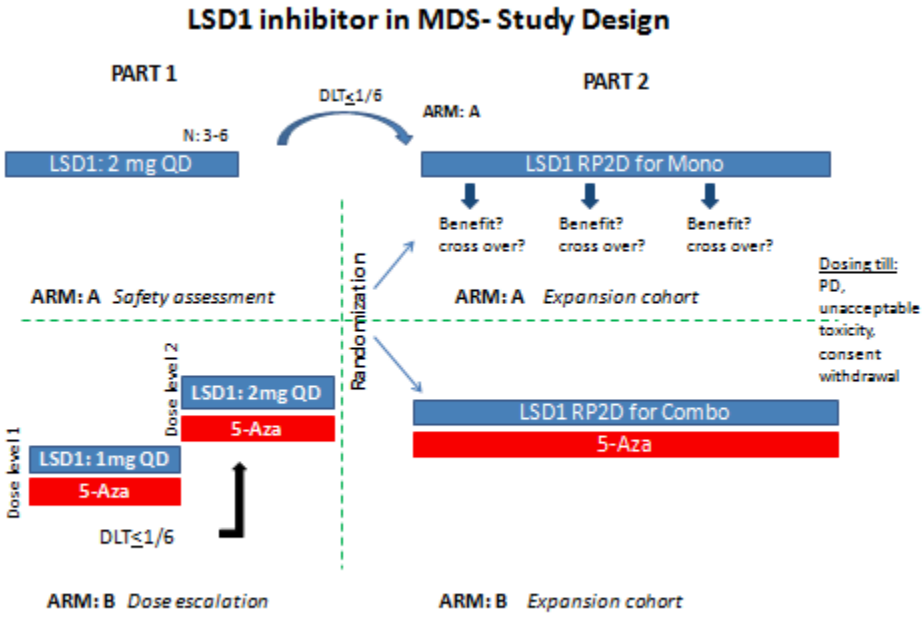
4.1. Overall Design

This is a Phase I/II, open-label, 2 arm study to evaluate the safety and clinical activity of GSK2879552 alone, or in combination with azacitidine in subjects with MDS. Eligible subjects with IPSS-R high or very high risk MDS by World Health Organization (WHO) classification, who have failed an HMA will be enrolled in the study.

This study consists of 2 Arms, i.e., monotherapy with GSK2879552 (Arm A) and combination therapy with GSK2879552 and azacitidine (Arm B). Each Arm has Part 1 for safety evaluation followed by Part 2 to evaluate clinical activity. Both Arms will proceed in parallel and subjects will be randomized in Part 2 to receive either GSK2879552 alone or GSK2879552 in combination with azacitidine. In Arm A, approximately 3-6 subjects will receive during Part 1 the RP2D of GSK2879552 determined in FTIH study (200858), i.e., 2 mg once daily to confirm the RP2D for MDS. In Arm B, traditional 3+3 dose escalation procedure will be followed in Part 1 to determine the RP2D of GSK2879552 in combination with azacitidine. Bayesian Logistic Regression Model (BLRM) prediction on DLT rate may also be provided at dose escalation meetings as the supplementary analysis to 3+3 design (See Section 4.3.2. for more details). Once the RP2D of GSK2879552 for MDS is confirmed in both Arms, Part 2 enrolment will open. Each treatment cycle is 28 days and subjects experiencing disease progression on monotherapy (Arm A) will be allowed to cross over (to Arm B) to be treated with the combination at RP2D.

The statistical design and number of subjects to be enrolled in Part 2 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. This study will stop only for futility. Final decisions on stopping enrolment will depend on the totality of the data collected.

Figure 1 Study Schematic



4.2. Treatment Schedule and Duration

Treatment with GSK2879552 in both arms will be administered orally as continuous daily dosing until progression. Azacitidine will be administered at 75 mg/m^2 on days 1-7 of each 28 day cycle by intravenous (iv) infusion or subcutaneous (sc) injection (route of administration: by physicians choice). Subcutaneous administration will be required during the first cycle as PK information will be collected.

Alterations to the dose and schedule of GSK2879552 may be incorporated based on emerging safety, tolerability, and PK data. The dose and schedule of azacitidine may be also altered based on emerging safety, tolerability and PK data. Azacitidine dosing on Mon-Fri (Days 1-5) and Mon-Tue (Days 8-9) may be allowed on a case by case basis.

Subjects may continue treatment in the study until disease progression, unacceptable toxicity, or withdrawal of consent. Subjects experiencing disease progression on mono therapy (Arm A) will be allowed to cross over to be treated with the combination (Arm B) once the RP2D has been established. All subjects will be followed after study treatment discontinuation until death, lost to follow-up or withdrawal of consent. The duration of the study will depend on recruitment rates, and timing of subject's duration on study. Subjects may be allowed to continue on study treatment after disease progression if the Investigator, in consultation with the sponsor's Medical Monitor, determines that continuing treatment will benefit the patient.

4.3. Part 1

4.3.1. Arm A (Monotherapy) - Safety Evaluation

Approximately 3-6 HR MDS subjects will receive GSK2879552 2 mg once daily to evaluate the safety and tolerability of GSK2879552. If the number of subjects with DLT is 0 (out of 3) or ≤ 1 (out of 6), RP2D for MDS will be considered defined. Subjects who fail to take at least 75% of their scheduled doses in the 4 weeks for reasons other than toxicity will be replaced.

If the 2 mg daily dose is not well tolerated, a reduced dose will be evaluated to determine RP2D for monotherapy in HR MDS. Part 2 enrolment will begin when the RP2D is confirmed in both mono therapy and combination arm. See Section 4.10 for dose justification.

4.3.2. Arm B (Combination) - Dose Escalation

Using the 3 + 3 procedure, up to six subjects will be enrolled at each dose level. Evaluation of a cohort of at least three subjects completing one cycle of treatment (defined as first 28 days) is required prior to opening the next dose level. Subjects who fail to take at least 75% of their scheduled doses in the 4 weeks for reasons other than toxicity will be replaced.

Dose escalation will progress as described in Table 1. Dose escalation decisions will take into account all available data, including the safety profile of prior cohorts.

Table 1 3 + 3 Dose Escalation Procedure

Number of Subjects with DLT	Action
0 out of 3 subjects	Escalate to next dose level
1 out of 3 subjects	Accrue three additional evaluable subjects at current dose level for a total of six evaluable subjects
1 out of 6 subjects	Escalate to the next dose level
2 or more out of 6 subjects	Maximum tolerated dose has been exceeded. Either evaluate an intermediate dose lower than current dose or expand a prior cohort up to 12 subjects.

Two dose levels for GSK2879552 are planned to be explored with a fixed dose of azacitidine (Table 2). In addition, alternate dose levels and schedules may also be explored based on emerging toxicity and PK data. The dose escalation will complete when emerging DLTs prohibit further escalation, or when pre-specified RP2D is reached. The RP2D will not exceed the MTD and may be chosen based on both PK and safety data.

In Part 1 Arm B, to facilitate dose escalation/de-escalation decisions, a Bayesian logistic regression model (BLRM) may be utilized to predict the probability of DLT at the dose levels yet to be tested. Specifically, a BLRM for combination treatment will be fitted on the dose limiting toxicity data (i.e., absence or presence of DLT) accumulated throughout

the dose-escalation to model the dose-toxicity relationship of GSK2879552 and azacitidine when given in combination.

Table 2 Planned Dose Levels

Dose Level	GSK2879552[a]	Azacitidine[b]
-1	0.5 mg once daily	75mg/m^2
1	**1 mg once daily**	**75 mg/m^2**
2	2 mg once daily	75 mg/m^2

a. Continuous daily dosing
b. Days 1-7 of 28 days cycle via IV or SC administration

4.3.3. Dose Limiting Toxicities

An event will be considered a DLT if it occurs within the first 28 days of treatment, and meets one of the following criteria unless it can be clearly established that the event is unrelated to treatment. Subjects unable to receive at least 75% of scheduled doses (of both agents, at the intended strength) for reasons other than toxicity (e.g., acute illness, disease progression) will not be evaluable for DLT purposes:

- Grade 4 thrombocytopenia associated with clinically significant bleeding
- Any Grade 3 or greater non-hematologic toxicity
- Fatigue, asthenia, nausea, vomiting or new electrolyte disturbance that respond to standard medical care within 72 hours are exceptions
- Any toxicity considered drug related that in the judgment of the investigator and GSK Medical Monitor is dose-limiting
- Drug related toxicities that prevent subjects from taking ≥75% of the intended doses during the first 28 days of treatment
- Treatment delay of 14 days or greater due to unresolved drug-related toxicity

4.3.4. Dose Escalation Committee

A data review team, consisting (at a minimum) of the investigator(s), GSK medical monitor, clinical pharmacologist, clinical scientist, and statistician, will be responsible for determining whether dose escalation during Part 1 should continue as planned according to the 3+3 design rules together with the predicted DLT rates at all dose levels under a Bayesian logistic regression model (BLRM). Prior to the dose escalation decision, the data review team will review all available data on adverse events including non-DLT toxicities, laboratory assessments and other safety evaluations.

4.4. Part 2

Part 2 of the study will be started once the dose escalation has been completed for both arms (A and B), and a dose has been selected for GSK2879552 monotherapy and combination of azacitidine with GSK2879552. Once deemed eligible, subjects will be randomly assigned at study entry to Arm A or Arm B in accordance with the randomization schedule generated by Clinical Statistics, prior to the start of the study, using validated internal software.

4.5. Intra-subject Dose-Escalation

Intra-subject dose escalations may be considered on a case-by-case basis, provided that the subject has not experienced a DLT, and a higher dose level cohort has been cleared.

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 may require additional limited PK sampling at the higher dose as determined by GSK Clinical Pharmacology.

4.6. Intra-subject Monotherapy to Combination Arm Crossover

Subjects on monotherapy (Arm A) will be allowed to cross over (to Arm B) to be treated with the combination at RP2D at the time of progression. The crossover is allowed if a patient has not experienced intolerable toxicity on mono therapy, and has experienced disease progression (including AML) according to 2006 IWG criteria. In each case, approval for crossover has to be granted by GSK Medical Monitor.

The study site is required to provide the safety and disease assessment data of the subject, and the completed crossover form (Refer to Study Procedure Manual) at least 48 hrs prior to the crossover. The medical monitor will review the data and provide the approval for crossover with a signed crossover form.

The crossover to combination treatment Arm B should occur as quickly as possible and no later than within 4 weeks of disease progression. All assessments and samples required at the “crossover visit” as described in the Time and Event table (Section 7.1) must be completed at the time of crossover. The disease assessment and safety laboratory results at the time of crossover will be considered a new baseline as the subject starts combination treatment and continue on with the next visit (from the mono therapy).

4.7. Permanent Discontinuation of Study Treatment

Subjects will receive study treatment until disease progression (according to IWG), death, withdrawal of consent, or unacceptable toxicity, including meeting stopping criteria for liver chemistry. The investigator may discuss with a GSK Medical Monitor continuing a subject who is receiving clinical benefit but has met the formal 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:

- Substantial deviation(s) from the protocol
- Request of the subject or proxy (withdrawal of consent by subject or proxy)
- Investigator's discretion
- A clinically significant adverse event leading to an interruption of treatment for greater than 14 days. If the investigator and GSK Medical Monitor conclude that the benefit: risk is positive and supports continued treatment in a subject who has had a > 14 day treatment delay, then the subject may continue therapy with the approval of the GSK Medical Monitor on case by case basis.
- 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.

Once a subject has permanently discontinued study treatment, the subject will not be allowed to re-enter this study. All subjects who discontinue from study treatment will have safety assessments at the time of discontinuation and during post-study treatment monthly follow-up.

4.8. Type and Number of Subjects

Approximately 3-12 subjects may be enrolled in Part 1 of each Arm. Later, approximately 28 subjects will be enrolled in Part 2 of each Arm with a total of 74 (Arm A: 6+28; Arm B: 12+28) subjects in the study. The number of subjects may change depending on the dose levels in Part 1.

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

If subjects prematurely discontinue the study, additional replacement subjects may be recruited at the discretion of the Sponsor.

4.9. Design Justification

The proposed study design will help to assess the GSK2879552 monotherapy safety and activity in MDS patients at doses which have been well tolerated in patients with SCLC

or with AML. The combination arm, in addition to safety assessments, will also provide the first clinical activity data of the combination of GSK2879552 with azacitidine in patients with HR MDS. Upon progression patients from the GSK2879552 mono therapy arm will, have the possibility to cross over to the combination arm to allow testing the hypothesis whether patients failing GSK2879552 might be rescued by combination treatment.

4.10. Dose Justification

4.10.1. Arm A: GSK2879552 Monotherapy

Dose limiting toxicities reported in the FTIH study in the SCLC population are thrombocytopenia and encephalopathy. Following 3 mg daily GSK2879552 administration (n=3), platelets started to decrease within days after initiation of treatment with a similar rate of decrease and Grade 4 thrombocytopenia was observed by Day 15 in all 3 subjects. Following dose interruption, the platelet count fully recovered after 1 week in all 3 subjects, but decreased again, with a delay, following treatment restart. Therefore, 2 mg once daily was determined to be the MTD and the RP2D.

GSK has conducted a thorough investigation on three encephalopathy cases reported in the SCLC study at 2mg-3 mg. Based on the likelihood that prior treatment with temozolomide predisposed the first two patients to encephalopathy, that meningeal carcinomatosis was the primary cause in the third case of encephalopathy, and that there have not been any cases of encephalopathy in AML patients treated at higher doses (including 7 patients at 4 mg once daily and 1 patient at 8 mg once daily dosing), GSK concluded that it is unlikely that GSK2879552 alone was the cause of any case of encephalopathy. It is quite typical for advanced SCLC patients to have pre-existing brain injury from radiation therapy, brain metastases, or meningeal disease. None of those factors predisposing to brain injuries are typical for the MDS population and prior treatment with temozolomide, dacarbazine or procarbazine as well as poly ADP ribose polymerase (PARP) inhibitors are exclusion criteria in this protocol.

Given all the above considerations, the proposed daily dose of 2 mg of GSK2879552, which is 25% of the 8 mg dose currently being tested in AML patients without occurrence of DLTs is expected to be tolerated by MDS subjects. The 2 mg dose is expected to achieve exposure where some clinical activity can be expected, while protecting subjects' safety. Therefore, the daily dose of 2mg will be evaluated for safety in Part 1 of the monotherapy arm. If the 2 mg daily dose is not well tolerated, a reduced dose will be evaluated to determine RP2D for MDS. Once the RP2D is confirmed in Part 1, clinical activity will be evaluated in the Part 2 expansion cohort. Treatment with GSK2879552 monotherapy will continue until intolerable toxicity, consent withdrawal, or progression. In the case of progression, the patients from arm A will be allowed to cross over to arm B, and to continue on the combination treatment arm of study.

4.10.2. Arm B: GSK2879552 and Azacitidine Combo

Azacitidine will be administered at a fixed dose of 75 mg/m^2/day on Days 1-7 of each 28 day-cycle, whereas GSK2879552 dose escalation will start at1 mg once daily. These starting doses were chosen based on the following considerations:

- This is the first time that both agents are going to be co-administered to humans, therefore a careful escalation is warranted.

- Azacitidine is an approved agent with proven activity in MDS patients, therefore azacitidine will be administered at the approved dose to maximize patients chances of having a response to treatment. A 1 mg daily dose of GSK2879552 represents a 50% reduction from the declared MTD in the SCLC study, and was very well tolerated in the SCLC study with no Grade 3 or 4 hematological AE. A 1 mg daily dose was the starting dose in the AML study and was also well tolerated. 1 mg is 12.5% of the dose currently being tested in AML (8mg).

