TITLE PAGE

Protocol Title: A Phase I/II study to investigate the safety and clinical activity of GSK3326595 and other agents in participants with myelodysplastic syndrome and acute myeloid leukaemia.

Protocol Number: 208809/Amendment 3

Compound Number: GSK3326595

Study Phase: Phase I/ Phase II

Short Title: Phase I/II Study of GSK3326595 and other agents to treat myelodysplastic syndrome (MDS) and acute myeloid leukaemia (AML)

Sponsor Name and Legal Registered Address:

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Medical Monitor Name and Contact Information

Can be found in the Study Reference Manual.

Regulatory Agency Identifying Number(s):

IND: 151531

Approval Date: 15-FEB-2021

SPONSOR SIGNATORY

Protocol Title: A Phase I/II study to investigate the safety and clinical activity of GSK3326595 and other agents in participants with myelodysplastic syndrome and acute myeloid leukaemia.

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Eleftherios Zografos, MD/PhD
Program Physician Lead

Date

The signed page is a separate document.

Medical Monitor Name and Contact Information can be found in the Study Reference Manual

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY		
Document	**Date**	**DNG Number**
Amendment 03	*15-FEB-2021*	*TMF-11785988*
Amendment 02	*21-APR-2020*	*2017N345622_05*
Amendment 01	*12-JUN-2019*	*2017N345622_04*
Republishing	*16-JUL-2018*	*2017N345622_03*
Republishing	*22-JUN-2018*	*2017N345622_02*
Republishing	*22-MAY-2018*	*2017N345622_01*
Original Protocol	*09-MAY-2018*	*2017N345622_00*

Amendment 3: 15-FEB-2021

Overall Rationale for the Amendment:

The primary driver for the protocol amendment is to discontinue further development with monotherapy GSK3326595 based on clinical activity meeting pre-specified futility criteria as specified in the Protocol (Part 1), while continuing to explore GSK3326595 in combination with 5-Azacitidine in the Part 2 Dose Escalation and Dose Expansion cohorts. The Part 2 Dose Escalation design of GSK3326595 with 5-Azacitidine is amended to include intermittent dose schedules of GSK3326595 in relapsed / refractory MDS, CMML and AML participants. Part 2 Dose Expansion cohorts will include treatment naïve MDS and CMML participants.

The other main driver for this protocol amendment is the inclusion of additional prohibited medications (strong / moderate inhibitors or inducers of MATE2-K, OAT3 and OCT2 transporters) listed in the latest supplement to the Investigator Brochure (cut off date 04 February 2020), as it has been identified that GSK3326595 is a substrate of MATE2-K, OAT3 and OCT2 uptake transporters; therefore, there is potential for drug-drug interactions.

Some non-clinical and clinical risk assessment and mitigation strategies (Section 2.3.2) for GSK3326595 have been updated.

Other changes are detailed below.

Updated literature with additional information for combination approaches with 5-Azacitidine in the front line setting and preclinical models and response to PRMT5.

Data from Interim Analysis of 300 mg Part 1 cohort has been added.

Explanation for starting dose in Part 1 Dose Confirmation cohort and clarification for dose change has been added.

Clarification on the N-CRM design for Part 1 has been added.

Clarification of definition of DLT and Clinical Benefit Rate has been added.

Clarification with regards to population, number of participants and endpoint in Part 2 has been added.

Statistical design and futility criteria in Part 2 has been revised.

Inclusion of 25 mg capsules given doses potentially to be explored in Part 2 Dose Escalation.

Clarification for tumor sample collection at baseline (14 days prior to first dose) has been added.

Correction that Laboratory assessments collected until 30 days post last dose.

Correction that all AE/SAE collected until 30 days post last dose.

Clarification added: 'for genomic testing done locally, any results and type of test to be recorded and provided'.

Thyroid function tests (TSH, free T3 and free T4) has been added to Clinical Laboratory Tests (Appendix 2).

Ophthalmology assessments and folate / B12 levels have been added to safety testing.

The assessment of Patient Reported Outcomes (PROs) has been removed from the study.

Clarification of IWG criteria as per Cheson 2006 has been added.

Updates to inclusion of Appendix 13 outlining clinical study delivery under circumstances of pandemic caused by COVID19 in future.

The Assessment of Intensity has been modified to remove mild/moderate/severe AE/SAE grading and replaces with NCI-CTCAE Version 4.0 criteria.

Typographical errors have been corrected and minor editorial changes have been made.

Section # and Name	**Description of Change**	**Brief Rationale**
Title Page	IND: 151531	Regulatory agency identifying number has been updated.
Sponsor Signatory	Eleftherios Zografos, MD	To update sponsor signatory.
Section 1.1 Synopsis: Objective and Endpoints, Rationale, Overall Design 2.1 Study Rationale, 4.1 Overall Design, 4.1.3 Part 2:	No further evaluation of GSK3326595 monotherapy will be explored in Study 208809. Part 2A and Part 2C will not be progressed. Part 2B (now referred to as Part 2)	Given prespecified criteria (described in body of the protocol) were met, futility was declared for GSK3326595

Section # and Name	Description of Change	Brief Rationale
Further Exploration of Efficacy in Myeloid Neoplas, 4.3 Scientific Rationale for study design	will explore combination with GSK3326595 and 5-Azacitidine in Dose Escalation with intermittent dosing in myeloid neoplasms as described in Section 5 and Dose Expansion cohorts in participants with newly diagnosed MDS or CMML. Explanation added regarding doses explored in study 204653 in the study rationale.	monotherapy in MDS/AML/CMML population. Intermittent dosing of 2 weeks on and 2 weeks off is introduced instead of continuous dosing in Part 2 as guided by data from safety, tolerability, PK, PD and given overlapping toxicities with GSK326595 and 5-Azacitidine. Clarification of text, based on updated information
Section 1.1 Synopsis, Number of Participants for Part 2; Section 4.1.3.1 Part 2: 5-Azacitidine plus GSK3326595, Section 4.2 Number of Participants	In Part 2 approximately 24 participants will be enrolled in each dose escalation cohort (QD or BID) in schedule of 2 weeks on and 2 weeks off. In Part 2 Dose Expansion, approximately 35 participants will be enrolled. Part 2A and Part 2C will not be progressed	Part 2 design changes: Dose Escalation for each QD or BID will follow N-CRM design. Part 2 Dose Expansion is based on Bayesian decision making approach.
Section 1.1 Synopsis and Section 3: Objectives and Endpoints, Part 2	• Removal of Part 2A and Part 2C Objectives as per decision to discontinue monotherapy development with GSK3326595 in Study 208809. • Split of Part 2B objectives for Part 2 Dose Escalation and Part 2 Dose Expansion objectives • Change to primary endpoint for Part 2 Dose Expansion to Complete Remission Rate • Removal of PFS, OS, TTR from Part 2 Dose	As explained above. In the pivotal AZA001 study in treatment naïve participants 5-Azacitidine demonstrated significant improvement in OS compared to conventional care (Fenaux 2009). In addition 5-Azacitidine yielded improvement in ORR including CR rate. In an ad hoc analysis of AZA001 using the 2006 IWG criteria participants who achieved CR had the best OS compared to mCR or PR, and hence CR can be considered as a

Section # and Name	Description of Change	Brief Rationale
	Escalation cohort exploratory objectives (• In Part 2 Dose Expansion cohort objectives, PFS moved from secondary to exploratory endpoint • Inclusion of frequency of dose interruptions, dose reductions and treatment discontinuations due to adverse events as part of primary endpoint in Dose Escalation or secondary endpoint in Dose Expansion. • Removal of PROs	surrogate endpoint for OS in higher-risk MDS pts (Komrokji, 2015). Frequency of dose interruptions, reductions and treatment discontinuations is an additional measure to determine safety, tolerability and recommended combination dose in Part 2. To reduce participant burden, hence exclusion of PRO
1.2 Schema and Figure 3	Part 2A and Part 2C will not be progressed. Part 2 will continue in combination with 5-Azacitidine in Dose Escalation Part as daily (QD) and twice daily (BID) cohorts in schedule of 2 weeks on and 2 weeks off with GSK3326595. 5-Azacitidine is administered as per prescribed information. Starting dose at QD cohort is 200 mg, and at BID cohort 100 mg. Once Recommended Combination dose and regimen is determined, dose expansion will be initiated in up to 35 participants.	Rationale of Part 2A and Part 2C as above. Proposed Dose Escalation schedule will explore both daily and twice daily dosing in a N-CRM design until maximum tolerated dose (MTD) is confirmed. Choice of patient population is explained in Section 5 of the Protocol and below.
1.3 Schedule of Activities (SoA), Part 2	Part 2A and Part 2C SoA is removed. Part 2 SoA is adapted to schedule of intermittent dosing of 2 weeks on and 2 weeks off including additional PK and PD samples, PD samples collected at Week 9 moved to Week 7 instead and	Rationale of Part 2A and Part 2C as above. Intermittent dosing rational as explained above. Additional PK samples collected as required for analysis.

Section # and Name	Description of Change	Brief Rationale
	footnote clarifications included. TSH, free T3 and free T4 is included as additional assessment at screening, Week 5 Day 1 and Week 9 Day 1, every 8 weeks thereafter and EOT. Inclusion of ocular assessments and folate testing at BSL and on treatment. PROs are removed. Collection of diary from Day 1 instead from Day 8 AE/SAE and laboratory assessments collected until 30 days post treatment Inclusion of requirement for Investigators to ask participants about vision symptoms at each routine visit and document responses	Additional PD samples collected as required for analysis. It is hypothesized thyroid function may be related to fatigue observed as common adverse event, hence introduction for TSH, free T3 and free T4 measurements. Ocular assessments and folate testing introduced to monitor a safety event observed.
Section 2.2.1 Clinical Background: MDL and AML	Inclusion of additional data and literature for combination approaches with 5-Azacitidine in front line setting	Updated literature included
Section 2.2.2.2 Spliceosomal Mutations and Potential Biomarkers for PRMT5 Inhibition in Myeloid Neoplasms	Inclusion of additional data from literature on preclinical models and response to PRMT5	Updated literature included
Section 2.2.3 Clinical experience with PRMT5 inhibitors	Addition of section to summarize experience with other clinical studies evaluating GSK3326595 and other PRMT5 inhibitors. Includes explanation of	Additional information is available.

Section # and Name	Description of Change	Brief Rationale
	ophthalmology findings potentially related to GSK3326595.	
2.3.2 Preclinical and clinical risk assessment	Table divided into two tables listing either Identified or Potential risks separately • Inclusion of statement on conclusions from GLP genotoxicity study and embryofetal development risks • Removal of Cardiac Effects risks • Inclusion of statement for the preclinical data for hepatic event risks • Addition of statement to the preclinical data for damage to exocrine tissue • Addition of ophthalmology adverse event findings in clinical study and mitigation approaches • Addition of fatigue	Update as required per updated information
Section 2.3.3 Pharmacokinetic Risk Assessment	Inclusion of MATE2-K, OAT3 and OCT2 as potential substrate of GSK3326595	Alignment with latest IB data cut off 04 February 2020
Section 2.3.4 Benefit Assessment and 2.3.5 Overall Benefit: Risk Conclusion	Inclusion of data from Interim Analysis of 300 mg Part 1 cohort and explanation of patient population for Part 2	Justification added given new patient population is enrolled in Part 2
Section 4.1.1.1 Part 1 Dose Confirmation and Section 4.1.1.1.2 Starting dose, planned dose level, and alternative dosing schedules	Explanation regarding starting dose in Part 1 Dose Confirmation cohort of Study 208809. And explanation added to clarify dose in Study 204653 have changed to 300 mg	Updated information included

Section # and Name	Description of Change	Brief Rationale
	during the study as well due to safety and tolerability.	
Section 4.1.1.1.3 Dose confirmation	Text clarification on the N-CRM design for Part 1.	Clarification included.
Section 4.1.1.1.4 Dose limiting toxicities, Table 5 and Section 4.1.3.1.1 Part 2 Dose escalation	Clarification of DLT definition included in ‘’other’’ category and in text in Section 4.1.3.1.1	Clarification included
Section 4.1.1.5 Statistical Design, Table 6	Clarification of definition of Clinical Benefit Rate as inclusive of mCR, PR, SD>=8 weeks or HI	Clarification included
Section 4.1.2 Decision whether to proceed to Part 2	Explanation on decision to proceed to Part 2	Explanation as above
Section 4.1.3 Part 2: Further Exploration of Efficacy in Myeloid Neoplasms	Part 2 high level objectives outlines and Part 2A and 2C outline of objectives deleted	Explanation as above
Section 4.1.3.1 Part 2: 5-Azacitidine plus GSK3326595 and Section 4.1.3.1.1 Part 2 Dose Escalation	Explanation on design of part 2 Dose Escalation and Expansion and Patient numbers and starting dose, dosing steps and dose reductions guidance. Statement included that the recommended combination Dose and Regimen will be based on safety, tolerability, and available PK and PD data	Changes in line with proposed design for Part 2 Starting dose at 200mg QD and 100mg BID at respective cohorts which is two dose levels lower than RP2D for Monotherapy given continuously. Clarification included on data required to guide decision for Recommended Combination Dose and Regimen
Section 4.1.3.1.2 Part 2, Dose Expansion: Clinical Efficacy in Newly Diagnosed MDS and CMM, Table 8	Clarification with regards to population, number of participants and endpoint used Revised statistical design and futility criteria	Explanation above. Revised statistical design and the futility criteria given the change in the primary endpoint and decision making approach.

Section # and Name	Description of Change	Brief Rationale
Section 4.2 Number of Participants	Change in number of participants	Explanation above
Section 4.3 Scientific Rationale for Study Design, 4.3.2 Part 2	Explanation of patient population added and corrected	Explanation above
Section 4.4 Justification for dose, Section 4.4.1.1 GSK3326595	Change to align with updated status of doses explored in 204653 and 208809 studies. Inclusion of starting dose in Part 2 and rationale	Explanation above
Section 4.5 End of Study definition	End of Study definition clarification	Clarification to align to design where Part 1 and Part 2 included, no Part 2A or Part 2C
Section 5.1 Inclusion criteria	Part 2A and 2C population deleted Part 2 population in Dose Escalation and Dose Expansion cohort listed out Circumstances under which HIV and HepB participants may be enrolled included in Section 5,2	Patient population in Dose Escalation selected to include patients with unmet medical need and with no additional options for standard therapy. R/R AML that has exhausted all treatment option with WBC <20,000 cells/µL (so not just AML evolving from MDS/MPN) enrolled to broaden the population covering additional area of unmet medical need where 5-Azacitidine is part of SoC)
Section 5.2 Exclusion criteria	Updated notes to include HIV/Hep B participants into study	To include HIV/Hep B participants
Section 5.3.1.1 Female Participants of Childbearing Potential Section 5.3.1.3 Male Participants	Clarification regarding use of contraception after last dose of GSK3326595 and 5-Azacitidine has been added.	Clarification added.

Section # and Name	Description of Change	Brief Rationale
Section 6.1 Study Intervention administered	Participants can be administered either tablets or capsules in Part 2. Inclusion of 25 mg capsules Clarification to administration of 5-Azacitidine as based on prescribed information in registered label Clarification that 5-Azacitidine may be obtained from registered manufacturers Allow to take drug with food on Cycle 1 Day 8 in part 2 dose escalation Change the GSK3326595 intake to 2 h pre dose and 1 h post dose	Relative bioavailability sub-study in study 204653 has enabled the use of tablets. Inclusion of 25 mg capsules given doses potentially to be explored in Part 2 Dose Escalation. Clarification of language Clarification of language Allows exploration of food effect on PK Clarification of food intake timing.
Section 6.2 Method of Treatment Assignment, Section 6.3 Blinding, Section 8.1 Visit Windows	Removal of Part 2A and Part 2C	As explained above
Section 6.6.1.2. Cautionary Medications	Perpetrator risk of GSK3326595 has been identified as a CYP1A2 inducer and therefore co-administration of GSK3326595 and substrates of CYP1A2 should be avoided in order to prevent inadvertent under-exposure to these agents.	Alignment with latest IB cut off 04 February 2020
Section 6.6.1.3. Prohibited Medications	GSK3326595 is a substrate of MATE2-K, OAT3 and OCT2 uptake transporters; therefore, GSK3326595 should not be co- administered with strong	Alignment with latest IB cut off 04 February 2020