- GSK2879552 and azacitidine may have an overlapping toxicity profile in respect to hematological toxicity with thrombocytopenia, neutropenia and anemia.

- The risk for a pharmacokinetic interaction between GSK2879552 and azacitidine is considered low.

4.11. Benefit:Risk Assessment

Summaries of findings from both clinical and non-clinical studies conducted with GSK2879552 can be found in the Investigator's Brochure (IB). The following section outlines the risk assessment and mitigation strategy for this protocol:

4.11.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
GSK2879552		
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. Thrombocytopenia has been observed in study 200858 including grade 4 thrombocytopenia. The extent of thrombocytopenia was dose-dependent with a steep relationship between platelet nadir and dose, Cmax, or AUC and grade 3/4 events occurring at higher doses. To date, withdrawal of GSK2879552 has resulted in the resolution of thrombocytopenia, but daily doses of 2mg did not cause clinically significant thrombocytopenia.. .	Informed Consent Form includes the risk of hematologic toxicity. Protocol specifies: - Exclusion criteria for - major bleeding (e.g. recent GI hemorrhage or neurosurgery) - Laboratory assessments (complete blood count [CBC] and coagulation panel) weekly for the first 4 weeks and monthly thereafter - Dose stopping/modification criteria based on CBC Signs and symptoms of bleeding or infection will be closely monitored and treated according to institutional standards during the study.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
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 - Montreal Cognitive Assessment (MOCA) at baseline (pre-dose Day 1) and weekly for the first 4 weeks and monthly thereafter. - Subjects with baseline (pre-dose Day 1) 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 (pre-dose Day 1) 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
Azacitidine		
Hematologic toxicity	Azacitidine causes anemia, neutropenia and thrombocytopenia.	Protocol specifies: - Subjects with major bleeding (e.g. recent GI hemorrhage or neurosurgery) within the past 4 weeks are excluded. - Laboratory assessments (complete blood count [CBC] and coagulation panel) are performed weekly for the first 4 weeks and monthly thereafter - Dose stopping/modification criteria based on CBC is provided. Signs and symptoms of bleeding or infection will be closely monitored and treated according to institutional standards during the study.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Hepatotoxicity	Azacitidine is potentially hepatotoxic in patients with severe pre-existing hepatic impairment.	- Subjects with elevated liver function test (LFT), history of/concurrent malignancy or current active liver or biliary disease are excluded. - LFT is monitored weekly for the first 4 weeks and monthly thereafter. - Treatment stopping criteria based on elevation in LFT is in place.
Renal impairment	Renal toxicity ranging from elevated serum creatinine to renal failure and death have been reported in patients treated with intravenous azacitidine in combination with other chemotherapeutic agents for nonMDS conditions. Renal tubular acidosis has been also reported in patients treated with azacitidine and etoposide. Patients with renal impairment may be at increased risk for renal toxicity. Also, azacitidine and its metabolites are primarily excreted by the kidney.	- Subjects with inadequate renal function are excluded - Chemistry panel including serum creatinine, BUN and electrolytes are monitored weekly for the first 4 weeks and monthly thereafter. - Treatment stopping criteria based on serum bicarbonate, creatinine and or BUN is provided.
Teratogenic effect	Azacitidine caused congenital malformations in animals and may cause fetal harm when administered to a pregnant woman. In animal studies, pre-conception treatment of male mice and rats resulted in increased embryofetal loss in mated females	- Pregnancy test will be performed at screening and monthly thereafter. - Female subjects with child bearing potential must have a negative serum pregnancy test within 7 days of first dose of study treatment and agree to use effective contraception, during the study and for 7 days following the last dose of study treatment. - Lactating females will be excluded. - Male subjects with a female partner of childbearing potential must have either had a prior vasectomy or agree to use effective contraception from the administration of the first dose of study treatment until 3 months after the last dose of study treatment.

4.11.2. Benefit Assessment

This is an open-label and the first time in human study of this agent to be conducted in subjects with MDS who have failed hypomethylating treatment 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 MDS, thus any potential beneficial effect for an individual subject attributable to GSK2879552 is unknown.

Azacitidine is used for treating MDS in clinical practice. The preclinical data suggest a potential combination benefit for use of a HMA and GSK2879552. GSK2879552 promotes increased expression of genes associated with myeloid differentiation. Mechanistically, HMA and GSK2879552 are similar in that they both cause de-repression of gene expression. This mechanistic overlap leads to the hypothesis that MDS patients may respond better to HMA when combined with GSK2879552. Any potential beneficial effect for an individual subject attributable to the combination of azacitidine with GSK2879552 in MDS is unknown.

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

4.11.3. Overall Benefit: Risk Conclusion

Current data from GSK2879552 preclinical studies, alone or in combination with 5-Aza-2'-deoxycytidine, indicate a potential for clinical activity by induction of differentiation in MDS. Taking into account the measures taken to minimise risks to subjects participating in this Phase I/II clinical trial, the potential risks identified in association with GSK2879552, alone or in combination with azacitidine, are justified by the anticipated benefits that may be afforded to subjects who failed HMA, for whom there are currently no effective available therapies.

5. SELECTION OF STUDY POPULATION AND WITHDRAWAL CRITERIA

Specific information regarding warnings, precautions, contraindications, adverse events, and other pertinent information on the GSK investigational product or other study treatment that may impact subject eligibility is provided in the IB for GSK2879552 [GlaxoSmithKline Document Number 2013N168888_02].

Deviations from inclusion and 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.

5.1. Inclusion Criteria

A subject will be eligible for inclusion in this study only if all of the following criteria apply:

AGE
1. ≥ 18 years of age and provided signed written informed consent

TYPE OF SUBJECT AND DIAGNOSIS INCLUDING DISEASE SEVERITY
2. Subjects must have IPSS-R high or very high risk myelodysplastic syndromes (MDS) by WHO classification 3. Subjects must have failed hypomethylating treatment where "failure" is defined as: a) Progression (according to 2006 IWG criteria) at any time after initiation of the hypomethylating treatment OR b) Failure to achieve complete or partial response or hematological improvement (HI) (according to 2006 IWG) after at least 4 cycles treatment OR c) Relapse after initial complete or partial response or HI (according to 2006 IWG criteria). 4. Subjects are not a candidate, or have failed allogeneic stem cell transplantation. Subjects who underwent allo-transplant in the past are eligible under following conditions: a) transplant was ≥2 year prior to enrolment, and b) no evidence of active GVHD 5. Eastern Cooperative Oncology Group (ECOG) performance status of 0-1. 6. Subjects must have a life expectancy of at least 12 weeks, in the opinion of the investigator. 7. 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. 8. 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).

LABORATORY

9. Adequate baseline organ function defined by:

System	Laboratory Values
Coagulation	
INR and aPTT	≤1.3 X ULN
Hematologic	
PLT	≥10,000 (transfusions permitted to bring platelet count to >10,000)
Hepatic	
Total bilirubin ALT	≤ 1.5 X ULN[a] ≤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

a. 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

GENDER and REPRODUCTIVE POTENTIAL

10. Women of childbearing potential must have a negative serum pregnancy test within 7 days of first dose of study treatment and agree to use effective contraception, as defined in Appendix 7 of this protocol, during the study and for 7 days following the last dose of study treatment.

11. Men with a female partner of childbearing potential must have either had a prior vasectomy or agree to use effective contraception, as defined in Appendix 7 of this protocol, 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.

5.2. Exclusion Criteria

A subject will not be eligible for inclusion in this study if any of the following criteria apply:

DIAGNOSTIC ASSESSMENTS AND OTHER CRITERIA
1. AML according to WHO criteria (i.e. bone marrow blasts >20%)
2. Active hepatitis B or hepatitis C treatment
3. Baseline (pre-dose Day 1) Montreal Cognitive Assessment (MOCA) score of 22 or lower

CONCURRENT CONDITIONS/MEDICAL HISTORY
4. History of or concurrent malignancy of solid tumours, except for below: Exception: Subjects who have been disease-free for 2 years, or subjects with a history of completely resected non-melanoma skin cancer or successfully treated in situ carcinoma are eligible. Consult GSK Medical Monitor if unsure whether second malignancies meet requirements specified above
5. Prior treatment with temozolomide, dacarbazine or procarbazine
6. Prior treatment with poly ADP ribose polymerase (PARP) inhibitors (e.g., olaparib, ABT-888)
7. Currently receiving other anti-cancer therapy (chemotherapy, radiation therapy, immuno- therapy, biologic therapy, hormonal therapy, surgery, and/or tumour embolization)
8. Received major surgery, radiotherapy, or immunotherapy within 4 weeks of GSK2879552 administration
9. 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
10. Current active liver or biliary disease (with the exception of Gilbert's syndrome or asymptomatic gallstones or otherwise stable chronic liver disease per investigator's assessment)
11. Patients with any major bleeding current or within the past 4 weeks. (e.g. recent GI hemorrhage or neurosurgery).
12. Administration of an investigational drug within 14 days or 5 half-lives, whichever is shorter, preceding the first dose of study treatment(s) in this study.
13. Cardiac abnormalities as evidenced by any of the following: • Clinically significant uncontrolled arrhythmias or uncontrolled hypertension. • History or evidence of current ≥Class II congestive heart failure as defined by New York Heart Association (NYHA) • History of acute coronary syndromes (including unstable angina and myocardial

infarction), coronary angioplasty, or stenting within the past 3 months • Baseline QTc interval using 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

CONCOMITANT MEDICATIONS/OTHER RESTRICTIONS
14. Current use of a prohibited medication including anticoagulants or platelet inhibitors or expected to require any of these medications during treatment with the investigational drug 15. Consumption of Seville oranges, grapefruit, grapefruit hybrids, grapefruit juice, pomelos, or exotic citrus fruits, from 1 day prior to the first dose of study treatment(s) until the last dose of study drug 16. Lactating female

CONTRAINDICATION
17. Have a known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to GSK2879552 or LSD1 inhibitors that contraindicates their participation 18. Known hypersensitivity to azacitidine or mannitol

5.3. Screening 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 Serious Adverse Events (see Section 7.3.1.6).

5.4. Withdrawal/Stopping Criteria

See Section 4.7. for the permanent discontinuation of study treatment.

The following actions must be taken in relation to a subject who fails to attend the clinic for a required study visit:

- The site must attempt to contact the subject and re-schedule the missed visit as soon as possible.
- In cases where the subject is deemed 'lost to follow up', the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and if necessary a certified letter to the subject's last

known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.

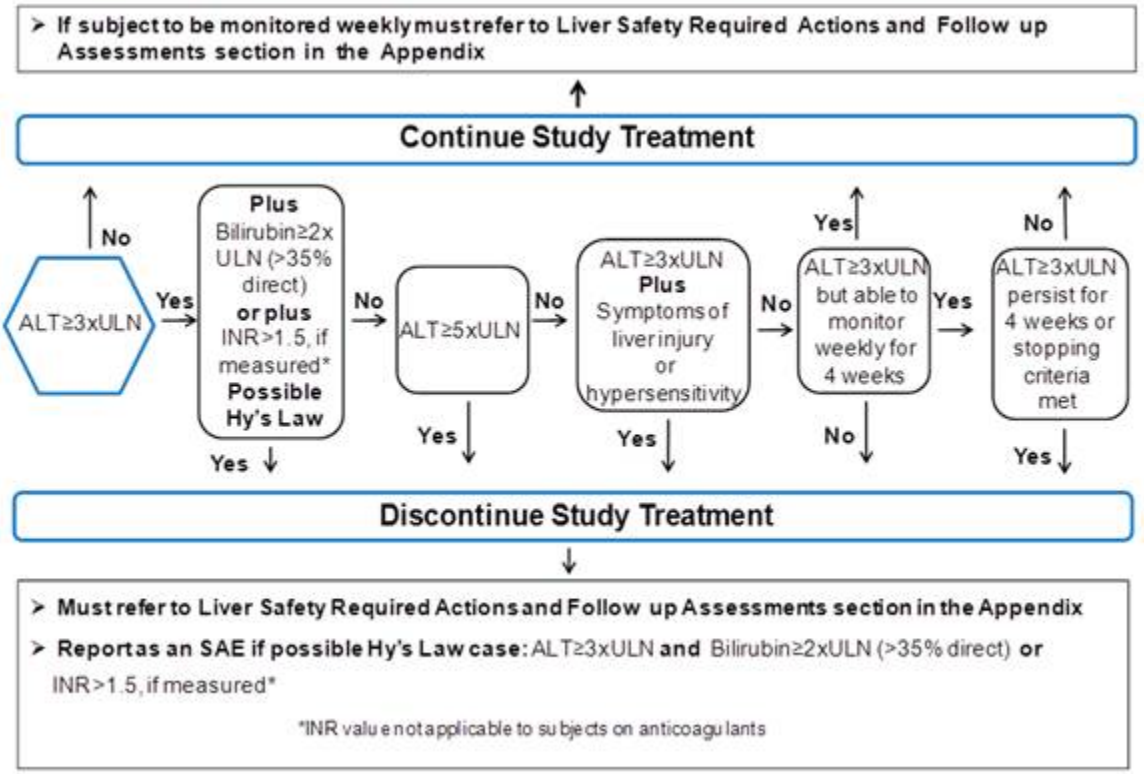
- Should the subject continue to be unreachable, only then will he/she be considered to have withdrawn from the study with a primary reason of "Lost to Follow-up".

5.4.1. Liver Chemistry Stopping Criteria

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

See Figure 2 for liver stopping criteria algorithm.

Figure 2 Liver Chemistry Stopping and Increased Monitoring Algorithm



See Appendix 2 for Liver Safety Required Actions and Follow up Assessments.

5.4.1.1. Study Treatment Restart or Rechallenge

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

- GSK Medical Governance approval **is granted**

- Ethics and/or IRB approval is obtained, if required, and
- Separate consent for treatment restart/rechallenge is signed by the subject

Refer to Appendix 3 for full guidance.

5.4.2. 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

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

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.

The QTc should be based on single or averaged QTc values of triplicate electrocardiograms obtained over a brief (e.g., 5-10 minute) recording period.

5.4.3. 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) Montreal Cognitive Assessment (MOCA) score (Section 7.3.7)

- 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 (pre-dose Day 1).
- 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 (pre-dose Day 1).

5.5. Safety Management

5.5.1. Events of Special Interest

5.5.1.1. Hematologic Events

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.

Transfusions are allowed throughout the study as clinically indicated.

Erythropoietin is not allowed on study.

The use of granulocyte stimulating growth factors is only allowed for treatment of febrile neutropenia and other life threatening infections.

5.5.1.2. Mental Status Change

When a subject presents with a possible indication of early encephalopathy, the subject should be admitted and study treatment held immediately. Below procedures should take place following the admission to support the diagnosis and/or exclude carcinomatous meningitis, unless contraindicated:

- Brain MRI scan with contrast
- Lumbar puncture with cytology analysis
- Electroencephalogram (EEG)
- Metabolic panel

5.5.2. Dose Adjustment for Non-Hematologic Toxicity

See Table 3 below. Dose Adjustment Guideline for drug related non-hematologic toxicities based on worst grade.

Table 3 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 GSK2879552 and/or azacitidine for up to 2 weeks for toxicity to resolve to baseline or ≤ Grade 1, then continue at the same dose OR dose reduce GSK2879552 and/or azacitidine by 25-50%.
G3 and 4	Hold GSK2879552 and/or azacitidine for up to 2 weeks for toxicity to resolve to baseline or ≤ Grade 1, then dose reduce GSK2879552 and/or azacitidine by 25-50%. If no recovery to ≤Grade 1* or baseline after 14 days, patient should be withdrawn.