Section # and Name	Description of Change	Brief Rationale
	and moderate inhibitors or inducers of MATE2-K, OAT3 and OCT2. The warning for GSK3326595 not to be co-administered with strong or moderate inhibitors of Breast Cancer Resistance Protein (BCRP) has been removed.	
Section 8.2.2 Tumor Sample	Tumor sample collection within 14 days prior to the first dose of study drug(s)	Clarification in language
Section 8.3.1 Disease Assessment	Removal of Part 2A and Part 2C	As explained above
Section 8.4.4 Electrocardiograms	Clarification that single 12-lead ECG are collected on treatment and additional details of triplicate ECG measurements to be moved to SRM. Locally collected ECGs may be read centrally.	Clarification added
Section 8.4.5 Bone Mineral Density	Clarification added that locally collected DEXA scans may be read centrally	Clarification added
Section 8.4.6 Clinical Safety Laboratory Assessments	Correction that Laboratory assessments collected until 30 days post last dose	Alignment with AE/SAE collection post last dose
Section 8.4.7 Adverse Events and Serious Adverse Events	Correction that all AE/SAE collected until 30 days post last dose	Clarification added
Section 8.7 Pharmacodynamics and Biomarker	Clarification for genomic testing done locally, any results and type of test to be recorded and provided.	Additional collection of results and type of tests from locally generated genomic testing

Section # and Name	Description of Change	Brief Rationale
Section 8.8 Patient Reported Outcomes	PRO assessments have been removed.	PRO assessments have been removed from Part 2 to reduce participant burden during the Dose Escalation phase.
Section 9 Statistical Consideration	Part 1 text clarifications. Part 2 Dose Escalation N-CRM design details and simulations were added for each QD and BID. Part 2 Dose Expansion revised statistical design including changes to the decision making framework and the futility time points.	Removal of duplicated information. Part 2 Dose Escalation operating characteristics assessment of the N-CRM design. Part 2 Dose Expansion changes due to the primary endpoint change and refinement of the decision making framework.
Section 10 References	Additional references are included	As above
Section 11.2 Appendix 2	Inclusion of TSH, free T3 and free T4	Explanation above
Section 11.9 Appendix 9	Clarification regarding IWG criteria as per Cheson 2006 included	Clarification needed
Section 11.11 Appendix 11	Clarification that Appendix 11 lists dose modification criteria for GSK3326595, 5-Azacitidine shall follow dose adjustments as per registered label	Clarification needed
Section 11.12 Appendix 12	Rationale for Response Assumptions included CR rate. Removal of Part 2A and Part 2C related information.	Due to change in Part 2 primary endpoint explanation and literature included

Section # and Name	Description of Change	Brief Rationale
Section 11.13 Appendix 13	COVID 19 Appendix included	Guidance under COVID19 pandemic as per GSK requirements included

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A Phase I/II study to investigate the safety and clinical activity of GSK3326595 and other agents in participants with myelodysplastic syndrome and acute myeloid leukaemia.

Short Title: Phase I/II Study of GSK3326595 and other agents to treat myelodysplastic syndrome (MDS) and acute myeloid leukaemia (AML)

Rationale:

MDS and AML are clonal neoplasms of myeloid progenitors that arise within the bone marrow. They are typically manifested by peripheral cytopenias (neutropenia, anemia, and/or thrombocytopenia), hypercellularity of the bone marrow (as a consequence of ineffective hematopoiesis), molecular and/or karyotypic abnormalities, and an expansion of immature myeloid cells. It is the quantitation of these immature myeloblasts ("blasts") that, in part, differentiates AML from MDS, with a 20% blast percentage marking the transition from MDS to AML. While multiple new targeted agents have been approved to treat AML in patients harbouring a limited number of mutations, the majority of patients with both MDS and AML are not eligible for these therapies. Current therapies for most patients are inadequate: a newly diagnosed MDS patient may expect only to live for one to two years before dying of the disease, and the lifespan of someone diagnosed with AML would be even shorter, despite modern therapy. Disease that relapses after standard treatment, or which fails to respond to therapy, confers an even more dismal prognosis. The median overall survival (OS) for relapsed MDS is approximately six months, and there is no generally accepted standard of care for these patients. As such, new therapies to prolong survival are desperately needed.

Protein arginine methyltransferases (PRMTs) are a family of enzymes that methylate arginines in proteins involved in various cellular processes, including precursor messenger ribonucleic acid (pre-mRNA) splicing, transcription factors, kinases and histones. One family member, PRMT5, is responsible for the majority of symmetric dimethylation of arginine *in vivo*. PRMT5 is overexpressed in a number of tumors, including myeloid malignancies [Tarighat, 2016]. Inhibition of PRMT5 leads to decreased proliferation and cell death in preclinical models of AML.

GSK3326595 is a potent, selective, reversible inhibitor of PRMT5 currently under investigation in solid and hematologic tumors in the first-in-human study 204653 evaluating subjects with solid tumors and non-Hodgkin's lymphoma (NHL). In Part 1 of the dose escalation phase, the QD dose escalation population consisted of 8 cohorts (12.5 mg, 25 mg, 50 mg, 100 mg, 200 mg, 300 mg, 400 mg, and 600 mg) and the twice daily (BID) dose-escalation population consisted of 4 cohorts (50 mg, 100 mg, 150 mg, and 200 mg). The starting dose in Part 2 was 400 mg daily; however, it was subsequently agreed to start participants at a dose of 300 mg daily due to safety and tolerability.

Study 208809 is a Phase I/II study to evaluate the safety, tolerability, and clinical activity of GSK3326595 in participants with relapsed and refractory MDS, chronic myelomonocytic leukaemia (CMML), and hypoproliferative AML that has evolved from an antecedent MDS (Part 1, "MDS cohort"). At the end of Part 1, pre-specified criteria (as described in the body of the protocol) for futility were met for GSK3326595 monotherapy. Therefore no further investigation of GSK3326595 monotherapy will be conducted in this patient population, but the study will be expanded to study GSK3326595 in combination with 5-Azacitidine in Part 2. Part 2 consists of a Dose Escalation phase where intermittent dosing schedule (2 weeks on, 2 weeks off), two regimens (daily and twice daily) of GSK3326595 will be administered in combination with 5-Azacitidine in participants with MDS, CMML or AML, followed by a Dose Expansion cohort using the Recommended Combination Dose and Regimen determined in the Dose Escalation phase. The inclusion of any additional agents will require a protocol amendment prior to implementation.

Objectives and Endpoints:

Part 1	
Objectives	**Endpoints**
Primary	
• To determine the clinical activity of GSK3326595 in participants with myeloid neoplasms	• Clinical Benefit Rate (CBR), as defined as the percentage of participants achieving a complete remission (CR), complete marrow remission (mCR), partial remission (PR), stable disease (SD) lasting at least 8 weeks, or hematologic improvement (HI), per International Working Group (IWG) criteria.
Secondary	
• To determine the safety, tolerability, and recommended myeloid monotherapy dose of orally-administered GSK3326595 in participants with relapsed and/or refractory myeloid neoplasms	• Frequency and severity of adverse events • Frequency of dose limiting toxicities (DLTs)
• To further describe the clinical activity of GSK3326595 in participants with relapsed and/or refractory myeloid neoplasms	• Overall response rate (ORR), defined as the percentage of participants achieving a CR, mCR, or PR, per IWG criteria. • Progression free survival (PFS), defined as time from first dose to disease progression, as defined by IWG criteria, or death due to any cause, whichever occurs earlier • Overall survival (OS), defined as time from first dose to death due to any cause

Part 1	
Objectives	**Endpoints**
• To characterize the pharmacokinetics (PK) of GSK3326595 in participants with relapsed and/or refractory myeloid neoplasms	• GSK3326595 PK parameters in plasma following single- (Day 1) and repeat-dose administration of GSK3326595
Exploratory	
CCI [redacted]	

Part 2 Dose Escalation	
Objectives	**Endpoints**
Primary	
• To determine the safety, tolerability, and recommended combination dose and regimen of orally-administered GSK3326595 when administered in combination with 5-Azacitidine in participants with myeloid neoplasms	• Frequency and severity of adverse events • Frequency of DLTs • Frequency of dose interruptions, dose reductions, and treatment discontinuation due to adverse events
Secondary	
• To determine the clinical activity of GSK3326595 plus 5-Azacitidine in participants with myeloid neoplasms	• Complete Remission (CR) rate, defined as the percentage of participants achieving a CR per IWG criteria
• To describe the pharmacokinetics (PK) of GSK3326595 and 5-Azacitidine after single- and repeat-dose administration	• GSK3326595 and 5-Azacitidine PK parameters in plasma following single- (Day 1) and repeat-dose administration of GSK3326595 in combination with 5-Azacitidine.
• To further describe the clinical activity of GSK3326595 plus 5-Azacitidine in participants with myeloid neoplasms	• ORR, defined as the percentage of participants achieving a CR, mCR, or PR, per IWG criteria.
Exploratory	
CCI [redacted]	

CCI [redacted]

Part 2 Dose Expansion	
Objectives	**Endpoints**
Primary	
• To determine the clinical activity of GSK3326595 plus 5-Azacitidine in participants with high risk newly diagnosed MDS or CMML	• Complete Remission (CR) rate, defined as the percentage of participants achieving a CR per IWG criteria
Secondary	
• To determine the safety and tolerability, of orally-administered GSK3326595 when administered in combination with 5-Azacitidine in participants with high risk newly diagnosed MDS or CMML	• Frequency and severity of adverse events • Frequency of dose interruptions, dose reductions, and treatment discontinuation due to adverse events
• To describe the pharmacokinetics of GSK3326595 and 5-Azacitidine after single- and repeat-dose administration	• GSK3326595 and 5-Azacitidine PK parameters in plasma following single- (Day 1) and repeat-dose administration of GSK3326595 in combination with 5-Azacitidine.
• To further describe the clinical activity of GSK3326595 plus 5-Azacitidine in participants with high risk newly diagnosed MDS or CMML	• ORR, defined as the percentage of participants achieving a CR, mCR, or PR, per IWG criteria.
Exploratory	

CCI [redacted]

Overall Design:

Study 208809 is an open-label, multicentre, multi-part study of GSK3326595 as monotherapy and in combination with 5-Azacitidine in participants with myeloid malignancies. Refer to Section 1.2 for the overall study schematic.

Additional agent(s) may be added, either as single agent or in combination, to any of the parts of this study based on emerging clinical and preclinical data. A protocol amendment will be required to include the additional agents to be used in this study.

Part 1 is composed of a safety evaluation, followed by a single-arm dose expansion cohort to determine the CBR of GSK3326595 in participants with relapsed and/or refractory MDS, CMML, and hypoproliferative AML that has evolved from an antecedent MDS. At the end of Part 1, pre-specified criteria (as described in the body of the protocol) for futility were met for GSK3326595 monotherapy. Therefore, no further investigation of GSK3326595 monotherapy will be conducted, but the study will be expanded to study GSK3326595 in combination with 5-Azacitidine in Part 2. Part 2 is composed of two dose escalation cohorts of intermittent dosing of GSK3326595 (**Regimen 1**: Once daily dosing [QD] with 2 weeks on, 2 weeks off GSK3326595 in combination with 5-Azacitidine administered as per prescribing information and **Regimen 2**: Twice daily dosing [BID] with 2 weeks on, 2 weeks off GSK3326595, with 5-Azacitidine administered as per prescribed information. Participants enrolled in the Dose Escalation portion of Part 2 will include patients with myeloid neoplasms.

Once the Recommended Combination Dose and Regimen is determined based on data from Dose Escalation cohorts, the Dose Expansion cohort in high risk treatment naïve MDS or CMML participants will be initiated to determine the CR rate of the combination of GSK3326595 plus 5-Azaciditine.

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

Disclosure Statement: This is a sequential treatment study with study arms that is not masked.

Number of Participants:

Participants enrolled in Part 1 of this study will have a diagnosis of relapsed / refractory (R/R) MDS, CMML, or AML for which no standard therapy is expected to provide a significant response. Part 2 Dose Escalation will enroll participants with myeloid neoplasms. Participants in the Part 2 Dose Expansion cohort will have newly diagnosed, high-risk MDS, CMML. Participants in both Part 2 Dose Escalation and Dose Expansion will receive IP in combination with the approved first-line agent 5-Azacitidine. It is estimated that a maximum of 113 participants will be enrolled in the study, divided as follows: in Part 1 30 participants were enrolled; in Part 2 Dose Escalation cohorts approximately 24 participants in each of the two dose regimens (QD and BID) and approximately 35 participants in Dose Expansion cohort.

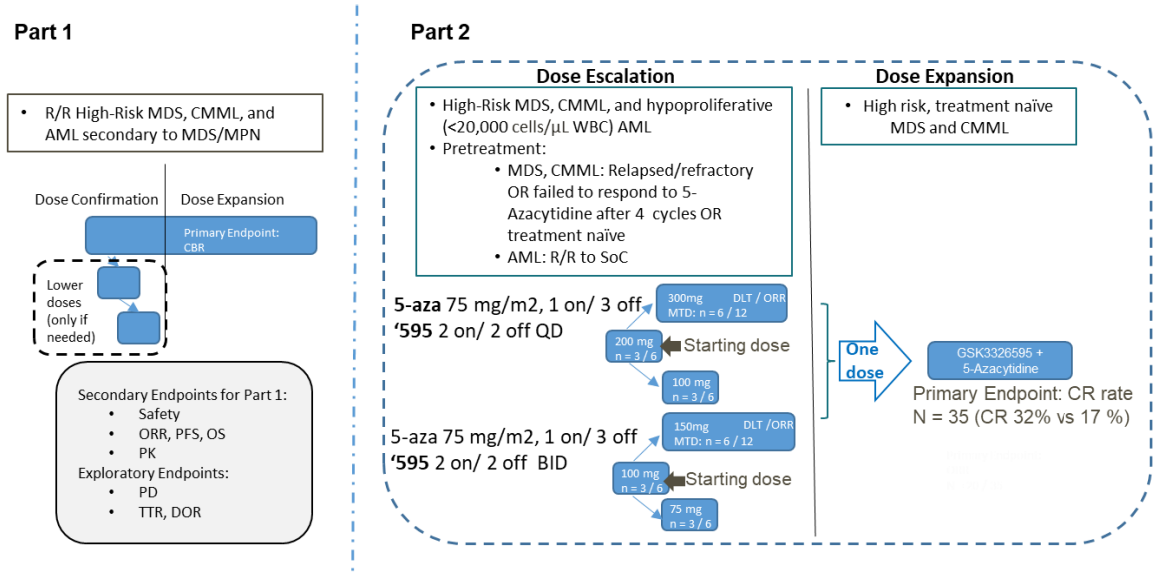
Intervention Groups and Duration:

All participants will receive GSK3326595, either as a single agent (Part 1) or in combination with 5-Azacitidine (Part 2 Dose Escalation and Dose Expansion). Participants will begin therapy on Day 1 of the study and continue until unacceptable toxicity, progression of disease, withdrawal of consent, death, or termination of the study by the sponsor. The total duration of study will depend on recruitment rates, withdrawals due to toxicity or progression or death, with an approximate duration of 5-6 years.

Once daily administration of GSK3326595 as monotherapy was explored in Part 1. Intermittent dosing schedule (2 weeks on, 2 weeks off),once daily and twice daily regimen will be explored in Part 2. The intermittent dosing schedule above was selected based on the available safety, tolerability, PK and PD data. More specifically: 1) the need to allow for sufficient bone marrow recovery as GSK3326595 and 5-Azacitidine both can induce sever cytopenias, 2) data on time to achieve maximum reduction of SDMA in plasma (nadir of SDMA achieved after day 14), 3) median time of onset of most common adverse events related to GSK3326595 (unpublished data).

Dose reductions for individual participants may be required, based on toxicity observed during the study, and the frequency and duration of dose reductions will be reported. There will not be any pre-planned dose reductions. In Part 2, participants who require permanent discontinuation of either one of the study treatments in the combination may continue on the second agent.

1.2. Schema



1.3. Schedule of Activities (SoA)

The schedule of activities for each Part of the study may be found on the following pages. For all Parts, the following apply:

- Permissible windows for visits and study assessments are provided in Section 8.1.
- The timing and number of planned study assessments, including safety, pharmacokinetic, pharmacodynamic/biomarker, or efficacy 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.
- Any changes in the timing or addition of time points for any planned study assessments must be documented and approved by the relevant study team member and then archived in the sponsor and site study files but will not constitute a protocol amendment. The Institutional Review Board/Independent Ethics Committee (IRB/IEC) will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the Informed Consent Form (ICF).
- Whenever vital signs, 12-lead ECG, and blood draws are scheduled for the same nominal time, the assessments should occur in the following order: 12-lead ECG, vital signs, and blood draws. Whenever vital signs and blood draws are scheduled for the same nominal time, vital signs should be performed prior to blood draws. The timing of the assessments should allow the blood draw to occur at the exact nominal time. Detailed procedures for obtaining each assessment are provided in the SRM.
- Unless otherwise stated in the SOA all assessments shall be performed pre dose.