*Note: Some AEs, such as rash and alopecia, may not be required to recover to Grade 1 or baseline. Additional AEs may be considered non-clinically significant and qualify for this exception if agreed upon by the GSK medical monitor.

If unexplained reductions in serum bicarbonate levels to <20 mEq/L occur, azacitidine dose should be reduced by 50% on the next course. Similarly, if unexplained elevations of BUN or serum creatinine occur, the next cycle should be delayed until values return to normal or baseline and the dose should be reduced by 50% on the next treatment course. A full dose of azacitidine will be administered in the subsequent treatment courses, once serum bicarbonate level returns to ≥ 20mEq/L, and BUN and serum creatinine level returns to normal or baseline, and no other toxicities are apparent.

If the non-hematologic toxicity or event resolves to baseline or ≤ Grade 1 within 14 days of stopping therapy, treatment with GSK2879552 and/or azacitidine may be restarted with at least **25%** dose reduction. For a non-DLT, the treatment with GSK2879552 and/or azacitidine 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. 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 of both drugs once the toxicity resolves to ≤ Grade 1 or baseline.

5.5.3. Dose Adjustment for Hematologic Toxicity

The dose of azacitidine and/or GSK2879552 may be adjusted based on neutrophil, platelet, WBC and bone marrow biopsy cellularity at baseline and nadir according to the guidelines below:

No dose adjustments are needed for anemia.

For patients with baseline (start of treatment) WBC ≥3.0 x10^9/L, ANC ≥1.5 x10^9/L, and platelets ≥75.0 x10^9/L, adjust the dose as follows, based on nadir counts for any given cycle:

Nadir Counts Course		% Dose of Azacitidine/GSK2879552 to be administered -
ANC (x109/L) <0.5 0.5 –1.5 >1.5	Platelets (x109/L) <25.0 25.0-50.0 >50.0	 50%/50-67% 67%/67-100% 100%/100%

For patients whose baseline counts are WBC <3.0 x10^9/L, ANC<1.5 x10^9/L, or platelets <75.0 x10^9/L, dose adjustments should be based on nadir counts and bone marrow biopsy cellularity at the time of the nadir as noted below, unless there is clear improvement in differentiation (percentage of mature granulocytes is higher and ANC is higher than at onset of that course) at the time of the next cycle, in which case the dose of the current treatment should be continued.

WBC or Platelet Nadir % decrease in counts from baseline	Bone Marrow Biopsy Cellularity at Time of Nadir (%)		
	30-60	15-30	<15
% Dose of Azacitidine/GSK2879552 to be administered -			
50 - 75	100%/100%	50%/33-67%	33%/25-50%
>75	75%/50-100%	50/33-67%	33%/25-50%

If a nadir as defined in the table above has occurred, the next course of treatment should be given 28 days after the start of the preceding course, provided that both the WBC and the platelet counts are >25% above the nadir and rising. If a >25% increase above the nadir is not seen by day 28, counts should be reassessed every 7 days. If a 25% increase is not seen by day 42, then the patient should be treated with 50% of the scheduled dose.

5.6. Subject and Study Completion

A subject will be considered to have completed the study if they are followed until death.

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.

The study will be considered completed for the purpose of a final analysis when 70% of subjects enrolled in Part 2 have progressed or died. If available, subjects continuing on treatment at the time of final analysis may be offered the option to continue in a rollover trial.

6. STUDY TREATMENT

6.1. Investigational Product and Other Study Treatment

The term 'study treatment' is used throughout the protocol to describe any combination of products 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.

6.2. Description of Investigational Product(s)

6.2.1. GSK2879552

Product name:	**GSK2879552 Capsule**
Formulation description:	GSK2879552 capsules contain 0.5 mg or 2 mg of GSK2879552 as parent.
Dosage form:	Capsule
Unit dose strength(s)	0.5 mg, 2 mg
Route/ Regimen	Oral The initial dosing regimen will be continuous oral daily dosing. Subjects should take their doses fasted (i.e. no food intake from 2 hours before dosing until 1 hour after dosing) 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.

GSK2879552 will be provided to sites by GSK.

6.2.2. Azacitidine

Azacitidine is a pyrimidine nucleoside analog of cytidine, which causes hypomethylation (demethylation) of DNA and has direct cytotoxicity on abnormal bone marrow hematopoietic cells.

Azacitidine is supplied as white lyophilised powder for injection in a single use vial

Azacitidine will be locally supplied, and stored and prepared according to local standards.

6.3. Treatment Assignment

In Part 1, subjects will be assigned to Arm A (GSK2879552 only) or Arm B (GSK2879552 in combination with azacitidine) according to the investigator discretion and/or the availability of the enrolment slot.

In Part 2, subjects will be assigned to Arm A (GSK2879552 only) or Arm B (GSK2879552 in combination with azacitidine) in accordance with the randomization schedule generated by Clinical Statistics, prior to the start of the study, using validated internal software.

Subjects will be identified by a unique subject number that will remain consistent for the duration of the study.

6.4. Blinding

This will be an open-label study

6.5. Packaging and Labeling

The contents of the label will be in accordance with all applicable regulatory requirements.

6.6. Preparation/Handling/Storage/Accountability

Azacitidine is a cytotoxic drug and, as with other potentially toxic compounds, caution should be exercised when handling and preparing azacitidine suspensions. If reconstituted azacitidine comes into contact with the skin, immediately and thoroughly wash with soap and water. If it comes into contact with mucous membranes, flush thoroughly with water. Refer to Study Procedure Manual (SPM) for preparation instructions for azacitidine.

No special preparation of GSK2879552 is required.

GSK2879552 is to be stored at a temperature range of 2-8°C (36-46°F), protected from moisture. Azacitidine vials are to be stored at 25º C (77º F); excursions permitted to 15º-30º C (59º-86º F). Maintenance of a temperature log (manual or automated) is required at the clinical sites.

- The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.

- Only subjects enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure environmentally controlled and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorized site staff.

- The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (i.e. receipt, reconciliation and final disposition records).

- Further guidance and information for final disposition of unused study treatment are provided in the SRM.

6.7. Compliance with Study Treatment Administration

On clinic days, GSK2879552 and azacitidine (if applicable) will be administered in the clinic after safety procedures including blood sampling for CBC and PK/PD samplings, if applicable, are completed. When subjects self-administer GSK2879552 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.

6.8. Treatment of Study Treatment 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.

One case of overdose with azacitidine was reported when a patient received a single IV dose of approximately 290 mg/m^2. The patient experienced diarrhea, nausea, and vomiting and the events resolved without sequelae. In the event of azacitidine overdose, the patient should be monitored with appropriate blood counts and should receive

supportive treatment, as necessary. There is no known specific antidote for azacitidine overdose.

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

6.9. Treatment after the End of the Study

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

6.10. Lifestyle and/or Dietary Restrictions

See Appendix 7 for the contraception requirements, when applicable.

6.10.1. 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 sample during each serial PK sampling day (e.g., Part 1, Days 1, 7 and 15).

Subjects should abstain from consumption of Seville oranges, grapefruit, grapefruit hybrids or grapefruit juice and/or pomelos, exotic citrus fruits which may inhibit efflux transporters and CYP enzyme, from 1 day prior to the first dose of study treatment until the last dose of study drug.

6.11. Concomitant Medications and Non-Drug Therapies

6.11.1. 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 (excluding platelet inhibitors), as appropriate.

6.11.2. Prohibited Medication(s)

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

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

Erythropoietin is not allowed on study.

6.11.3. 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.

6.11.4. 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. Pharmacokinetics of co-meds that are substrates of CYP enzymes is unlikely altered by GSK2879552.

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 transporter 2 (OCT2) and multidrug and toxin extrusion transporter 2-K (MATE2-K). Pharmacokinetics of co-meds that are substrates of the above transporters are unlikely altered by GSK2879552.

6.12. Non-Drug Therapies

Transfusions are allowed as clinically indicated.

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

7. STUDY ASSESSMENTS AND PROCEDURES

Protocol waivers or exemptions are not allowed with the exception of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the Time and Events Table, are essential and required for study conduct.

This section lists the procedures and parameters of each planned study assessment. The exact timing of each assessment is listed in the Time and Events Table Section 7.1

- The timing and number of planned study assessments, including safety, PK, PD/biomarker 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.
- The change in timing or addition of time points for any planned study assessments must be documented in a Note to File which is approved by the relevant GSK

study team member and then archived in the study sponsor and site study files, but this will not constitute a protocol amendment.

- The IRB/IEC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the Informed Consent Form.
- In Arm B, all procedures planned on Day 7 will be conducted on Day 9, if azacitidine is administered on 5+2 schedule: Mon-Fri (Days 1-5) and Mon-Tue (Days 8-9) schedule instead of 7 consecutive daily dosing on Days 1-7.

Whenever vital signs, 12-lead ECGs and blood draws are scheduled for the same nominal time, the assessments should occur in the following order: 12-lead ECGs, vital signs, blood draws.

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

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

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.

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.

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

0.5 and 1 hours post dose sampling: ±5 minutes

3 hours post dose sampling: ±15 minutes

24 hours post dose sampling: ±2 hour and should be done before the next dose administration.

7.1. Time and Events Table for Arm A – Part 1

	SCR	Cycle 1 (28 days)						C2 and beyond	Crossover Visit	End of Treatment Visit	Post Treatment Bi-Monthly Follow-Up[16]
		D 1	D2	D4	D7	D 15	D22				
Office Visit for Arm A (mono)	X	X	X[1]	X	X	X	X	C2: D1, 7, 15 and 22 C3 and after: D1	X	X	
Informed consent	X										
Demography	X										
Medical history	X										
Disease characteristics	X										
GSK2879552 Dosing[9]		< ---------- Daily or per dosing schedule ----------→									
Azacitidine dosing									X[14]		
Review subject dosing diary					X	X		Day 1	X	X	
GSK2879552 Drug Dispensing		X						Day 1			
Complete physical exam	X								X	X	
Brief physical exam		X[7]			X			Day 1			
Montreal Cognitive Assessment	X	X			X	X	X	Day 1			
ECOG PS	X	X[7]			X			Day 1	X	X	
Vital Signs	X	X[7]			X	X		Day 1	X	X	
Height and weight[6]	X	X[7]			X			Day 1	X	X	
ECHO/MUGA	X										
12-lead ECGs	X	X[7]			X			Day 1	X	X	
HIV, HBV and HCV Ab testing	X										
CBC	X	X[7]			X[12]	X	X	C2: D1, 7[12], 15 and 22	X	X	

	SCR	Cycle 1 (28 days)						C2 and beyond	Crossover Visit	End of Treatment Visit	Post Treatment Bi-Monthly Follow-Up[16]
		D 1	D2	D4	D7	D 15	D22				
								C3 and after: D1			
Chemistry Panel including LFT	X	X[7]			X[12]	X	X	Day 1	X	X	
Coagulation Panel including a PTT and INR	X				X[12]	x	X	Day 1	X	X	
PK Blood samples		X[1]	X[1]	X[8]	X[2]	X[5]	X[8]	C2: D1, 7, 15 and 22 D1 of C3-C12[8]			
Pregnancy test[4]	X							Day 1	X	X	
Blood samples for exploratory studies (peripheral blood)[3, 11]	X			X	X	X		Day 1	X	X	
Bone marrow aspirate for exploratory studies [11]	X							At time of disease assessment[17]	X[17]	X[15]	
Disease assessment	X							Day 1	X		
Bone marrow for disease assessment	X							as clinically indicated	X[18]	X[15]	
PGX samples (saliva sample)	X										
PK blood sample (corresponding with exploratory BMA)[13]								X[17]	X[17]	X[17]	
Transfusion Need Assessment[10]	X				X	X	X	D1			
Adverse Events		Continuous									
Con Meds		Continuous									
OS/PFS Assessment											X

1. A blood sample will be collected for GSK2879552 PK analysis on D1 at pre-dose, 0.5, 1 hr, and 3 hrs post dose..An additional optional PK sample will be collected at 24 hours post Day 1 dose for GSK2879552 measurement.
2. A blood sample will be collected for GSK2879552 PK analysis on D7 at pre-dose, 0.5, 1 hr, and 3 hrs post dose.
3. Samples should be collected at pre-dose.
4. For women of child bearing potential only. Serum pregnancy test is required for screening, crossover and EOT visits. Urine pregnancy test is adequate during study visits.
5. A blood sample will be collected for GSK2879552 PK analysis on D15 at pre-dose and 0.5-1 hr post dose.
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 for GSK2879552 should be taken pre-dose. PK sample will not be collected beyond 48 weeks.
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. Collection of exploratory sample (peripheral blood and/or BMA) time points may be terminated at the sponsor's discretion
12. Safety laboratory blood samples (CBC, chemistry and coagulation panel) should be collected post dose on Day 7.
13. PK blood sample should be collected prior to dosing on biopsy days.
14. Azacitidine dosing can start on Day 1 of the next cycle after the cross over visit is completed.
15. Optional for all subjects
16. Subjects are followed every 2 months to collect the survival, PFS data and the start of new treatment via chart review, or phone call contact. The follow-up will continue until death, lost to follow-up, withdrawal of consent or up to 12 months from end of treatment visit, whichever occurs first.
17. The exploratory BM sample is collected whenever the bone marrow is done for disease assessment and/or at the time of crossover, unless the sample collection is stopped per sponsor discretion; the PK blood sample will be collected pre-dose at the crossover visit if the exploratory BM sample is collected. The PK corresponding blood sample will not be collected if a regularly scheduled PK sample is already being collected during the visit.
18. A mandatory BM sample will be collected at the time of the crossover visit to establish the new baseline. A window of 14 days is allowed for this BM assessment.

Time and Events Table for Arm A – Part 2

	SCR	Cycle 1 (28 days)					Cycle 2 and beyond	Crossover Visit	End of Treatment Visit	Post Treatment Bi-monthly Follow-Up[16]
		D 1	D4	D 7	D 15	D22				
Office Visit for Arm A (mono)	X	X	X	X	X	X	C2: D1, 7, 15 and 22 C3 and after: D1	X	X	
Informed consent	X									
Demography	X									
Medical history	X									
Disease characteristics	X									
GSK2879552 Dosing[9]		< ---------- Daily or per dosing schedule ----------→								
Azacitidine dosing[14]								X[14]		
Review subject dosing diary				X	X		Day 1	X	X	
GSK2879552 Drug Dispensing		X					Day 1			
Complete physical exam	X							X	X	
Brief physical exam		X[7]		X			Day 1			
Montreal Cognitive Assessment	X	X		X	X	X	Day 1			
ECOG PS	X	X[7]		X			Day 1	X	X	
Vital Signs	X	X[7]		X	X		Day 1	X	X	
Height and weight[6]	X	X[7]		X			Day 1	X	X	
ECHO/MUGA	X									
12-lead ECGs	X	X[7]		X			Day 1	X	X	
HIV, HBV and HCV Ab	X									

	SCR	Cycle 1 (28 days)					Cycle 2 and beyond	Crossover Visit	End of Treatment Visit	Post Treatment Bi-monthly Follow-Up[16]
		D 1	D4	D 7	D 15	D22				
testing										
CBC	X	X[7]		X[12]	X	X	C2: D1, 7[12], 15 and 22 C3 and after: D1	X	X	
Chemistry Panel including LFT	X	X[7]		X[12]	X	X	Day 1	X	X	
Coagulation Panel including a PTT and INR	X			X[12]	x	X	Day 1	X	X	
PK Blood samples		X[1]	X[8]	X[5]	X[2]	X[8]	C2: D1, 7, 15 and 22 D1 of C3-C12[8]			
Pregnancy test[4]	X						Day 1	X	X	
Blood samples for exploratory studies (peripheral blood)[3, 11]	X		X	X	X		Day 1	X	X	
Bone marrow aspirate for exploratory studies [11]	X						At time of disease assessment[17]	X[17]	X[15]	
Disease assessment	X						Day 1	X		
Bone marrow for disease assessment	X						as clinically indicated	X[18]	X[15]	
PGX samples (saliva sample)	X									
PK blood sample (corresponding with exploratory BMA)[13]							X[17]	X[17]	X[17]	
Transfusion Need Assessment[10]	X			X	X	X	D1			
Adverse Events		Continuous								
Con Meds		Continuous								
OS/PFS Assessment										X

1. A blood sample will be collected for PK analysis on D1 at pre-dose, 0.5hr, 1 hr and 3 hrs post dose. .
2. A blood sample will be collected for PK analysis on D15 at pre-dose and between 0.5 to 1 hour.
3. Samples should be collected at pre-dose.
4. For women of child bearing potential only. Serum pregnancy test is required for screening, crossover and EOT visits. Urine pregnancy test is adequate during study visits.
5. A blood sample will be collected for PK analysis on D7 at pre-dose, 0.5, 1 hr, and 3 hrs post dose. .
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 for GSK2879552 should be taken pre-dose around the same time as CBC. PK sample will not be collected beyond 48 weeks.
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. Collection of exploratory sample (peripheral blood and/or BMA) time points may be terminated at the sponsor's discretion
12. Safety laboratory blood samples (CBC, chemistry and coagulation panel) should be collected post dose on Day 7.
13. PK corresponding blood sample should be collected prior to dosing
14. Azacitidine dosing can start on Day 1 of the next cycle after the cross over visit is completed.
15. Optional for all subjects
16. Subjects are followed every 2 months to collect the survival, PFS data and the start of new treatment via chart review, or phone call contact. The follow-up will continue until death, lost to follow-up, withdrawal of consent or up to 12 months from end of treatment visit, whichever occurs first.
17. The exploratory BM sample is collected whenever the bone marrow is done for disease assessment and/or at time of crossover, unless the sample collection is stopped per sponsor discretion; the PK corresponding blood sample will be collected pre-dose at the crossover visit if the exploratory BM sample is collected. The PK corresponding blood sample will not be collected if a regularly scheduled PK sample is already being collected during the visit.
18. A mandatory BM sample will be collected at the time of the crossover visit to establish the new baseline. A window of 14 days is allowed for this BM assessment.

Time and Events Table – Arm B (Combination with Azacitidine), Part 1

	SCR	Cycle 1 (28 days)						Subsequent Cycles	End of Treatment Visit	Post Treatment Bi-Monthly Follow-Up[16]
		D 1	D2	D4	D7[19]	D 15	D22			
Office Visit for Arm B (combo)	X	X	X	X	X	X	X	C2: D1- 7[19], 15 and 22 C3 and after: D1-7[19]	X	
Informed consent	X									
Demography	X									
Medical history	X									
Disease characteristics	X									
GSK2879552 Dosing[9]		< ---------- Daily or per dosing schedule ----------→								
Azacitidine dosing[14]		<--Days 1-7--->						Days 1-7		
Review subject dosing diary					X	X		Day 1	X	
GSK2879552 Drug Dispensing		X						Day 1		
Complete physical exam	X								X	
Brief physical exam		X[7]			X			Day 1		
Montreal Cognitive Assessment	X	X			X	X	X	Day 1		
ECOG PS	X	X[7]			X			Day 1	X	
Vital Signs	X	X[7]			X	X		Day 1	X	
Height and weight[6]	X	X[7]			X			Day 1	X	
ECHO/MUGA	X									
12-lead ECGs	X	X[7]			X			Day 1	X	
HIV, HBsAg and HCV Ab testing	X									
CBC	X	X[7]			X[12]	X	X	C2: D1, 7[12, 19], 15 and 22 C3 and after: D1	X	

	SCR	Cycle 1 (28 days)						Subsequent Cycles	End of Treatment Visit	Post Treatment Bi-Monthly Follow-Up[16]
		D 1	D2	D4	D7[19]	D 15	D22			
Chemistry Panel including LFT	X	X[7]			X[12]	X	X	Day 1	X	
Coagulation Panel including a PTT and INR	X				X[12]	x	X	Day 1	X	
PK Blood samples		X[1]	X[1]	X[8]	X[2]	X[5]	X[8]	C2: D1, 7[19], 15 and 22 D1 of C3-C12[8]		
Pregnancy test[4]	X							Day 1	X	
Blood samples for exploratory studies (peripheral blood)[3, 11]	X			X	X	X		Day 1	X	
Bone marrow aspirate for exploratory studies [11]	X							At time of disease assessment[17]	X[15]	
Disease assessment	X							Day 1	X	
Bone marrow for disease assessment	X[18]							as clinically indicated	X[15]	
PGX samples (saliva sample)	X									
PK blood sample (corresponding with exploratory BMA)[13]								X[17]	X[17]	
Transfusion Need Assessment[10]	X				X	X	X	D1		
Adverse Events		Continuous								
Con Meds		Continuous								
OS/PFS Assessment										X

1. A blood sample will be collected for GSK2879552 and azacitidine PK analysis on D1 at pre-dose, 0.5, 1 hr, and 3 hrs post dose.. An additional PK sample will be collected at 24 hours post Day 1 dose for GSK2879552 measurement in the combination arm.
2. A blood sample will be collected for GSK2879552 and azacitidine PK analysis on D7 at pre-dose, 0.5, 1 hr, and 3 hrs post dose.
3. Samples should be collected at 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. A blood sample will be collected for GSK2879552 PK analysis on D15 at pre-dose and 0.5-1 hr post dose.
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 for GSK2879552 should be taken pre-dose. PK sample will not be collected beyond 48 weeks.
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. Collection of exploratory sample (peripheral blood and/or BMA) time points may be terminated at the sponsor's discretion
12. Safety laboratory blood samples (CBC, chemistry and coagulation panel) should be collected post dose on Day 7 or the last day of Azacitidine in the cycle.
13. PK corresponding blood sample should be collected prior to dosing
14. Azacitidine dosing on Mon-Fri (Days 1-5) and Mon-Tue (Days 8-9) may be allowed on a case by case.
15. Optional for all subjects
16. Subjects are followed every 2 months to collect the survival, PFS data and the start of new treatment via chart review, or phone call contact. The follow-up will continue until death, lost to follow-up, withdrawal of consent or up to 12 months from end of treatment visit, whichever occurs first.
17. The exploratory BM sample is collected whenever the bone marrow is done for disease assessment and/or at time of crossover, unless the sample collection is stopped per sponsor discretion; the PK corresponding blood sample will be collected pre-dose at the crossover visit if the exploratory BM sample is collected. The PK corresponding blood sample will not be collected if a regularly scheduled PK sample is already being collected during the visit.
18. A window of 14 days is allowed for BM exam. Subjects who progressed to AML and cross over to Arm B will be required to have bone marrow for disease assessment prior to the start of combination dosing
19. All procedures scheduled on Day 7 visit (of any cycle) should move to Day 9, if azacitidine is given on Mon-Fri (Days 1-5) and Mon-Tue (Days 8-9) instead of Days 1-7.

Time and Events Table - Arm B (Combination with Azacitidine), Part 2

	SCR	Cycle 1 (28 days)					Subsequent Cycles	End of Treatment Visit	Post Treatment Bi-monthly Follow-Up[16]
		D 1	D4	D7[18]	D 15	D22			
Office Visit for Arm B (combo)	X	X	X	X	X	X	C2: D1- 7[18], 15 and 22 C3 and after: D1-7	X	
Informed consent	X								
Demography	X								
Medical history	X								
Disease characteristics	X								
GSK2879552 Dosing[9]		< ---------- Daily or per dosing schedule ----------→							
Azacitidine dosing[14]		<--Days 1-7--->					Days 1-7		
Review subject dosing diary				X	X		Day 1	X	
GSK2879552 Drug Dispensing		X					Day 1		
Complete physical exam	X							X	
Brief physical exam		X[7]		X			Day 1		
Montreal Cognitive Assessment	X	X		X	X	X	Day 1		
ECOG PS	X	X[7]		X			Day 1	X	
Vital Signs	X	X[7]		X	X		Day 1	X	
Height and weight[6]	X	X[7]		X			Day 1	X	
ECHO/MUGA	X								
12-lead ECGs	X	X[7]		X			Day 1	X	
HIV, HBsAg and HCV Ab testing	X								

	SCR	Cycle 1 (28 days)					Subsequent Cycles	End of Treatment Visit	Post Treatment Bi-monthly Follow-Up[16]
		D 1	D4	D7[18]	D 15	D22			
CBC	X	X[7]		X[12]	X	X	C2: D1, 7[12, 18], 15 and 22 C3 and after: D1	X	
Chemistry Panel including LFT	X	X[7]		X[12]	X	X	Day 1	X	
Coagulation Panel including a PTT and INR	X			X[12]	x	X	Day 1	X	
PK Blood samples		X[1]	X[8]	X[5]	X[2]	X[8]	C2: D1, 7[18], 15 and 22 D1 of C3-C12[8]		
Pregnancy test[4]	X						Day 1	X	
Blood samples for exploratory studies (peripheral blood)[3, 11]	X		X	X	X		Day 1	X	
Bone marrow aspirate for exploratory studies [11]	X						At time of disease assessment[17]	X[15]	
Disease assessment	X						Day 1	X	
Bone marrow for disease assessment	X[19]						bone marrow if clinically indicated	X[15]	
PGX samples (saliva sample)	X								
PK blood sample (corresponding with exploratory BMA)[13]							X[17]	X[17]	
Transfusion Need Assessment[10]	X			X	X	X	D1		
Adverse Events		Continuous							
Con Meds		Continuous							
Survival Assessment									X

1. A blood sample will be collected for GSK2879552 and azacitidine PK analysis on D1 at pre-dose, 0.5hr, 1 hr and 3 hrs post dose..
2. A blood sample will be collected for PK analysis on D15 at pre-dose and between 0.5 to 1 hour.
3. Samples should be collected at 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. A blood sample will be collected for GSK2879552 and azacitidine PK analysis on D7 at pre-dose, 0.5, 1 hr, and 3 hrs post dose.
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 for GSK2879552 should be taken pre-dose around the same time as CBC. PK sample will not be collected beyond 48 weeks.
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. Collection of exploratory sample (peripheral blood and/or BMA) time points may be terminated at the sponsor's discretion
12. Safety laboratory blood samples (CBC, chemistry and coagulation panel) should be collected post dose on Day 7.
13. PK corresponding blood sample should be collected prior to dosing
14. Azacitidine dosing on Mon-Fri (Days 1-5) and Mon-Tue (Days 8-9) may be allowed on a case by case.
15. Optional for all subjects.
16. Subjects are followed every 2 months to collect the survival, PFS data and the start of new treatment via chart review, or phone call contact. The follow-up will continue until death, lost to follow-up, withdrawal of consent or up to 12 months from end of treatment visit, whichever occurs first.
17. The exploratory BM sample is collected whenever the bone marrow is done for disease assessment and/or at time of crossover, unless the sample collection is stopped per sponsor discretion; the PK corresponding blood sample will be collected pre-dose at the crossover visit if the exploratory BM sample is collected. The PK corresponding blood sample will not be collected if a regularly scheduled PK sample is already being collected during the visit.
18. All procedures scheduled on Day 7 visit (of any cycle) should move to Day 9, if azacitidine is given on Mon-Fri (Days 1-5) and Mon-Tue (Days 8-9) instead of Days 1-7.
19. A window of 14 days is allowed for BM exam. Subjects who progressed to AML and cross over to Arm B will be required to have bone marrow for disease assessment prior to the start of combination dosing

7.2. Screening and Critical Baseline Assessments

Cardiovascular medical history/risk factors (as detailed in the CRF) will be assessed at screening.

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

Medical/medication/family history will be assessed as related to the inclusion/exclusion criteria listed in Section 5.

Procedures conducted as part of the subject's routine clinical management [e.g. blood count] 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 within the timeframe defined in the Time and Events Schedule.

7.3. Safety

Planned time points for all safety assessments are listed in the Time and Events Table (Section 7.1). Additional time points for safety tests may be added during the course of the study based on newly available data to ensure appropriate safety monitoring.

7.3.1. Adverse Events (AE) and Serious Adverse Events (SAEs)

The definitions of an AE or SAE can be found in Appendix 5.

The investigator and their designees are responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE.

7.3.1.1. Time period and Frequency for collecting AE and SAE information

- Any SAEs assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product will be recorded from the time a subject consents to participate in the study up to and including any follow-up contact.
- AEs will be collected from the start of Study Treatment until the follow-up contact (see Section 7.3.1.3), at the timepoints specified in the Time and Events Table (Section 7.1).
- Medical occurrences that begin prior to the start of study treatment but after obtaining informed consent may be recorded on the Medical History/Current Medical Conditions section of the CRF.
- All SAEs will be recorded and reported to GSK within 24 hours, as indicated in Appendix 5.
- Investigators are not obligated to actively seek AEs or SAEs in former study subjects. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the

event reasonably related to the study treatment or study participation, the investigator must promptly notify GSK.

NOTE: The method of recording, evaluating and assessing causality of AEs and SAEs plus procedures for completing and transmitting SAE reports to GSK are provided in Appendix 5.

7.3.1.2. Method of Detecting AEs and SAEs

Care will 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?"

7.3.1.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs, and non-serious AEs of special interest (as defined in Section 4.11.1) will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up (as defined in Section 5.4). Further information on follow-up procedures is given in Appendix 5.

7.3.1.4. Cardiovascular and Death 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.

7.3.1.5. 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.

7.3.1.6. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to GSK of SAEs related to study treatment (even for non- interventional post-marketing studies) is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a product under clinical investigation 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)/Independent Ethics Committee (IEC) 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/IEC, if appropriate according to local requirements.

7.3.2. Pregnancy

Details of all pregnancies in female subjects or female partners of male subjects will be collected after the start of dosing and until 7 days post-last dose.

If a pregnancy is reported then the investigator should inform GSK within 2 weeks of learning of the pregnancy and should follow the procedures outlined in Appendix 7.

7.3.3. Physical Exams

A complete physical examination will include, at a minimum, assessment of the Cardiovascular, Respiratory, Gastrointestinal and Neurological systems. Height and weight will also be measured and recorded.

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

- Investigators should pay special attention to clinical signs related to previous serious illnesses

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 (ECG)

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.

7.3.6. ECOG Performance Status

The performance status will be assessed using the Eastern Cooperative Oncology Group (ECOG) scale (Appendix 6) as specified in the Time and Events Table (Section 7.1).

7.3.7. 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.

7.3.8. 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).

7.3.9. Clinical Safety Laboratory Assessments

All protocol required laboratory assessments, as defined in Table 4 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 14 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 4:

Table 4 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)		
Other tests			
Coagulation Panel including aPTT and INR			
Other screening tests			
Follicle stimulating hormone (FSH) and estradiol (as needed in women of non-child bearing potential only)			
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)

7.4. Evaluation of Anti-Cancer Activity

Disease assessments will be made by physical examination and laboratory evaluation, which includes a complete blood count with differential. Bone marrow aspiration should be performed if clinically indicated, and to confirm the response. Response criteria are listed in Appendix 10.

7.5. Pharmacokinetics

7.5.1. Blood Sample Collection

Blood samples for pharmacokinetic (PK) analysis of GSK2879552, GSK2879552 metabolite(s), as deemed appropriate, and azacitidine will be collected 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.