1.3.1. Part 1: Single Agent in Relapsed/Refractory Myeloid Disease

Table 1 Schedule of Activities, Part 1

Procedure[1]	Screening	DLT Observation Period				Week 5	Week 7	Week 9 and thereafter			Week 13 and thereafter	End of Treatment (EOT)	Survival Follow-up
		Day 1	Day 8	Day 15	Day 22	Day 1	Day 1	Week 9 Day 1 only	Every 4 Weeks[1]	Every 8 Weeks	Every 12 Weeks		
Screening													
Informed consent	X												
Inclusion/Exclusion criteria	X												
Demography	X												
Medical History	X												
Disease Characteristics	X												
Prior Therapy	X												
Register Participant	X												
Dispense Study Drug [2]		X				X			X				
Safety													
Physical Examination[3]	X	X	X	X	X	X	X		X			X	
Eastern Cooperative Oncology Group (ECOG) Performance Status	X	X	X	X	X	X	X		X			X	
Vital Signs	X	X	X	X	X	X	X		X			X	
12-lead Electrocardiogram (ECG)	X	X	X	X	X	X	X		X			X	
Pregnancy test[4]	X	X				X			X			X	
Follicle Stimulating Hormone (FSH)/Estradiol[5]	X												
Human Immunodeficiency virus HIV, Hepatitis B Surface Antigen (HBsAg), Hepatitis C Virus (HCV) Antibody Screening	X												
DEXA Bone Densitometry[6]	X									X		X[7]	
Clinical Laboratory Assessments[8]	X	X	X	X	X	X	X		X			X	

Procedure[1]	Screening	DLT Observation Period				Week 5	Week 7	Week 9 and thereafter			Week 13 and thereafter	End of Treatment (EOT)	Survival Follow-up
		Day 1	Day 8	Day 15	Day 22	Day 1	Day 1	Week 9 Day 1 only	Every 4 Weeks[1]	Every 8 Weeks	Every 12 Weeks		
Study Intervention													
Administer Study Drug		←========== [Daily Dosing]==========→											
Adverse Events (AE)/ Serious Adverse Event (SAE) review	←========== [Continuous from Signing of Informed Consent to EOT Visit] ==========→												
Concomitant medication review	←========== [Continuous from Signing of Informed Consent to EOT Visit] ==========→												
Review Diary Card	←========== [Continuous from Day 8 to EOT Visit] ==========→												
Pharmacokinetics (PK), Pharmacodynamics (PD) & Pharmacogenomics (PGx)													
PK Plasma Samples[9]		X		X		X	X		X				
Plasma Samples (Symmetric Dimethylarginine(SDMA) and Circulating Biomarkers)[10]		X		X		X		X			X		
Whole Blood Samples (Transcriptomics)[10]		X		X		X		X			X		
Serum Sample (Translational Studies)[10]		X				X		X			X		
Bone Marrow Biopsy (SDMA and Translational Studies)[11]	X					X					X	X	
Genetic Sample (Saliva)[12]		X											
Efficacy													
Bone Marrow Biopsy	X					X					X	X	
Survival Follow-up[13]													X

1. After Week 49, the assessment frequencies may be reduced to every 8 weeks at the discretion of the Investigator. Refer to Section 8.1 of the full protocol for visit/procedure windows
2. Study drug (GSK3326595) will be dispensed every 4 weeks at the clinic. If after Week 49, the assessment frequencies are reduced to every 8 weeks, then the study drug would then be dispensed every 8 weeks
3. Refer to Section 8.4.1 for components of physical examination that must be performed at each visit
4. Pregnancy testing only required for female participants of childbearing potential; see Section 5.3.1.1 for details. Must be within 7 days of first dose.
5. FSH/Estradiol testing only required for perimenopausal women whose childbearing potential is questionable; see Section 5.3.1.2 for details
6. If possible, DEXA to be performed on same machine for particular participant (see SRM)
7. Only if EOT is > 8 weeks from prior DEXA
8. Refer to Appendix 2: Clinical Laboratory Tests for list of required laboratory assessments. Note that routine serum and urinalysis studies are required for all participants enrolled; additional serum and urine tests for participants with a baseline creatinine clearance < 60 ml/min/1.73 m^2 should be performed as described in Appendix 2: Clinical Laboratory Tests.
9. PK samples following Day 1 and Day 15 dose will be collected at pre-dose (within 1 hour prior to dosing), 5 min±2 min, 30m±5min, 1h±5min, 2h±5min, 3h±5min, 4h±10 min, 6h±10 min, 8h± 15min, 12h±2h, 24h±2h. PK samples on days of subsequent visits should be collected within 1 hour Pre-dose
10. Plasma, serum, and whole blood samples should be collected Pre-dose on Day 1 and 6h (±3h) after dosing with GSK3326595 on the other days indicated. Unscheduled samples for translational studies (see Section 8.7) should also be collected 6h (±3h) after dosing with GSK3326595
11. Bone marrow (BM) biopsies for translational studies should be collected at screening and then 6h (±3h) on the days indicated, after dosing with GSK3326595. Unscheduled biopsies for translational studies (see Section 8.7) should also be collected 6h (±3h) after dosing with GSK3326595
12. Informed consent for optional genetics research should be obtained before collecting a sample. The sample will be collected at the first opportunity after a participant has met all eligibility requirements on Day 1 (pre- or post-dose)
13. Survival Follow-Up may be via telephone, email, or other form of communication

1.3.2. Part 2: GSK3326595 in combination with 5-Azacitidine

Table 2 Schedule of Activities, Part 2 Dose Escalation

Procedure[1]	Screening	DLT Observation Period				Week 5	Week 7	Week 9	Week 9 and thereafter		Week 13 and thereafter	Every 26 weeks	End of Treatment[2]
		Day 1	Day 8	Day 15	Day 22	Day 1	Day 1	Day 1	Every 4 Weeks[1]	Every 8 Weeks	Every 12 Weeks		
Screening													
Informed consent	X												
Inclusion/Exclusion criteria	X												
Demography	X												
Medical History	X												
Disease Characteristics	X												
Prior Therapy	X												
Register Participant	X												
Safety													
Physical Examination[3]	X	X	X	X	X	X	X		X				X
ECOG Performance Status	X	X	X	X	X	X	X		X				X
Vital Signs	X	X	X	X	X	X	X		X				X
12-lead ECG[4]	X	X	X	X	X	X	X		X				X
Pregnancy test[5]	X	X				X			X				X
FSH/Estradiol[6]	X												
HIV, HBsAg, HCV Antibody Screening[7]	X												
Clinical Laboratory Assessments[8]	X	X	X	X	X	X	X		X				X
Folate and selected vitamins[8]	X					X				X			X
TSH, free T3, free T4	X					X		X		X			X
Opthalmic Assessment[9]	X											X	X
DEXA Bone Densitometry[10]	X									X			X[11]

Procedure[1]	**Screening**	**DLT Observation Period**				**Week 5**	**Week 7**	**Week 9**	**Week 9 and thereafter**		**Week 13 and thereafter**	**Every 26 weeks**	**End of Treatment**[2]
		Day 1	**Day 8**	**Day 15**	**Day 22**	**Day 1**	**Day 1**	**Day 1**	**Every 4 Weeks**[1]	**Every 8 Weeks**	**Every 12 Weeks**		
Study Intervention													
Administer GSK3326595[12]		X	X			X		X	X				
Dispense Study Drug (GSK3326595)[13]		X				X		X	X				
Administer 5-Azacitidine[14]		X	(X)[14]			X		X	X				
Vision Symptom Review[15]	X	X	X	X	X	X	X		X				X
AE review		←==========[Continuous from Start of Treatment to 30 days after last treatment] ==========→											
SAE review	←==========[Continuous from Signing of Informed Consent to 30 days after last treatment] ==========→												
Concomitant medication review	←========== [Continuous from Signing of Informed Consent to EOT Visit] ============→												
Review Diary Card		←========== [Continuous from Day 1 to EOT Visit] ====================→											
Pharmacokinetics (PK), Pharmacodynamics (PD) & Pharmacogenomics (PGx)													
PK Plasma Samples[16]		X	X[17]	X[18]		X	X[18]	X	X				
Plasma Samples (SDMA and Circulating Biomarkers)[19]		X	X	X		X	X				X		
Plasma Sample for cfDNA[20]		X				X					X		
Whole Blood Samples (Transcriptomics)[19]		X		X		X	X				X		
Serum Sample (Translational Studies)[19]		X				X	X				X		
Bone Marrow Biopsy (SDMA and Translational Studies)[21]	X					X					X		X
Genetic Sample (Saliva)[22]		X											
Efficacy													
Bone Marrow Biopsy	X					X					X		X