7.5.2. Sample Analysis

Plasma sample analysis will be performed under the control of Bioanalysis, Immunogenicity & Biomarkers (BIB), In Vitro/In Vivo Translation (IVIVT), Platform Technology and Science (PTS), GlaxoSmithKline. Concentrations of GSK2879552, GSK2879552 metabolite(s), as deemed appropriate, and azacitidine will be determined in plasma samples using the currently approved bioanalytical methodology. Raw data will be archived at the bioanalytical site. 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.

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 azacitidine in MDS as well as identifying indicators of sensitivity or resistance. 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 drug combinations. Similarly, pre- and on-treatment blood and bone marrow specimens will be evaluated for target engagement, therapeutic 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 may be 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. Biomarker Analysis

All subjects will be asked to submit peripheral blood samples at baseline, during the study, and at the end of treatment. All subjects will also be asked to submit fresh bone marrow aspirate at baseline and during the study. There is an optional bone marrow aspirate collection at the end of treatment. These samples will be used to conduct retrospective tests to understand the mechanistic activity of GSK2879552 alone and in combination with azacitidine, therapeutic response and the identification of potential markers of sensitivity or resistance through the assessment of DNA, RNA and/or protein. These studies may include but are not limited to DNA methylation, transcriptomic, and genomic analyses.

7.7. Genetics

A 2 mL saliva sample for DNA isolation will be collected from participants who have consented to participate in the genetics analysis component of the study. Participation is optional. Participants who do not wish to participate in the genetic research may still participate in the study.

In the event of DNA extraction failure, a replacement genetic saliva sample may be requested from the participant. Signed informed consent will be required to obtain a replacement sample unless it was included in the original consent.

See Appendix 4 for Information regarding genetic research. Details on processes for collection and shipment and destruction of these samples can be found in the Time and Events Schedule (Section 7.1).

8. 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.

9. STATISTICAL CONSIDERATIONS AND DATA ANALYSES

9.1. Hypotheses

9.1.1. Part 1:

With respect to the primary objectives and endpoints, no specific statistical hypotheses are being tested. The primary focus will be on determining the recommended dose for further exploration, based upon the safety, PK and efficacy profiles of GSK2879552 plus azacitidine in subjects with relapsed/refractory HR MDS.

9.1.2. Part 2: Disease-Specific Expansion Cohorts

The primary goal of Part 2 is to evaluate disease-specific clinical activity in subjects with GSK2879552, alone or in combination with azacitidine, in adult subjects with MDS. Clinical activity is defined as a clinical benefit rate (% of subjects achieving CR, PR, HI or SD [per 2006 IWG criteria]). This will be conducted by testing the null hypothesis that P0<=0.3 versus the alternative that P1 ≥0.5, Subjects in Part 1 and Part 2 treated with the same starting dose will be analyzed together.

The Part 2 portion of the study will employ a Bayesian predictive adaptive design [Lee, 2008] for Arm A and Arm B separately that allows the trial to be monitored more frequently at multiple stages. The criteria will be based on a historically unimportant response rate of 30% versus a response rate of interest of 50%. Bayesian statistics will be employed to calculate the predictive probability that the response rate ≥50% and ≥30% at interim assuming a Beta prior for the Binomial distributed data. Predictive probability calculates the probability that the response rate ≥50% or ≥30% at the end of Part 2 given the responses that are currently being observed at interim. It predicts what is likely to happen at the end of Part 2 so it is more meaningful and straightforward than posterior probability. A weak prior Beta (0.005, 0.005) is used, which is equivalent to the information present in 0.01 subjects. The first interim analysis may be conducted when at least 10 subjects are recruited for each Arm. Futility interim analysis decision rules for the 10^{th} to 28^{th} evaluable subjects, specifying the number of subjects with clinical activity (CR, PR, HI or SD) needed for continuing enrolment or stopping for futility when total sample size is up to 28, is presented in Table 5. These rules are intended as a guideline. Actual decisions will depend on the totality of the data.

Table 5 Decision Making Criteria for Futility

Number of Evaluable Subjects	≤ This Number of Responses to Stop Early for Futility	Probability of continuing enrolling when CBR=0.3	Probability of continuing enrolling when CBR=0.5
10	1	0.8507	0.9893
12	2	0.7363	0.9783
14	3	0.6242	0.9655
16	3	0.6242	0.9655
18	4	0.5739	0.9620
20	5	0.5087	0.9566
22	6	0.4414	0.9500
24	8	0.2601	0.9103
26	9	0.2059	0.8927
28	11	0.0000	0.0000

For the separate interim looks in each cohort in Part 2, the enrollment for that cohort may be stopped due to futility if the predictive probability that the confirmed response rate ≥30% (historical control) is small (e.g., less than a 2% chance for a total sample size of 28 subjects). Enrollment may also be stopped due to futility if the equivalent of less than 2 responses is observed in the first 10 enrolled evaluable subjects in that cohort or less than 3 responses are observed in the first 12 evaluable subjects. The evaluable subject is defined as a subject, who has either progressed, withdrew from the study, was lost to follow-up, or is ongoing and has completed at least one post treatment disease assessment. For example, when there are 10 evaluable subjects available at the time of interim analysis with only one response, then the Arm may be stop for futility. Otherwise, the enrolment of the respective Arm will continue to the target sample size.

When the total sample size in a treatment arm is 28 and at least 12 responders out of 28 subjects are observed, we can claim null hypothesis is rejected.

No formal hypotheses are set up to compare the activity between Arm A and Arm B. The CBR and ORR will be reported for both arms separately at the end of Part 2.

9.2. Sample Size Considerations

9.2.1. Sample Size Assumptions

Part 1: Dose Escalation

The total number of subjects to be enrolled in the dose escalation phase of Part 1 will depend on the number of subjects needed to characterize individual dose combination cohorts. The sample size is not driven by statistical considerations. However, it is anticipated that approximately 10-12 evaluable subjects will be enrolled.

Part 2: Expansion Cohorts

To determine the maximum sample size for Arm A or Arm B, Bayesian predictive adaptive design will be used for testing hypotheses:

H_0: CBR≤30%

H_A: CBR≥50%

When maximum sample size is 28, the design will have a Type I error (α) of 0.099 and 81% power with the probability of termination is 0.90 when the treatment is futile and probability of early termination 0.183 when the treatment is effective (true RR=0.5).

In Part 2, a maximum of 28 subjects will be enrolled in Arm A and Arm B expansion cohort, respectively. If both arms enroll the maximum number of subjects, this will result in 56 subjects total randomized to Arm A and Arm B with 1:1 randomization ratio.

Enrollment into Arm A or Arm B may be halted early based on results from interim analyses incorporating emerging response data. Response data from a minimum of 10 evaluable subjects will be required per arm before it may discontinue enrollment for futility.

9.2.2. Sample Size Sensitivity

There was no need to perform sample size sensitivity analysis.

9.2.3. Sample Size Re-estimation or Adjustment

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

9.3. Data Analysis Considerations

9.3.1. 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 Crossover Population will comprise the subset of subjects in Part 1 and Part 2 who had intra-subject Arm A to Arm B crossover. It will be the primary population when summarizing data in Part 1, Part 2 crossover phase.

9.3.2. Interim Analysis

No formal interim analysis will be performed. Review of all available safety and pharmacokinetic data will be performed after completion of each dosing cohort.

In Part 1, to further facilitate dose escalation/de-escalation decisions, an adaptive Bayesian logistic regression model (BLRM) may be utilized to predict the probability of DLT at the dose levels yet to be tested.

Prior distribution of the parameter for azacitidine will be calculated based on the toxicity data observed in the first time in human (FTIH) study of GSK2879552 where GSK2879552 is administered alone; similarly, prior distribution of the parameter for Azacitidine will be determined based on data observed in the study where Azacitidine is administered alone; a non-informative prior will be assumed for the other parameters which accounts for the combination of the two compounds. The model will be used only as a guide for what further doses to study in the presence of DLTs. The primary considerations for dose escalation/de-escalation will be based on the rules described in Section 4.3. Further details on the model as well as prior distributions will be included in the Reporting and Analysis Plan (RAP).

9.3.2.1. Part 2 Cohort Expansion

Interim data will be evaluated to monitor efficacy and safety. Enrollment may be stopped early for futility, should various criteria occur based on accrued data. The decision criteria for early stop for futility based on Bayesian Adaptive design are described in Section 9.1.2. The decision will be made for each individual cohort.

The study population used for decision-making at the interim analyses during Part 2 (Expansion Cohort) will be termed All Evaluable Subjects defined in Section 9.1.2. This will be the population for Bayesian adaptive design described in Section 9.1.2 and summaries of response if data warrant. Any evaluable subject from Part 1 of the study who has the same initial dose as in Part 2 will be included in this analysis. Because subjects enroll at different times, not all subjects will have been on the study long enough to have a single or multiple disease assessments. Since disease assessments and are to be completed every 4 weeks, subjects who have at least one post-baseline disease assessment or have progressed or died or permanently withdraw from the study will be included in this population.

9.4. 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 unlikely be informative, therefore 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.

9.4.1. Clinical Activity Analyses

The clinical benefit rate (CBR) is defined as the percentage of subjects with a Complete Remission (CR), marrow complete remission (mCR) or a Partial Remission (PR) or a Hematologic Improvement (HI) or Stable Disease (SD) at any time as per disease-specific criteria (Appendix 5 and Appendix 6). Subjects with unknown or missing response will be treated as non-responders, i.e. these subjects will be included in the denominator when calculating the percentage. The number and types of responses, as outlined in IWG criteria [Cheson, 2006], will be listed and summarized separately, as appropriate.

The ORR will be reported at the interim and final analysis for each arm specified in Part 2 as well as all evaluable subjects in Part 1 treated at or above RP2D. Part 1 and Part 2 subjects who received the same dose within the same treatment arm may be combined together in the analysis. The estimates along with 95% exact confidence interval (CI) will be provided.

The CBR and ORR differences between the two cohorts will be provided along with corresponding 95% CI. A chi-square test will be used to test for differences between arms if data warrant.

Duration of response is defined as the subset of subjects who show a response (CR, mCR, PR, or HI), the time from first documented evidence of response until the first documented sign of disease progression or death. Duration of response will be summarized descriptively for each arm, if data warrant, using Kaplan-Meier medians and quartiles. Details on rules for censoring will be provided in the RAP.

For the analysis of **Progression-free survival (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, mCR, PR, HI or SD) prior to the initiation of therapy. Progressive disease (PD) will also be defined per standard criteria. Otherwise, if the subject does not have a documented date of events, PFS will be censored at the date of the last adequate assessment. Further details on rules for censoring will be provided in the RAP. PFS will be summarized by arm and dose using Kaplan-Meier quantile estimates along with 2-sided 95% CIs at the time of final analysis, if data warrant.

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. OS will be

summarized by arm and dose using Kaplan-Meier quantile estimates along with 2-sided 95% CIs at the time of final analysis, if data warrant.

9.4.2. 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).

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.

9.4.2.1. Extent of Exposure

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

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

9.4.2.2. Adverse Events

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.

9.4.2.3. Clinical Laboratory Evaluations

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 criterion will be summarized using proportions. Further details will be provided in the Reporting and Analysis Plan (RAP).

9.4.2.4. Other Safety Measures

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).

9.4.3. Pharmacokinetic Analyses

9.4.3.1. Pharmacokinetic Parameters

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

Population Pharmacokinetics

Plasma concentration-time data for GSK2879552 from all Arms and Parts may be combined with data from other studies and may be 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 (e.g. Cmax, AUC and Cav = AUC/τ) and identify relevant covariates (e.g., age, weight, or disease related covariates). Results may be reported separately.

9.4.3.2. Statistical Analysis of Pharmacokinetic Data

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

Plasma concentration-time data for GSK2879552, GSK2879552 metabolite(s) as deemed appropriate, and azacitidine will be listed by dose and arm and summarized using descriptive statistics (n, mean, standard deviation [SD], median, minimum and maximum) by planned relative assessment time. Mean and/ or median values may be plotted over time.

9.4.4. Pharmacokinetic/Pharmacodynamic Analyses

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

Quantitative safety parameters 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.

9.4.4.1. 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 disease biology or between therapeutic 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.

9.4.4.2. 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.

10. STUDY GOVERNANCE CONSIDERATIONS

10.1. Posting of Information on Publicly Available Clinical Trial Registers

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

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

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

The study will be conducted in accordance with all applicable regulatory requirements, and with GSK policy.

The study will also be conducted in accordance with ICH Good Clinical Practice (GCP), all applicable subject privacy requirements, and the guiding principles of the current version of the Declaration of Helsinki. This includes, but is not limited to, the following:

- IRB/IEC review and favorable opinion/approval of the study protocol and amendments as applicable
- Obtaining signed informed consent
- Investigator reporting requirements (e.g. reporting of AEs/SAEs/protocol deviations to IRB/IEC)
- GSK will provide full details of the above procedures, either verbally, in writing, or both.
- Signed informed consent must be obtained for each subject prior to participation in the study
- The IEC/IRB, and where applicable the regulatory authority, approve the clinical protocol and all optional assessments, including genetic research.
- Optional assessments (including those in a separate protocol and/or under separate informed consent) and the clinical protocol should be concurrently submitted for approval unless regulation requires separate submission.

- Approval of the optional assessments may occur after approval is granted for the clinical protocol where required by regulatory authorities. In this situation, written approval of the clinical protocol should state that approval of optional assessments is being deferred and the study, with the exception of the optional assessments, can be initiated.

10.3. Quality Control (Study Monitoring)

- In accordance with applicable regulations including GCP, and GSK procedures, GSK monitors will contact the site 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 also include identification, agreement and documentation of data items for which the eCRF will serve as the source document.

GSK will monitor the study and site activity to verify 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, GCP, and all applicable regulatory requirements.

The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents

10.4. Quality Assurance

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

10.5. Study and Site Closure

- Upon completion or premature discontinuation of the study, the GSK monitor will conduct site closure activities with the investigator or site staff, as appropriate, in accordance with applicable regulations including GCP, and GSK Standard Operating Procedures.

- GSK reserves the right to temporarily suspend or prematurely discontinue this study at any time for reasons including, but not limited to, safety or ethical issues or severe non-compliance. For multicenter studies, this can occur at one or more or at all sites.
- If GSK determines such action is needed, GSK will discuss the reasons for taking such action with the investigator or the head of the medical institution (where applicable). When feasible, GSK will provide advance notification to the investigator or the head of the medical institution, where applicable, of the impending action.
- If the study is suspended or prematurely discontinued for safety reasons, GSK will promptly inform all investigators, heads of the medical institutions (where applicable) and/or institution(s) conducting the study. GSK will also promptly inform the relevant regulatory authorities of the suspension or premature discontinuation of the study and the reason(s) for the action.
- If required by applicable regulations, the investigator or the head of the medical institution (where applicable) must inform the IRB/IEC promptly and provide the reason for the suspension or premature discontinuation.

10.6. Records Retention

- Following closure of the study, the investigator or the 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 maintained to allow easy and timely retrieval, 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 these records can be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution needs to 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 and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the investigator must ensure there is an acceptable back-up of these reproductions and that an acceptable quality control process exists for making these reproductions.
- GSK will inform the investigator of the time period for retaining these records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to that site for the study, as dictated by any institutional requirements or local laws or regulations, GSK standards/procedures, and/or institutional requirements.
- The investigator must notify GSK of any changes in the archival arrangements, including, but not limited to, archival at an off-site facility or transfer of

ownership of the records in the event the investigator is no longer associated with the site.

10.7. Provision of Study Results to Investigators, Posting of Information on Publically 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 procedures and timing for public disclosure of the results summary and for development of a manuscript for publication will be in accordance with GSK Policy.

11. REFERENCES

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12. APPENDICES

12.1. Appendix 1: Abbreviations and Trademarks

Abbreviations

AE(s)	Adverse Event(s)
AML	Acute Myeloid Leukemia
ALP	Alkaline Phosphatase
ALT	Alanine aminotransferase
ANC	Absolute Neutrophil Count
aPTT	Activated Partial Thromboplastin Time
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
DAC	5-Aza-2'-deoxycytidine
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
GVHD	Graft-versus-Host-Disease
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
HMA	Hypomethlating Agent
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
IPSS-R	The Revised International Prognostic Scoring System
IRB	Institutional Review Board
IU	International Unit
IV	Intravenous
IWG	International Working Group
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

MATE-1	Multidrug And Toxin Extrusion Transporter 1
uM	Micromole
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MDS	Myelodysplastic syndromes
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
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)
sc	subcutaneous
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

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
NONE

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None

12.2. Appendix 2: Liver Safety Required Actions and Follow up Assessments

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

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

Liver Chemistry Stopping Criteria – Liver Stopping Event	
ALT-absolute	ALT ≥ 5xULN
ALT Increase	ALT ≥ 3xULN persists for ≥4 weeks
Bilirubin[1, 2]	ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin)
INR[2]	ALT ≥ 3xULN **and** INR>1.5, if INR measured
Cannot Monitor	ALT ≥ 3xULN **and** cannot be monitored weekly for 4 weeks
Symptomatic[3]	ALT ≥ 3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity

Required Actions and Follow up Assessments following Liver Stopping Event	
Actions	**Follow Up Assessments**
• **Immediately** discontinue study treatment • Report the event to GSK **within 24 hours** • Complete the liver event CRF and complete an SAE data collection tool if the event also meets the criteria for an SAE[2] • Perform liver event follow up assessments • Monitor the subject until liver chemistries resolve, stabilize, or return to within baseline (see **MONITORING** below) • **Do not restart/rechallenge** subject with study treatment unless allowed per protocol and GSK Medical Governance approval **is granted** (refer to Appendix	• Viral hepatitis serology[4] • Blood sample for pharmacokinetic (PK) analysis, obtained approximately 48h after last dose[5] • Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH). • Fractionate bilirubin, if total bilirubin≥2xULN • Obtain complete blood count with differential to assess eosinophilia • Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form • Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications

3 for more details) • If restart/rechallenge is **not granted**, permanently discontinue study treatment and may continue subject in the study for any protocol specified follow up assessments **MONITORING:** **For bilirubin or INR criteria:** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24 hrs** • Monitor subjects twice weekly until liver chemistries resolve, stabilize or return to within baseline • A specialist or hepatology consultation is recommended **For All other criteria:** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24-72 hrs** • Monitor subjects weekly until liver chemistries resolve, stabilize or return to within baseline	• Record alcohol use on the liver event alcohol intake case report form **For bilirubin or INR criteria:** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG or gamma globulins). • Serum acetaminophen adduct high pressure liquid chromatography (HPLC) assay (quantifies potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week [James, 2009]). • Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy CRF forms.

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that subject if ALT ≥ 3xULN **and** bilirubin ≥ 2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin) or ALT ≥ 3xULN **and** INR>1.5, if INR measured which may indicate severe liver injury (possible 'Hy's Law'), **must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis)**; INR measurement is not required and the threshold value stated will not apply to subjects receiving anticoagulants
3. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia)
4. Includes: Hepatitis A IgM antibody; Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM); Hepatitis C RNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody
5. Record the date/time of the PK blood sample draw and the date/time of the last dose of study treatment prior to blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the subject's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SRM.

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

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

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

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12.3. Appendix 3: Liver Safety – Study Treatment Restart or Rechallenge Guidelines

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

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

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

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

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

Risk factors for a fatal drug rechallenge outcome include:

- hypersensitivity[1] with initial liver injury (e.g. fever, rash, eosinophilia)
- 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 rechallenge with study treatment can be considered where:

- Investigator requests consideration of rechallenge with study treatment for a subject who is receiving compelling benefit with study treatment that exceeds risk, and no effective alternative therapy is available.
- Ethics Committee or Institutional Review Board approval for rechallenge with study treatment must be obtained, as required.

- If the rechallenge is approved by GSK Medical Governance in writing, the subject must be provided with a clear description of the possible benefits and risks of study treatment administration, including the possibility of recurrent, more severe liver injury or death.
- The subject must also provide signed informed consent specifically for the rechallenge with study treatment. Documentation of informed consent must be recorded in the study chart.
- Study treatment must be administered at the dose specified by GSK.
- Subjects approved by GSK Medical Governance for rechallenge with study treatment must return to the clinic twice a week for liver chemistry tests until stable liver chemistries have been demonstrated and then standard laboratory monitoring may resume as per protocol.
- If after study treatment rechallenge, subject meets protocol-defined liver chemistry stopping criteria, study treatment should be permanently discontinued.
- 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 Appendix 5.

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

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

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

- Investigator requests consideration for study treatment restart if liver chemistries have a clear underlying cause (e.g., biliary obstruction, hypotension and liver chemistries have improved to normal or are within 1.5 x baseline and ALT <3xULN).
- Restart risk factors (e.g. fever, rash, eosinophilia, or hypersensitivity, alcoholic hepatitis, possible study treatment-induced liver injury or study treatment has an HLA genetic marker associated with liver injury (e.g. lapatinib, abacavir, amoxicillin/clavulanate) are reviewed and excluded
- Ethics Committee or Institutional Review Board approval of study treatment restart must be obtained, as required.
- If restart of study treatment is approved by GSK Medical Governance in writing, the subject must be provided with a clear description of the possible benefits and risks of study treatment administration, including the possibility of recurrent, more severe liver injury or death.

- The subject must also provide signed informed consent specifically for the study treatment restart. Documentation of informed consent must be recorded in the study chart.
- Study treatment must be administered at the dose specified by GSK.
- Subjects approved by GSK Medical Governance for restarting study treatment must return to the clinic once a week for liver chemistry tests until stable liver chemistries have been demonstrated and then laboratory monitoring may resume as per protocol.
- If after study treatment re-start, subject meets protocol-defined liver chemistry stopping criteria, follow usual stopping criteria instructions.
- 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 Appendix 5.

References:

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

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

12.4. Appendix 4: Genetic Research

USE/ANALYSIS OF DNA

- Genetic variation may impact a participant's response to therapy, susceptibility, severity and progression of disease. Variable response to therapy may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a saliva sample will be collected for DNA analysis
- DNA samples will be used for research related to GSK2879552 or GSK2879552 in combination with azacitidine or any concomitant medicines, or MDS and related diseases. They may also be used to develop tests/assays including diagnostic tests) related to GSK2879552 or GSK2879552 in combination with azacitidine or study treatments of this drug class, and MDS. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome or analysis of the entire genome (as appropriate)
- DNA samples will be analyzed if it is hypothesized that this may help further understand the clinical data.
- DNA samples will be analyzed for describe planned analyses. Additional analyses may be conducted if it is hypothesized that this may help further understand the clinical data.
- The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to GSK2879552 or GSK2879552 in combination with azacitidine or study treatments of this class. The results of genetic analyses may be reported in the clinical study report or in a separate study summary.
- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on GSK2879552 or GSK2879552 in combination with azacitidine or study treatments of this class or MDS continues but no longer than 15 years or other period as per local requirements.

12.5. Appendix 5: Definition of and Procedures for Recording, Evaluating, Follow-Up and Reporting of Adverse Events

12.5.1. Definition of Adverse Events

Adverse Event Definition:
• An AE is any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product.

Events <u>meeting</u> AE definition include:
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECGs, radiological scans, vital signs measurements), including those that worsen from baseline, and felt to be clinically significant in the medical and scientific judgement of the investigator. • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present prior to the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication (overdose per se will not be reported as an AE/SAE unless this is an intentional overdose taken with possible suicidal/self-harming intent. This should be reported regardless of sequelae). • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. However, the signs and symptoms and/or clinical sequelae resulting from lack of efficacy will be reported if they fulfil the definition of an AE or SAE. •

Events <u>NOT</u> meeting definition of an AE include:
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition. • 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.

- 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.

12.5.2. Definition of Serious Adverse Events

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease, etc).

Serious Adverse Event (SAE) is defined as 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-patient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in disability/incapacity

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. Other situations: • 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. Is associated with liver injury <u>and</u> impaired liver function defined as: • ALT ≥ 3xULN and total bilirubin* ≥ 2xULN (>35% direct), **or** • ALT ≥ 3xULN and INR** > 1.5. * Serum bilirubin fractionation should be performed if testing is available; if unavailable, measure urinary bilirubin via dipstick. If fractionation is unavailable and ALT ≥ 3xULN and total bilirubin ≥ 2xULN, then the event is still to be reported as an SAE. ** INR testing not required per protocol and the threshold value does not apply to subjects receiving anticoagulants. If INR measurement is obtained, the value is to be recorded on the SAE form.

12.5.3. Definition of Cardiovascular Events

Cardiovascular Events (CV) Definition:
Investigators will be required to fill out the specific CV event page of the CRF 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
- Revascularization

12.5.4. Recording of AEs and SAEs

AEs and SAE Recording:

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) relative to the event.
- The investigator will then record all relevant information regarding an AE/SAE in the CRF
- It is **not** acceptable for the investigator to send photocopies of the subject's medical records to GSK in lieu of completion of the GSK, AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by GSK. In this instance, all subject identifiers, with the exception of the subject number, will be blinded on the copies of the medical records prior to submission of to GSK.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis will be documented as the AE/SAE and not the individual signs/symptoms.

12.5.5. Evaluating AEs and SAEs

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and will assign it to one of the following categories:

- Mild: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that is sufficiently discomforting to interfere with normal everyday activities
- Severe: An event that prevents normal everyday activities. - an AE that is assessed as severe will not be confused with an SAE. Severity is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.
- An event is defined as 'serious' when it meets at least one of the pre-defined outcomes as described in the definition of an SAE.

Assessment of Causality

- The investigator is obligated to assess the relationship between study treatment and the occurrence of each AE/SAE.
- A "reasonable possibility" is meant to convey that there are facts/evidence or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the study treatment will be considered and investigated.
- The investigator will also consult the Investigator Brochure (IB) and/or Product Information, for marketed products, in the determination of his/her assessment.
- For each AE/SAE the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations when an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. However, **it is very important that the investigator always make an assessment of causality for every event prior to the initial transmission of the SAE data to GSK.**
- The investigator may change his/her opinion of causality in light of follow-up information, amending the SAE data collection tool accordingly.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as may be indicated or as requested by GSK to elucidate as fully as possible the nature and/or causality of the AE or SAE.
- The investigator is obligated to assist. This may include additional laboratory tests or investigations, histopathological examinations or consultation with other health care professionals.
- If a subject dies during participation in the study or during a recognized follow-up period, the investigator will provide GSK with a copy of any post-mortem findings, including histopathology, if available.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to GSK within the designated reporting time frames.

12.5.6. Reporting of SAEs to GSK

SAE reporting to GSK via electronic data collection tool
• Primary mechanism for reporting SAEs to GSK will be the electronic data collection tool • If the electronic system is unavailable for greater than 24 hours, the site will use the paper SAE data collection tool and fax it to the Medical Monitor • Site will enter the serious adverse event data into the electronic system as soon as it becomes available. • The investigator will be required to confirm review of the SAE causality by ticking the 'reviewed' box at the bottom of the eCRF page within 72 hours of submission of the SAE. • After the study is completed at a given site, the electronic data collection tool (e.g., InForm system) will be taken off-line to prevent the entry of new data or changes to existing data • If a site receives a report of a new SAE from a study subject or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, the site can report this information on a paper SAE form or to the Medical Monitor by telephone. • Contacts for SAE receipt can be found at the beginning of this protocol on the Sponsor/Medical Monitor Contact Information page.

12.6. Appendix 6: ECOG Performance Status[1]

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

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.

12.7. Appendix 7: Modified List of Highly Effective Methods for Avoiding Pregnancy in FRP and Collection of Pregnancy Information

This appendix is **optional** and should **ONLY** be included if study treatment is supplied and information on pregnancies is to be collected for female subjects or for female partners of male study subjects. Female subjects with non-reproductive potential are defined as below:

Pre-menopausal females with one of the following:

- Documented tubal ligation
- Documented hysteroscopic tubal occlusion procedure with follow-up confirmation of bilateral tubal occlusion
- Hysterectomy
- Documented Bilateral Oophorectomy

Postmenopausal defined as 12 months of spontaneous amenorrhea [in questionable cases a blood sample with simultaneous follicle stimulating hormone (FSH) and estradiol levels consistent with menopause (refer to laboratory reference ranges for confirmatory levels)]. Females on hormone replacement therapy (HRT) and whose menopausal status is in doubt will be required to use one of the highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of post-menopausal status prior to study enrolment.

12.7.1. Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP)

The list does not apply to FRP with same sex partners or for subjects who are and will continue to be abstinent from penile-vaginal intercourse on a long term and persistent basis, when this is their preferred and usual lifestyle. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

1. Contraceptive subdermal implant
2. Intrauterine device or intrauterine system
3. Combined estrogen and progestogen oral contraceptive [Hatcher, 2011])
4. Injectable progestogen [Hatcher, 2011]
5. Contraceptive vaginal ring [Hatcher, 2011]
6. Percutaneous contraceptive patches [Hatcher, 2011]
7. Male partner sterilization with documentation of azoospermia prior to the female subject's entry into the study, and this male is the sole partner for that subject [Hatcher, 2011]. The documentation on male sterility can come from the site

personnel's: review of subject's medical records, medical examination and/or semen analysis, or medical history interview provided by her or her partner.

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

Contraceptive requirements for male subjects with female partners of reproductive potential.

Male subjects with female partners of child bearing potential must comply with the following contraception requirements from the time of first dose of study medication until [at least five half-lives of study medication OR for a cycle of spermatogenesis following five terminal half-lives] after the last dose of study medication.

1. Vasectomy with documentation of azoospermia. The documentation on male sterility can come from the site personnel's: review of subject's medical records, medical examination and/or semen analysis, or medical history interview.
2. Male condom plus partner use of one of the contraceptive options below that meets the SOP effectiveness criteria including a <1% rate of failure per year, as stated in the product label:
   - Contraceptive subdermal implant
   - Intrauterine device or intrauterine system
   - Combined estrogen and progestogen oral contraceptive [Hatcher, 2011]
   - Injectable progestogen [Hatcher, 2011]
   - Contraceptive vaginal ring [Hatcher, 2011]
   - Percutaneous contraceptive patches [Hatcher, 2011]

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 that subjects understand how to properly use these methods of contraception.

12.7.2. Collection of Pregnancy Information

- Investigator will collect pregnancy information on any female subject, who becomes pregnant while participating in this study
- Information will be recorded on the appropriate form and submitted to GSK within 2 weeks of learning of a subject's pregnancy.
- Subject will be followed to determine the outcome of the pregnancy. The investigator will collect follow up information on mother and infant, which will be forwarded to GSK. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.
- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.

- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the investigator will be reported to GSK as described in Appendix 5. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Any female subject who becomes pregnant while participating

- will be withdrawn from the study
- Investigator will attempt to collect pregnancy information on any female partner of a male study subject who becomes pregnant while participating in this study.
- After obtaining the necessary signed informed consent from the female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to GSK within 2 weeks of learning of the partner's pregnancy
- Partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to GSK.
- Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for procedure.

12.7.3. References

CHMP, 2005 - EMA - Guideline on Adjuvants in Vaccines for Human Use, (CHMP/VEG/134716/2004), January 2005.