1. After Week 49, the assessment frequencies will be reduced to every 8 weeks. Refer to Section 8.1 of the full protocol for visit/procedure windows
2. EOT visit to occur within 30 days from the last dose of the study treatment
3. Refer to Section 8.4.1 for components of physical examination that must be performed at each visit
4. On Day 1 and Day 8 triplicate ECGs will be obtained at or about the time of PK sample collection as described in the SRM
5. Pregnancy testing only required for female participants of childbearing potential; see Section 5.3.1.1 for details. Must be within 7 days prior to the first dose.
6. FSH/Estradiol testing only required for perimenopausal women whose childbearing potential is questionable; see Section 5.3.1.2 for details
7. If test performed within 3 months prior to first dose of study treatment, testing at screening may not be required. Discuss with Medical Monitor if unclear
8. Refer to Appendix 2: Clinical Laboratory Tests for list of required laboratory assessments. Note that routine serum and urinalysis studies are required for all participants enrolled; additional serum and urine tests for participants with a baseline creatinine clearance < 60 ml/min/1.73 m2 should be performed as described in Appendix 2: Clinical Laboratory Tests. Clinical labs performed during screening within 72 hours prior to first dose do not need to be repeated on Day 1. Folate and selected vitamins to be drawn at Screening, Week 5, Week 9, and every 8 weeks thereafter and at EOT. If a participant's folate or selected vitamins result(s) remain borderline or low at EOT visit, further testing may be requested until no longer deemed necessary in the opinion of the Investigator and Medical Monitor.
9. Refer to Section 8.4.6 for description of components of ocular assessment. If a participant's ocular result(s) remain abnormal at EOT visit, further testing may be requested until no longer deemed necessary in the opinion of the Investigator and Medical Monitor.
10. DEXA scheduling should allow for a 7 day washout period of CT IV and/or oral contrast agents. DEXA must be performed on the same machine for all evaluations on a particular participant. On Week 8 and every 8 weeks thereafter DEXA scan can be collected within ±1 week. DEXA scans should be performed prior to CT scans, as both examination are to be done every 8 weeks.
11. Only if EOT is >8 weeks from prior DEXA
12. GSK3326595 will be administered for 2 weeks, followed by 2 weeks off in a 4 week cycle. This SoA will be the same for alternative dosing schedules, assuming cycle is 4 weeks long. In Dose Escalation cohorts participants will receive GSK3326595 either daily or twice daily. GSK3326595 will be administered orally with water (approximately 200 mL) at approximately the same time of day (±4 hours for QD dosing and ±1 hour for BID dosing) with no food or antacids for 2h before and 1h after each dose. On serial PK day D1 participants should fast from 8 h prior to dose until 2 h after dose. On serial PK days and for two days prior participants should attempt to take GSK3326595 within a 2 hour window (i.e. 10-12 hours for BID or 23-25 hours for continuous QD dosing after the last dose).Only for Cycle 1 Day 8 visit participants should take the drug with food (within 30 minutes).(in case of BID dosing participants, both Day 8 doses must be taken with food).
13. Study drug (GSK3326595) will be dispensed every 4 weeks at the clinic. If after Week 49, the assessment frequencies are reduced to every 8 weeks, then the study drug would then be dispensed every 8 weeks
14. 5-Azacitidine should be administered according to registered label, dose frequency can be as per local standard, for seven doses per cycle starting on the days indicated. Doses may be administered on seven consecutive days or, to allow for clinic scheduling and eliminate weekend dosing, once daily for 5 consecutive days starting on day 1, with no treatment on days 6-7, and then once daily for 2 consecutive days starting on Day 8 (e.g., Monday through Friday followed by the next Monday and Tuesday)
15. At each visit, the investigator should specifically ask the participant about any changes in vision since their last visit/contact (Section 8.4.8.2). The investigator should document the response, consider if there are any reported events which meet the definition of an AE or SAEs, and intervene as clinically appropriate following discussion with the Medical Monitor if necessary.
16. PK samples for GSK3326595 and 5-Azacitidine following Day 1 and Day 8 dose will be collected at pre-dose (within 1 hour prior to dosing), 5 min±2 min, 30min±5min, 1h±5min, 2h±5min, 3h±5min, 4h±10 min, 6h±10 min, 8h± 15min, 12h±2h (to be analyzed for GSK3326595 only, for BID GSK3326595 this will be prior to evening dose

administration), 24h±2h (to be analyzed for GSK3326595 only, for BID GSK3326595 this sample will be post second dose administration). PK samples on days of subsequent visits should be collected within 1 hour Pre-dose. If 5-Azacitidine is administered on a schedule that does not include dosing on Day 8 (e.g., Monday through Sunday), then steady-state PK collection should be obtained on a day (last dosing day of cycle 1) when both 5-Azacitidine and GSK3326595 are administered (e.g., on Day 7 or on Day 9).

17. Serial PK samples for GSK3326595 and 5-Azacitidine will be collected on the last dosing day of cycle 1 for 5-Azacitidine
18. PK pre-dose sample will be analysed for GSK3326595 only (not 5-Azacitidine)
19. Plasma, serum, and whole blood samples should be collected Pre-dose on Day 1 and 4h (±0.5h) after dosing with GSK3326595 on the other days indicated. Day 8 sample collections may be performed 4h (±0.5h) after the last dose of 5-Azacitidine (Day 8 ±1 Day). Unscheduled samples for translational studies (see Section 8.7) should also be collected 4h (±0.5h) after dosing with GSK3326595
20. Plasma for cfDNA will be collected on pre-dose on Day 1 and 4 hours post dose (±0.5h), Week 5 Day 1, Week 13 Day 1 and every 12 weeks thereafter for the duration of the study.
21. Bone marrow biopsies for translational studies should be collected at screening and then 4h (±0.5h) on the days indicated, after dosing with GSK3326595. Unscheduled biopsies for translational studies (see Section 8.7) should also be collected 4h (±0.5h) after dosing with GSK3326595
22. Informed consent for optional genetics research should be obtained before collecting a sample. The sample will be collected at the first opportunity after a participant has met all eligibility requirements on Day 1 (pre- or post-dose) or later.

1.3.3. Part 2: GSK3326595 in combination with 5-Azacitidine

Table 3 Schedule of Activities, Part 2 Dose Expansion

Procedure[1]	Screening	Week 1 - Week 4				Week 5	Week 7	Week 9	Week 9 and thereafter		Week 13 and thereafter	Every 26 Weeks	End of Treatment[2]	Survival Follow-up
		Day 1	Day 8	Day 15	Day 22	Day 1	Day 1	Day 1	Every 4 Weeks[1]	Every 8 Weeks	Every 12 Weeks			
Screening														
Informed consent	X													
Inclusion/Exclusion criteria	X													
Demography	X													
Medical History	X													
Disease Characteristics	X													
Prior Therapy	X													
Register Participant	X													
Safety														
Physical Examination[3]	X	X	X	X	X	X	X		X				X	
ECOG Performance Status	X	X	X	X	X	X	X		X				X	
Vital Signs	X	X	X	X	X	X	X		X				X	
12-lead ECG[4]	X	X	X	X	X	X	X		X				X	
Pregnancy test[5]	X	X				X			X				X	
FSH/Estradiol[6]	X													
HIV, HBsAg, HCV Antibody Screening[7]	X													
Clinical Laboratory Assessments[8]	X	X	X	X	X	X	X		X				X	
Folate and selected vitamins[8]	X					X				X			X	
TSH, free T3, free T4	X					X		X		X			X	
Ophthalmic Assessment[9]	X											X	X	
DEXA Bone Densitometry[10]	X									X			X[11]	

Procedure[1]	Screening	Week 1 - Week 4				Week 5	Week 7	Week 9	Week 9 and thereafter		Week 13 and thereafter	Every 26 Weeks	End of Treatment[2]	Survival Follow-up
		Day 1	Day 8	Day 15	Day 22	Day 1	Day 1	Day 1	Every 4 Weeks[1]	Every 8 Weeks	Every 12 Weeks			
Study Intervention														
Administer GSK3326595[12]		X	X			X		X	X					
Dispense Study Drug (GSK3326595)[13]		X				X		X	X					
Administer 5-Azacitidine[14]		X	(X)[14]			X		X	X					
Vision Symptom Review[15]	X	X	X	X	X	X	X		X				X	
AE Review		←==========[Continuous from Start of Treatment to 30 days after last treatment] =========→												
SAE review	←========== [Continuous from Signing of Informed Consent to 30 days after last treatment] =========→													
Concomitant medication review	←========== [Continuous from Signing of Informed Consent to EOT Visit] ==========→													
Review Diary Card		←========== [Continuous from Day 1 to EOT Visit] ==========→												
Pharmacokinetics (PK), Pharmacodynamics (PD) & Pharmacogenomics (PGx)														
PK Plasma Samples[16]		X	X[17]	X[18]		X	X[18]	X	X					
Plasma Samples (SDMA and Circulating Biomarkers)[19]		X	X	X		X	X				X			
Plasma Sample for cfDNA[20]		X				X					X			
Whole Blood Samples (Transcriptomics)[19]		X		X		X	X				X			
Serum Sample (Translational Studies)[19]		X				X	X				X			
Bone Marrow Biopsy (SDMA and Translational Studies)[21]	X					X					X		X	
Genetic Sample (Saliva)[22]		X												
Efficacy														
Bone Marrow Biopsy	X					X					X		X	
Survival Follow-up[23]														X