Cole LA, Khanlian SA, Sutton JM, Davies S, Rayburn WF. Accuracy of home pregnancy tests at the time of missed menses. Am J Ob Gyn 2004(190):100-5.

EMA/CHMP/ICH/449035/2009: General principles to address virus and vector shedding. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002680.pdf Accessed 28 Nov 2014.

EMEA/CHMP/GTWP/125459/2006: Guideline on the Nonclinical Studies Required Before First Clinical Use of Gene Therapy Medicinal Products [2008]

FDA CBER Guidance for industry, "Considerations for Developmental Toxicity Studies for Preventive and Therapeutic Vaccines for Infectious Disease Indications. U.S. FDA; Feb. 2006.

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Hatcher RA, Trussell J, Nelson AL, Cates W Jr, Stewart F, Kowal D, Policar MS, editors. Contraceptive Technology. 20th edition. Atlanta, Georgia: Ardent Media, Inc., 2011: 50. Table 3-2.

International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals For Human Use. ICH Harmonized Tripartite Guideline. Detection of Toxicity to Reproduction for Medicinal Products & Toxicity to Male Fertility. Parent Guideline dated 24 June 1993 (Addendum dated 9 November 2000 incorporated in November 2005. ICH S5 (R2)

International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals For Human Use. ICH Harmonized Tripartite Guideline. Nonclinical Evaluation for Anticancer Pharmaceuticals. ICH S9. 2009.

International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals For Human Use. ICH Harmonized Tripartite Guideline. Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals. ICH M3 (R2). 2009.

International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals For Human Use. ICH Harmonized Tripartite Guideline. Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals. ICH S6 and Addendum ICH S6 (R1). 2011.

Investigator Brochure for GSK2879552 [GlaxoSmithKline Document Number 2013N168888_02]. Report Date: 29-FEB-2016.

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Strauss JF, Barbieri RL, editors. Yen and Jaffe's Reproductive Endocrinology. 5th edition, Philadelphia, Elsevier/Saunders, 2004.

U.S. Dept of Health and Human Services, FDA, Center For Biologics Evaluation and Research: Guidance for Human Somatic Cell Therapy and Gene Therapy [1998]

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World Health Organization. WHO/CONRAD Technical Consultation on Nonoxynol-9. World Health Organization; Department of Reproductive Health and Research; Geneva; 9-10 October 2001. Summary Report. 2001. WHO/RHR/03.8.

12.8. 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.

12.9. Appendix 9: Country Specific Requirements

No country-specific requirements exist.

12.10. Appendix 10: IWG CRITERIA FOR RESPONSE

Category	Response Criteria
Complete Remission	Bone marrow: ≤ 5% myeloblasts with normal maturation of all cell linesa Persistent dysplasia will be noteda,b Peripheral blood (Response must be maintained for at least 4 weeks) Hgb ≥ 11 g/dL Platelets ≥ 100 Gi/L Neutrophils ≥ 1.0 Gi/Lb Blasts 0%
Partial Remission	All CR criteria if abnormal before treatment except: Bone marrow blasts decreased by ≥ 50% over pre-treatment but still > 5% Cellularity and morphology not relevant
Marrow CR[b]	Bone marrow: ≤ 5% myeloblasts and decrease by ≥ 50% over pre-treatment[b] Peripheral blood: if HI responses, they will be noted in addition to marrow CR[b]
HI	Erythroid (HI-E): hgb increase of > 1.5 g/dL decrease of > RBC transfusions/8weeks versus pretreatment requirement in previous 8 weeks; only RBC transfusions given for a pretreatment Hgb of < 9.0 g/dL count Platelet (HI-P): increase of > 30,000/mL (starting with > 20,000/mL) increase from < 20,000/mL to >20,000/mL by > 100% Neutrophil (HI-N): increase of > 100% and > 500/uL
Stable Disease	Failure to achieve at least PR, but no evidence of progression > 8 wks
Disease Progression	For subjects with: • Less than 5% BM blasts: ≥ 50% increase in blasts to > 5% blasts • 5%-<10% BM blasts: ≥ 50% increase to > 10% blasts • 10%-<20% BM blasts: ≥ 50% increase to > 20% blasts • 20%-30% BM blasts: ≥ 50% increase to > 30% blasts Any of the following: • At least 50% decrement from maximum remission/response in granulocytes or platelets • Reduction in Hgb by ≥ 2 g/dL • Transfusion dependence
Non-evaluable	Subject does not meet any of the above criteria

BM = bone marrow ; CR = complete remission; Hgb = hemoglobin;; PR = partial remission

a. Dysplastic changes should consider the normal range of dysplastic changes (modification).

b. Modification to IWG response criteria [Cheson, 2006].

12.11. Appendix 11: Protocol Changes

12.11.1. Protocol Changes for Amendment 1 (08-MAY-2017) from the original Protocol (15-Jul-2016)

Where the Amendment applies

Amendment 1 applies to all sites.

Summary of Amendment Changes with Rationale

Addition of 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. Minor clarifications, correction of typographical errors, reformatting of tables, administrative and grammatical changes to text and Time and Events tables/footnotes.

List of Specific Changes: (**bold** indicates text added and ~~strikethrough~~ indicates text removed)

General change: Abbreviations were defined at first instance throughout the document.

List of Authors

Rationale for Change

The list of authors was updated based on internal GSK team personnel changes.

Revised Text

PPD

Oncology, Clinical, PA, USA

~~Biomarker discovery, Epigenetics DPU, PA, USA~~

Oncology Epigenetics Clinical, PA, USA

Clinical Pharmacology Modeling & Simulation, PA, USA

Clinical Biomarkers and Translational Research, PA, USA

Biology, Epigenetics DPU, PA, USA

Discovery Biometrics, PA, USA

Biology, Epigenetics DPU, PA, USA

~~Oncology Epigenetics Clinical, PA, USA~~

Global Clinical Safety & Pharmacovigilance, PA, USA

In Vivo In Vitro Translation, PA, USA

Oncology Epigenetics Clinical, PA, USA

~~Discovery Biometrics, PA, USA~~

Sponsor Signatory

Rationale for Change

Designation of the sponsor was updated.

Revised Text

PPD MD, Ph.D.
Senior Vice President, Epigenetics DPU Head ~~SVP, TA I lead, Oncology R&D~~

MEDICAL MONITOR/SPONSOR INFORMATION PAGE

Medical Monitor/SAE Contact Information:

Rationale for Change

The medical monitoring information was updated to reflect the current contact information for medical monitoring.

Revised Text

Role	Name	Day Time Phone Number and email address	After-hours Phone/Cell/ Pager Number	Site Address
Primary Medical Monitor	PPD **MD, MPH** PPD ~~MD, PhD~~	PPD		GlaxoSmithKline 1250 South Collegeville **Road**~~Rd~~ Mailstop UP 4~~4~~310 Collegeville, PA 19426, USA PPD
Secondary Medical Monitor	PPD **MD, PhD** PPD ~~MD, MPH~~			GlaxoSmithKline 1250 South Collegeville **Road** ~~Rd~~ Mailstop UP 4~~4~~310 Collegeville, PA 19426, USA PPD

Investigator Protocol Agreement Page

Rationale for Change

Investigator address and Phone number details were added.

Revised Text

Investigator Name: _____		
Investigator Address:		
Investigator Phone Number:		
Investigator Signature		Date

Synopsis

Rationale for Change: References were removed from the synopsis section as synopsis need to be a stand alone document. Also, study stopping criteria was modified for clarification.

Revised Text

Overall Design

2nd and 3rd paragraph

Bayesian Logistic Regression Model (BLRM) prediction on **Dose-Limiting Toxicity** (DLT) rate may also be provided at dose escalation meetings as the supplementary analysis to 3+3 design ~~(See Section 4.3.2. for more details)~~. Once the RP2D of GSK2879552 for MDS is confirmed in both Arms, Part 2 enrolment will open. Each treatment cycle is 28 days and subjects experiencing disease progression on monotherapy (Arm A) will be allowed to cross over (to Arm B) to be treated with the combination at the RP2D.

The statistical design and number of subjects to be enrolled in Part 2 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. The study will stop ~~only~~ for futility, **while also taking into account subject and study termination criteria as defined in the protocol.** Final decisions on stopping enrolment will depend on the totality of the data collected.

Type and Number of Subjects

Point 9, 10, 11 and Diagnostic assessment

LABORATORY	
9. 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

GENDER and REPRODUCTIVE POTENTIAL
10. Women of childbearing potential must have a negative serum pregnancy test within 7 days of first dose of study treatment and agree to use effective contraception, ~~as defined in Appendix 7 of this protocol,~~ during the study and for 7 days following the last dose of study treatment. 11. Men with a female partner of childbearing potential must have either had a prior vasectomy or agree to use effective contraception, ~~as defined in Appendix 7 of this protocol,~~ 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.

DIAGNOSTIC ASSESSMENTS AND OTHER CRITERIA
1. AML according to WHO criteria (i.e. bone marrow blasts >20%) ~~[Vardiman, 2009].~~ 2. Active hepatitis B or hepatitis C treatment 3. Baseline **(pre-dose Day 1)** Montreal Cognitive Assessment (MOCA) score of 22 or lower

4.11.1 Risk Assessment

Rationale for change

Text was added to clarify the term Baseline to mean pre-dose Day 1

Revised Text

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
GSK2879552		
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 - Montreal Cognitive Assessment (MOCA) at baseline **(pre-dose Day 1)** and weekly for the first 4 weeks and monthly thereafter. - Subjects with baseline **(pre-dose Day 1)** 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 **(pre-dose Day 1)** 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

5. SELECTION OF STUDY POPULATION AND WITHDRAWAL CRITERIA

5.2 Exclusion Criteria

Rationale for Change

Text was added to clarify the term Baseline to mean pre-dose Day 1

Revised Text

DIAGNOSTIC ASSESSMENTS AND OTHER CRITERIA
1. AML according to WHO criteria (i.e. bone marrow blasts >20%)
2. Active hepatitis B or hepatitis C treatment
3. Baseline **(pre-dose Day 1)** Montreal Cognitive Assessment (MOCA) score of 22 or lower

5.4.3 Mental Status Stopping Criteria

Rationale for Change

Stopping criteria were updated based on the FDA mandated language resulting from a recent Dear Investigator Letter (DIL) of encephalopathy dated 24 Apr 17 reported in LSD1 study 200858

Revised Text

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)** Montreal Cognitive Assessment (MOCA) score (Section 7.3.7)
- 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 **(pre-dose Day 1).**
- 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 **(pre-dose Day 1).**

6. STUDY TREATMENT

6.2.1 GSK2879552

Rationale for Change

Only two doses were to be used in the study – 0.5 mg and 2 mg. Table was updated to remove 5 mg dose.

Revised Text

Product name:	**GSK2879552 Capsule**
Formulation description:	GSK2879552 capsules contain 0.5 mg or 2 mg~~, 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 (i.e. no food intake from 2 hours before dosing until 1 hour after dosing) 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.

7.1 Time and Events Table for Arm A – Part 1

Rationale for Change

Table was updated for correction of superscripts in tables, simplification/clarification of wording in footnotes and correction of numbering in footnotes to match tables.

Revised Text

	SCR	Cycle 1 (28 days)						C2 and beyond	Crossover Visit	End of Treatment Visit	Post Treatment Bi-Monthly Follow-Up[16]
		D 1	D2	D4	D7	D 15	D22				
Office Visit for Arm A (mono)	X	X	X[1]	X	X	X	X	C2: D1, 7, 15 and 22 C3 and after: D1	X	X	
Informed consent	X										
Demography	X										
Medical history	X										
Disease characteristics	X										
GSK2879552 Dosing[9]		< ---------- Daily or per dosing schedule ----------→									
Azacitidine dosing									X[14]		
Review subject dosing diary					X	X		Day 1	X	X	
GSK2879552 Drug Dispensing		X						Day 1			
Complete physical exam	X								X	X	
Brief physical exam		X[7]			X			Day 1			
Montreal Cognitive Assessment	X	X			X	X	X	Day 1			
ECOG PS	X	X[7]			X			Day 1	X	X	
Vital Signs	X	X[7]			X	X		Day 1	X	X	
Height and weight[6]	X	X[7]			X			Day 1	X	X	
ECHO/MUGA	X										
12-lead ECGs	X	X[7]			X			Day 1	X	X	
HIV, HBV and HCV Ab testing	X										
CBC	X	X[7]			X[12]	X	X	C2: D1, 7[12], 15 and 22 C3 and after: D1	X	X	

	SCR	Cycle 1 (28 days)						C2 and beyond	Crossover Visit	End of Treatment Visit	Post Treatment Bi-Monthly Follow-Up[16]
		D 1	D2	D4	D7	D 15	D22				
Chemistry Panel including LFT	X	X[7]			X[12]	X	X	Day 1	X	X	
Coagulation Panel including a PTT and INR	X				X[12]	x	X	Day 1	X	X	
PK Blood samples		X[1]	X[1]	X[8]	X[2]	X[5]	X[8]	C2: D1, 7, 15 and 22 D1 of C3-C12[8]			
Pregnancy test[4]	X							Day 1	X	X	
Blood samples for exploratory studies (peripheral blood)[3, 11]	X			X	X	X		Day 1	X	X	
Bone marrow aspirate for exploratory studies [11]	X							At time of disease assessment[17]	X[17]	X[15]	
Disease assessment	X							Day 1	X		
Bone marrow for disease assessment	X[17]							as clinically indicated	X[18]	X[15]	
PGX samples (saliva sample)	X										
PK blood sample (corresponding with exploratory BMA)[13]								X[17]	X[17]	X[17]	
Transfusion Need Assessment[10]	X				X	X	X	D1			
Adverse Events		Continuous									
Con Meds		Continuous									
OS/PFS Assessment											X

1. A blood sample will be collected for GSK2879552 PK analysis on D1 at pre-dose, 0.5, 1 hr, and 3 hrs post dose. ~~In the combination cohort, a blood sample for azacitidine PK analysis will be collected at the same time points.~~ An additional **optional** PK sample will be collected at 24 hours post Day 1 dose for GSK2879552 measurement ~~in the combination arm, but it is optional in mono therapy arm~~.

2. A blood sample will be collected for GSK2879552 PK analysis on D7 at pre-dose, 0.5, 1 hr, and 3 hrs post dose~~. In the combination cohort, a blood sample for azacitidine PK analysis will be collected at the same time points.~~
3. Samples should be collected at pre-dose.
4. For women of child bearing potential only. Serum pregnancy test is required for screening, crossover and EOT visits. Urine pregnancy test is adequate during study visits.
5. A blood sample will be collected for GSK2879552 PK analysis on D15 at pre-dose and 0.5-1 hr post dose.
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 for GSK2879552 should be taken pre-dose. PK sample will not be collected beyond 48 weeks.
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. Collection of exploratory sample (peripheral blood and/or BMA) time points may be terminated at the sponsor's discretion
12. Safety laboratory blood samples (CBC, chemistry and coagulation panel) should be collected post dose on Day 7.
13. PK blood sample should be collected prior to dosing on biopsy days.
14. Azacitidine dosing can start on Day 1 of the next cycle after the cross over visit is completed.
15~~2~~. Optional for all subjects
16~~3~~. Subjects are followed every 2 months to collect the survival, PFS data and the start of new treatment via chart review, or phone call contact. The follow-up will continue until death, lost to follow-up, withdrawal of consent or up to 12 months from end of treatment visit, whichever occurs first.
17~~4~~. The exploratory BM sample is collected whenever the bone marrow is done for disease assessment and/or at the time of crossover, unless the sample collection is stopped per sponsor discretion; the PK blood sample will be collected pre-dose at the crossover visit if the exploratory BM sample is collected. The PK corresponding blood sample will not be collected if a regularly scheduled PK sample is already being collected during the visit.
18~~5~~. A mandatory BM sample will be collected at the time of the crossover visit to establish the new baseline. A window of 14 days is allowed for this BM assessment.