1. After Week 49, the assessment frequencies will be reduced to every 8 weeks. Refer to Section 8.1 of the full protocol for visit/procedure windows
2. EOT visit to occur within 30 days from the last dose of the study treatment
3. Refer to Section 8.4.1 for components of physical examination that must be performed at each visit
4. On Day 1 and Day 8 triplicate ECGs will be obtained at or about the time of PK sample collection, as described in the SRM
5. Pregnancy testing only required for female participants of childbearing potential; see Section 5.3.1.1 for details. Must be within 7 days prior to the first dose.
6. FSH/Estradiol testing only required for perimenopausal women whose childbearing potential is questionable; see Section 5.3.1.2 for details
7. If test performed within 3 months prior to first dose of study treatment, testing at screening may not be required. Discuss with Medical Monitor if unclear
8. Refer to Appendix 2: Clinical Laboratory Tests for list of required laboratory assessments. Note that routine serum and urinalysis studies are required for all participants enrolled; additional serum and urine tests for participants with a baseline creatinine clearance < 60 ml/min/1.73 m^2 should be performed as described in Appendix 2: Clinical Laboratory Tests. Clinical labs performed during screening within 72 hours prior to first dose do not need to be repeated on Day 1. Folate and selected vitamins to be drawn at Screening, Week 5, Week 9, and every 8 weeks thereafter and at EOT. If a participant's folate or selected vitamins result(s) remain low or borderline at EOT visit, further testing may be requested until no longer deemed necessary in the opinion of the Investigator and Medical Monitor.
9. Refer to Section 8.4.6 for description of components of ocular assessment. If a participant's ocular result(s) remain abnormal at EOT visit, further testing may be requested until no longer deemed necessary in the opinion of the Investigator and Medical Monitor
10. DEXA scheduling should allow for a 7 day washout period of CT IV and /or oral contrast agents. DEXA must be performed on the same machine for all evaluations on a particular participant (see SRM).
11. Only if EOT is >8 weeks from prior DEXA
12. GSK3326595 will be administered for 2 weeks, followed by 2 weeks off in a 4 week cycle. This SoA will be the same for alternative dosing schedules, assuming cycle is 4 weeks long. In Dose Expansion cohort participants will receive Recommended Combination Dose and Regimen. GSK3326595 will be administered orally with water (approximately 200 mL) at approximately the same time of day (± 4 hours) with no food or antacids for 2h before and 1h after each dose
13. Study drug (GSK3326595) will be dispensed every 4 weeks at the clinic. If after Week 49, the assessment frequencies are reduced to every 8 weeks, then the study drug would then be dispensed every 8 weeks.
14. 5-Azacitidine should be administered according to registered label, dose frequency can be as per local standard, for seven doses per cycle starting on the days indicated. Doses may be administered on seven consecutive days or, to allow for clinic scheduling and eliminate weekend dosing, once daily for 5 consecutive days starting on day 1, with no treatment on days 6-7, and then once daily for 2 consecutive days starting on Day 8 *(*e.g., Monday through Friday followed by the next Monday and Tuesday)
15. At each visit, the investigator should specifically ask the participant about any changes in vision since their last visit/contact (Section 8.4.8.2). The investigator should document the response, consider if there are any reported events which meet the definition of an AE or SAEs, and intervene as clinically appropriate following discussion with the Medical Monitor if necessary.
16. PK samples for GSK3326595 and 5-Azacitidine following Day 1 and Day 8 dose will be collected at pre-dose (within 1 hour prior to dosing), 5 min±2 min, 30min±5min, 1h±5min, 2h±5min, 3h±5min, 4h±10 min, 6h±10 min, 8h± 15min, 12h±2h (to be analyzed for GSK3326595 only, for BID GSK3326595 this will be prior to evening dose administration), 24h±2h (to be analyzed for GSK3326595 only, for BID GSK3326595 this sample will be post second dose administration). PK samples on days of subsequent visits should be collected within 1 hour Pre-dose. If 5-Azacitidine is administered on a schedule that does not include dosing on Day 8 (e.g., Monday through Sunday), then steady-state PK collection should be obtained on a day (last dosing day of cycle 1) when both 5-Azacitidine and GSK3326595 are administered (e.g., on Day 7 or on Day 9).
17. Serial PK samples for GSK3326595 and 5-Azacitidine will be collected on the last dosing day of cycle 1 for 5-Azacitidine

18. PK pre-dose sample will be analysed for GSK3326595 only (not 5-Azacitidine)
19. Plasma, serum, and whole blood samples should be collected Pre-dose on Day 1 and 4h (± 0.5h) after dosing with GSK3326595 on the other days indicated. Day 8 sample collections may be performed 4h (± 0.5h) after the last dose of 5-Azacitidine (Day 8 ± 1 Day). Unscheduled samples for translational studies (see Section 8.7) should also be collected 4h (± 0.5h) after dosing with GSK3326595
20. Plasma for cfDNA will be collected on pre-dose on Day 1 and 4 hours (±0.5h) post-dose Week 5 Day 1, Week 13 Day 1 and every 12 weeks thereafter for the duration of the study.
21. Bone marrow biopsies for translational studies should be collected at screening and then 4h (± 0.5h) on the days indicated, after dosing with GSK3326595. Unscheduled biopsies for translational studies (see Section 8.7) should also be collected 4h (± 0.5h) after dosing with GSK3326595
22. Informed consent for optional genetics research should be obtained before collecting a sample. The sample will be collected at the first opportunity after a participant has met all eligibility requirements on Day 1 (pre- or post-dose) or later.
23. All participants will be followed for survival approximately every 6 months ± 2 weeks until the study is completed (See Section 4.5.2 for definition of Study completion)

2. INTRODUCTION

GSK3326595 is a potent, selective, reversible inhibitor of the protein arginine methyltransferase 5 (PRMT5) that is being tested as an oral treatment for human participants with cancer. Myelodysplastic syndrome (MDS) and acute myeloid leukaemia (AML) are bone marrow neoplasms for which novel, effective therapies are desperately needed. Study 208809 aims to test the safety, tolerability, and clinical activity of GSK3326595 in participants with MDS, chronic myelomonocytic leukemia (CMML) and AML. While GSK3326595 (either as a single agent or in combination with the standard of care drug 5-Azacitidine) will be the only investigational agent initially under investigation in study 208809, additional agents such as other investigational compounds or standards of care may be added at a later date. The inclusion of additional agents will require a protocol amendment.

2.1. Study Rationale

MDS and AML are clonal neoplasms of myeloid progenitors that arise within the bone marrow. They are typically manifested by peripheral cytopenias (neutropenia, anemia, and/or thrombocytopenia), hypercellularity of the bone marrow (as a consequence of ineffective hematopoiesis), molecular and/or karyotypic abnormalities, and an expansion of immature myeloid cells. It is the quantitation of these immature myeloblasts ("blasts") that, in part, differentiates AML from MDS, with a 20% blast percentage marking the transition from MDS to AML. While multiple new targeted agents have been approved to treat AML in patients harbouring a limited number of mutations, the majority of patients with both MDS and AML are not eligible for these therapies. Current therapies for most patients are inadequate: a newly diagnosed MDS patient may expect only to live for one to two years before dying of the disease, and the lifespan of someone diagnosed with AML would be even shorter, despite modern therapy. Disease that relapses after standard treatment, or which fails to respond to therapy, confers an even more dismal prognosis. The median OS for relapsed MDS is approximately six months, and there is no generally accepted standard of care for these patients. As such, new therapies to prolong survival are desperately needed.