Time & Events Table for Arm A - Part 2

	SCR	Cycle 1 (28 days)					Cycle 2 and beyond	Crossover Visit	End of Treatment Visit	Post Treatment Bi-monthly Follow-Up16
		D 1	D4	D 7	D 15	D22				
Office Visit for Arm A (mono)	X	X	X	X	X	X	C2: D1, 7, 15 and 22 C3 and after: D1	X	X	
Informed consent	X									
Demography	X									
Medical history	X									
Disease characteristics	X									
GSK2879552 Dosing[9]		< ---------- Daily or per dosing schedule ----------→								
Azacitidine dosing[14]								X[14]		
Review subject dosing diary				X	X		Day 1	X	X	
GSK2879552 Drug Dispensing		X					Day 1			
Complete physical exam	X							X	X	
Brief physical exam		X[7]		X			Day 1			
Montreal Cognitive Assessment	X	X		X	X	X	Day 1			
ECOG PS	X	X[7]		X			Day 1	X	X	
Vital Signs	X	X[7]		X	X		Day 1	X	X	
Height and weight[6]	X	X[7]		X			Day 1	X	X	
ECHO/MUGA	X									
12-lead ECGs	X	X[7]		X			Day 1	X	X	
HIV, HBV and HCV Ab testing	X									
CBC	X	X[7]		X[12]	X	X	C2: D1, 7[12], 15 and 22	X	X	

	SCR	Cycle 1 (28 days)					Cycle 2 and beyond	Crossover Visit	End of Treatment Visit	Post Treatment Bi-monthly Follow-Up16
		D 1	D4	D 7	D 15	D22				
							C3 and after: D1			
Chemistry Panel including LFT	X	X[7]		X[12]	X	X	Day 1	X	X	
Coagulation Panel including a PTT and INR	X			X[12]	x	X	Day 1	X	X	
PK Blood samples		X[1]	X[8]	X[5]	X[2]	X[8]	C2: D1, 7, 15 and 22 D1 of C3-C12[8]			
Pregnancy test[4]	X						Day 1	X	X	
Blood samples for exploratory studies (peripheral blood)[3, 11]	X		X	X	X		Day 1	X	X	
Bone marrow aspirate for exploratory studies [11]	X						At time of disease assessment[17]	X[17]	X[15]	
Disease assessment	X						Day 1	X		
Bone marrow for disease assessment	X[17]						as clinically indicated	X[18]	X[15]	
PGX samples (saliva sample)	X									
PK blood sample (corresponding with exploratory BMA)[13]							X[17]	X[17]	X[17]	
Transfusion Need Assessment[10]	X			X	X	X	D1			
Adverse Events		Continuous								
Con Meds		Continuous								
OS/PFS Assessment										X

1. A blood sample will be collected for PK analysis on D1 at pre-dose, 0.5hr, 1 hr and 3 hrs post dose. ~~In the combination cohort, a blood sample for azacitidine 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 and between 0.5 to 1 hour.
3. Samples should be collected at pre-dose.
4. For women of child bearing potential only. Serum pregnancy test is required for screening, crossover and EOT visits. Urine pregnancy test is adequate during study visits.
5. A blood sample will be collected for PK analysis on D7 at pre-dose, 0.5, 1 hr, and 3 hrs post dose. ~~In the combination cohort, a blood sample for azacitidine PK analysis will be collected at the same time points.~~
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 for GSK2879552 should be taken pre-dose around the same time as CBC. **PK sample will not be collected beyond 48 weeks**
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. Collection of exploratory sample (peripheral blood and/or BMA) time points may be terminated at the sponsor's discretion
12. Safety laboratory blood samples (CBC, chemistry and coagulation panel) should be collected post dose on Day 7.
13. PK corresponding blood sample should be collected prior to dosing
14. Azacitidine dosing can start on Day 1 of the next cycle after the cross over visit is completed.
15. Optional for all subjects
16. Subjects are followed every 2 months to collect the survival, PFS data and the start of new treatment via chart review, or phone call contact. The follow-up will continue until death, lost to follow-up, withdrawal of consent or up to 12 months from end of treatment visit, whichever occurs first.
17. The exploratory BM sample is collected whenever the bone marrow is done for disease assessment and/or at time of crossover, unless the sample collection is stopped per sponsor discretion; the PK corresponding blood sample will be collected pre-dose at the crossover visit if the exploratory BM sample is collected. The PK corresponding blood sample will not be collected if a regularly scheduled PK sample is already being collected during the visit.
18. A mandatory BM sample will be collected at the time of the crossover visit to establish the new baseline. A window of 14 days is allowed for this BM assessment.

Time and Events Table – Arm B (Combination with Azacitidine), Part 1

	SCR	Cycle 1 (28 days)						Subsequent Cycles	End of Treatment Visit	Post Treatment Bi-Monthly Follow-Up[16]
		D 1	D2	D4	D7[19]	D 15	D22			
Office Visit for Arm B (combo)	X	X	X	X	X	X	X	C2: D1- 7[19], 15 and 22 C3 and after: D1-7[19]	X	
Informed consent	X									
Demography	X									
Medical history	X									
Disease characteristics	X									
GSK2879552 Dosing[9]		< ---------- Daily or per dosing schedule ----------→								
Azacitidine dosing[14]		<--Days 1-7--->						Days 1-7		
Review subject dosing diary					X	X		Day 1	X	
GSK2879552 Drug Dispensing		X						Day 1		
Complete physical exam	X								X	
Brief physical exam		X[7]			X			Day 1		
Montreal Cognitive Assessment	X	X			X	X	X	Day 1		
ECOG PS	X	X[7]			X			Day 1	X	
Vital Signs	X	X[7]			X	X		Day 1	X	
Height and weight[6]	X	X[7]			X			Day 1	X	
ECHO/MUGA	X									
12-lead ECGs	X	X[7]			X			Day 1	X	
HIV, HBsAg and HCV Ab testing	X									
CBC	X	X[7]			X[12]	X	X	C2: D1, 7[12, 19], 15 and 22 C3 and after: D1	X	

	SCR	Cycle 1 (28 days)						Subsequent Cycles	End of Treatment Visit	Post Treatment Bi-Monthly Follow-Up[16]
		D 1	D2	D4	D7[19]	D 15	D22			
Chemistry Panel including LFT	X	X[7]			X[12]	X	X	Day 1	X	
Coagulation Panel including a PTT and INR	X				X[12]	x	X	Day 1	X	
PK Blood samples		X[1]	X[1]	X[8]	X[2]	X[5]	X[8]	C2: D1, 7[19], 15 and 22 D1 of C3-C12[8]		
Pregnancy test[4]	X							Day 1	X	
Blood samples for exploratory studies (peripheral blood)[3, 11]	X			X	X	X		Day 1	X	
Bone marrow aspirate for exploratory studies [11]	X							At time of disease assessment[17]	X[15]	
Disease assessment	X							Day 1	X	
Bone marrow for disease assessment	X[18]							as clinically indicated	X[15]	
PGX samples (saliva sample)	X									
PK blood sample (corresponding with exploratory BMA)[13]								X[17]	X[17]	
Transfusion Need Assessment[10]	X				X	X	X	D1		
Adverse Events		Continuous								
Con Meds		Continuous								
OS/PFS Assessment										X

1. A blood sample will be collected for GSK2879552 **and azacitidine**. PK analysis on D1 at pre-dose, 0.5, 1 hr, and 3 hrs post dose~~. In the combination cohort, a blood sample for azacitidine PK analysis will be collected at the same time points~~. An additional PK sample will be collected at 24 hours post Day 1 dose for GSK2879552 measurement in the combination arm~~, but it is optional in mono therapy arm~~.
2. A blood sample will be collected for GSK2879552 **and azacitidine**. PK analysis on D7 at pre-dose, 0.5, 1 hr, and 3 hrs post dose~~. In the combination cohort, a~~

~~blood sample for azacitidine PK analysis will be collected at the same time points.~~

3. Samples should be collected at 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. A blood sample will be collected for GSK2879552 PK analysis on D15 at pre-dose and 0.5-1 hr post dose.
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 for GSK2879552 should be taken pre-dose. PK sample will not be collected beyond 48 weeks.
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. Collection of exploratory sample (peripheral blood and/or BMA) time points may be terminated at the sponsor's discretion
12. Safety laboratory blood samples (CBC, chemistry and coagulation panel) should be collected post dose on Day 7 or the last day of Azacitidine in the cycle.
13. PK corresponding blood sample should be collected prior to dosing
14. Azacitidine dosing on Mon-Fri (Days 1-5) and Mon-Tue (Days 8-9) may be allowed on a case by case.
15. Optional for all subjects
16. Subjects are followed every 2 months to collect the survival, PFS data and the start of new treatment via chart review, or phone call contact. The follow-up will continue until death, lost to follow-up, withdrawal of consent or up to 12 months from end of treatment visit, whichever occurs first.
17. The exploratory BM sample is collected whenever the bone marrow is done for disease assessment and/or at time of crossover, unless the sample collection is stopped per sponsor discretion; the PK corresponding blood sample will be collected pre-dose at the crossover visit if the exploratory BM sample is collected. The PK corresponding blood sample will not be collected if a regularly scheduled PK sample is already being collected during the visit.
18. A window of 14 days is allowed for BM exam. Subjects who progressed to AML and cross over to Arm B will be required to have bone marrow for disease assessment prior to the start of combination dosing
19. All procedures scheduled on Day 7 visit (of any cycle) should move to Day 9, if azacitidine is given on Mon-Fri (Days 1-5) and Mon-Tue (Days 8-9) instead of Days 1-7.

Time and Events Table - Arm B (Combination with Azacitidine), Part 2

	SCR	Cycle 1 (28 days)					Subsequent Cycles	End of Treatment Visit	Post Treatment Bi-monthly Follow-Up[16]
		D 1	D4	D7[18]	D 15	D22			
Office Visit for Arm B (combo)	X	X	X	X	X	X	C2: D1- 7[18], 15 and 22 C3 and after: D1-7	X	
Informed consent	X								
Demography	X								
Medical history	X								
Disease characteristics	X								
GSK2879552 Dosing[9]		< ---------- Daily or per dosing schedule ----------→							
Azacitidine dosing[14]		<--Days 1-7--->					Days 1-7		
Review subject dosing diary				X	X		Day 1	X	
GSK2879552 Drug Dispensing		X					Day 1		
Complete physical exam	X							X	
Brief physical exam		X[7]		X			Day 1		
Montreal Cognitive Assessment	X	X		X	X	X	Day 1		
ECOG PS	X	X[7]		X			Day 1	X	
Vital Signs	X	X[7]		X	X		Day 1	X	
Height and weight[6]	X	X[7]		X			Day 1	X	
ECHO/MUGA	X								
12-lead ECGs	X	X[7]		X			Day 1	X	
HIV, HBsAg and HCV Ab testing	X								
CBC	X	X[7]		X[12]	X	X	C2: D1, 7[12, 18], 15 and 22 C3 and after: D1	X	

	SCR	Cycle 1 (28 days)					Subsequent Cycles	End of Treatment Visit	Post Treatment Bi-monthly Follow-Up[16]
		D 1	D4	D7[18]	D 15	D22			
Chemistry Panel including LFT	X	X[7]		X[12]	X	X	Day 1	X	
Coagulation Panel including a PTT and INR	X			X[12]	x	X	Day 1	X	
PK Blood samples		X[1]	X[8]	X[5]	X[2]	X[8]	C2: D1, 7[18], 15 and 22 D1 of C3-C12[8]		
Pregnancy test[4]	X						Day 1	X	
Blood samples for exploratory studies (peripheral blood)[3, 11]	X		X	X	X		Day 1	X	
Bone marrow aspirate for exploratory studies [11]	X						At time of disease assessment[17]	X[15]	
Disease assessment	X						Day 1	X	
Bone marrow for disease assessment	X[19]						bone marrow if clinically indicated	X[15]	
PGX samples (saliva sample)	X								
PK blood sample (corresponding with exploratory BMA)[13]							X[17]	X[17]	
Transfusion Need Assessment[10]	X			X	X	X	D1		
Adverse Events		Continuous							
Con Meds		Continuous							
Survival Assessment									X

1. A blood sample will be collected for **GSK2879552 and azacitidine**. PK analysis on D1 at pre-dose, 0.5hr, 1 hr and 3 hrs post dose. ~~In the combination cohort, a blood sample for azacitidine 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 and between 0.5 to 1 hour.

3. Samples should be collected at 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. A blood sample will be collected for **GSK2879552 and azacitidine**. PK analysis on D7 at pre-dose, 0.5, 1 hr, and 3 hrs post dose. ~~In the combination cohort, a blood sample for azacitidine PK analysis will be collected at the same time points.~~
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 for GSK2879552 should be taken pre-dose around the same time as CBC. **PK sample will not be collected beyond 48 weeks**
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. Collection of exploratory sample (peripheral blood and/or BMA) time points may be terminated at the sponsor's discretion
12. Safety laboratory blood samples (CBC, chemistry and coagulation panel) should be collected post dose on Day 7.
13~~2~~. PK corresponding blood sample should be collected prior to dosing
14~~3~~. Azacitidine dosing on Mon-Fri (Days 1-5) and Mon-Tue (Days 8-9) may be allowed on a case by case.
15~~4~~. Optional for all subjects
16~~5~~. Subjects are followed every 2 months to collect the survival, PFS data and the start of new treatment via chart review, or phone call contact. The follow-up will continue until death, lost to follow-up, withdrawal of consent or up to 12 months from end of treatment visit, whichever occurs first.
17~~6~~. The exploratory BM sample is collected whenever the bone marrow is done for disease assessment and/or at time of crossover, unless the sample collection is stopped per sponsor discretion; the PK corresponding blood sample will be collected pre-dose at the crossover visit if the exploratory BM sample is collected. The PK corresponding blood sample will not be collected if a regularly scheduled PK sample is already being collected during the visit.
18~~7~~. All procedures scheduled on Day 7 visit (of any cycle) should move to Day 9, if azacitidine is given on Mon-Fri (Days 1-5) and Mon-Tue (Days 8-9) instead of Days 1-7.
19~~8~~. A window of 14 days is allowed for BM exam. Subjects who progressed to AML and cross over to Arm B will be required to have bone marrow for disease assessment prior to the start of combination dosing

7.7 Genetics

Rationale for Change

Text was updated to reflect use of saliva, in place of blood for genetic sample collection.

Revised Text

2nd paragraph

A 2 mL saliva sample for DNA isolation will be collected from participants who have consented to participate in the genetics analysis component of the study. Participation is optional. Participants who do not wish to participate in the genetic research may still participate in the study.

In the event of DNA extraction failure, a replacement genetic **saliva** ~~blood~~ sample may be requested from the participant. Signed informed consent will be required to obtain a replacement sample unless it was included in the original consent.

11. References

Rationale for Change

Format of references was updated as per the GSK protocol template standards..

Revised Text

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12. Appendices

12.1 Abbreviations and Trademarks

Rationale for Change

Abbreviation and Trademarks table were updated as required by GSK protocol template standards.

Revised Text

Abbreviations

aPTT	**Activated Partial Thromboplastin Time**
DAC	**5-Aza-2'-deoxycytidine**
GVHD	**Graft-versus-Host-Disease**
MATE-1	**Multidrug And Toxin Extrusion Transporter 1**
~~PI~~	~~Principal Investigator~~
sc	**Subcutaneous**

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
NONE

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~~WinNonlin~~ **NONE**