Protein arginine methyltransferases (PRMTs) are a family of enzymes that methylate arginines in proteins involved in various cellular processes, including precursor messenger ribonucleic acid (pre-mRNA) splicing, transcription factors, kinases and histones [Karkhanis, 2011; Wang, 2008; Pal, 2007]. One family member, PRMT5, is responsible for the majority of symmetric dimethylation of arginine *in vivo*. PRMT5 is overexpressed in a number of tumors, including myeloid malignancies [Tarighat, 2016]. Inhibition of PRMT5 leads to decreased proliferation and cell death in preclinical models of AML. GSK3326595 is a potent, selective, reversible inhibitor of PRMT5 currently under investigation in solid and hematologic tumors. The first-in-human clinical study, 204653 is evaluating subjects with solid tumors and non-Hodgkin's lymphoma (NHL). In Part 1 of the dose escalation phase, the QD dose escalation population consisted of 8 cohorts (12.5 mg, 25 mg, 50 mg, 100 mg, 200 mg, 300 mg, 400 mg, and 600 mg) and the twice daily (BID) dose-escalation population consisted of 4 cohorts (50 mg, 100 mg, 150 mg, and 200 mg). The starting dose in Part 2 was 400 mg daily; however, it was

subsequently agreed to start subjects at a dose of 300 mg daily due to safety and tolerability.

Study 208809 is a Phase I/II study to evaluate the safety, tolerability, and clinical activity of GSK3326595 in participants with relapsed and refractory MDS and hypoproliferative AML that has evolved from an antecedent MDS (Part 1, "MDS cohort"). Based on the interim analysis results of 300 mg cohort, further development in monotherapy setting is discontinued. Based on unmet medical need in MDS, CMML and AML patients, the modest clinical benefit seen in monotherapy setting and preclinical data showing combination activity and increased cytotoxicity of GSK3326595 with 5-Azacitidine in AML cell lines (data not published) further development in combination setting with 5-Azacitidine will be explored in Part 2. Part 2 consists of a Dose Escalation phase where intermittent dosing schedule, two regimens of GSK3326595 will be administered in combination with 5-Azacitidine in participants with MDS, CMML or AML followed by a Dose Expansion cohort using the Recommended Combination Dose and Regimen verified within the Dose Escalation phase. While GSK3326595 (Part 1) and 5-Azacitidine in combination with GSK3326595 (Part 2) are initially the only agents to be tested in this trial, other agents may be added at a later date. The inclusion of any additional agents will require a protocol amendment prior to implementation.

2.2. Background

2.2.1. Clinical Background: MDS and AML

MDS and AML are closely related neoplastic diseases of hematopoietic myeloid progenitors. In the United States in 2017, approximately 21,000 new cases of AML (Surveillance, Epidemiology and End Results (SEER) data) and 15,000 new cases of MDS (Leukemia and Lymphoma Society ([LLS]) data) were reported; the incidence rate is similar in other developed nations including Western Europe and Australia [Deschler, 2006]. This incidence is expected to rise in coming decades due to an aging population; the majority of cases of both diseases are diagnosed in patients greater than the age of 60. While curative approach to both diseases is possible via allogeneic stem cell transplant, the reality is that most patients will not be transplant eligible due to advanced age, lack of a suitable stem cell donor, or medical comorbidity.

Patients with MDS and CMML are typically treated with a hypomethylating agent (either 5-Azacitidine or decitabine). Patients with AML who are ineligible for intensive therapy or who fail intensive therapy, may also be treated with either Azacitidine or decitabine [Almeida, 2016]. However, both agents are associated with a low ORR (15-30% in studies of MDS, per Vidaza and Dacogen package inserts). Moreover, only 5-Azacitidine improves OS in patients with high-risk MDS [Fenaux, 2009] and low-blast percentage AML [Fenaux, 2010]; while decitabine has failed to improve OS in either population [Kantjarian, 2006; Kantjarian, 2012].

For patients with MDS who fail to respond to first-line therapy, or who progress on the therapy, there are currently no approved options. Many proceed onto clinical trials, while others are treated with low-dose cytotoxic agents or with best supportive care (e.g., transfusion and growth factors). Recent data with the multi-kinase inhibitor rigosertib in

high-risk MDS patients with relapsed and refractory disease demonstrated clinical benefit (including an ORR of 27%), though this clinical response did not result in improved OS [Garcia-Manero, 2016]. Increasingly, clinical trials have been conducted to evaluate the combination of novel agents with 5-Azacitidine with some promising early results. These combinations have been pursued in the relapsed setting, as well as in the front-line setting as the sole approved agents have an underwhelming rate of response and clinical benefit [Ball, 2017]. In front line setting, Magrolimab (monoclonal antibody against CD47) in Phase 1b study (NCT03248479) showed 91% ORR and 42% Complete Response in participants with Higher-Risk MDS Treated with Magrolimab Plus Azacitidine [Sallman, 2020]. In addition, in front line setting of MDS combinations of Azacitidine are studied in Phase 3 with Venetoclax, BCL-2 Inhibitor (NCT04401748); with MBG453, anti-TIM-3 monoclonal antibody (NCT04266301); with pevonedistat, inhibitor of NEDD8-activating enzyme (NCT03268954) and with APR-246 molecule (NCT03745716). Often, these combinations are designed based on clinical considerations – utilizing an agent with some single-agent activity and evaluating it in combination with the only agent with proven efficacy, as a way of improving response rates in the front line.

While treatment of MDS is currently limited to hypomethylating agents and intensive chemotherapy, the approach towards AML has become more complicated following recent advances in understanding the genetic and genomic landscape of the disease. Recent papers have characterized recurrent mutations and analysed them as they relate to one another [The Cancer Genome Atlas Research Network (TCGA), 2013]. Additional work has attempted to cluster these mutations into a novel classification scheme driven by the presence or absence of key genetic drivers of disease [Papaemmanuil, 2016]. While a limited number of these mutations have yielded therapeutic benefit to date [Perl, 2017], it raises the possibility that agents targeting other driver pathways may result in effective therapy of myeloid diseases.

2.2.2. PRMT5 as a Target in Myeloid Neoplasms

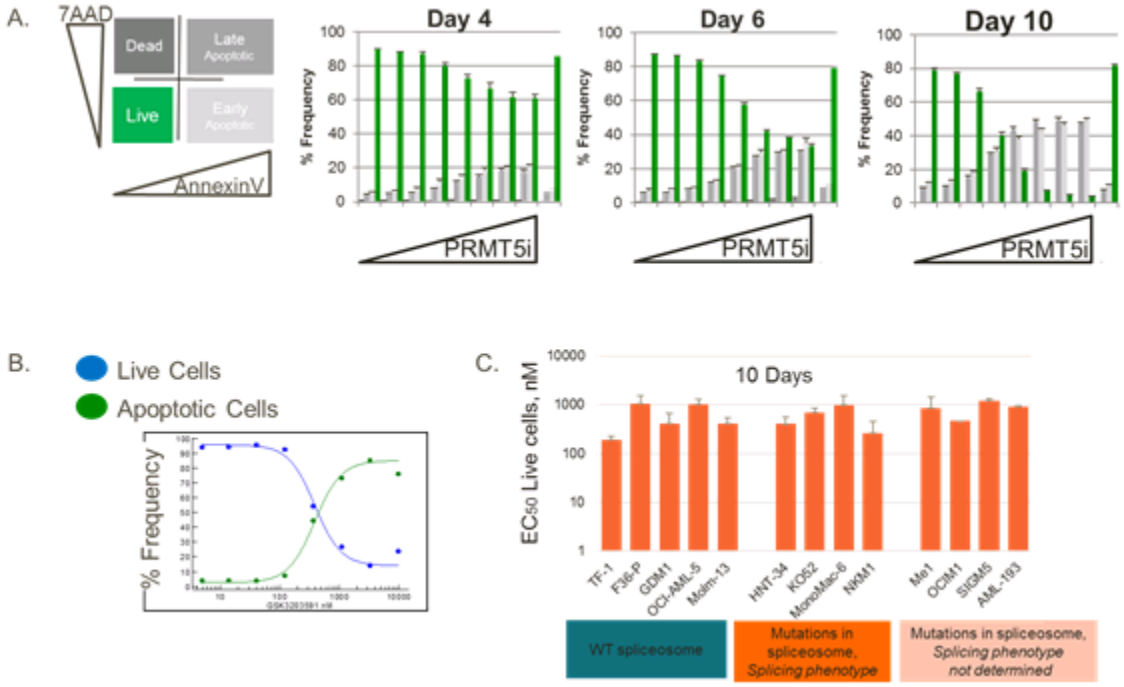
2.2.2.1. PRMT5 in MDS and AML

Due to the poor overall prognosis for patients with myeloid neoplasms, and the lack of generally accepted therapies, novel targets are under investigation. One such target is PRMT5, an enzyme that catalyzes the symmetric dimethylation of arginines in target proteins. These targets include splicing factors, transcription factors, kinases and others [Karkhanis, 2011]. PRMT5 also methylates histone arginine residues (H3R8, H2AR3 and H4R3), and these histone marks are associated with transcriptional silencing of tumor suppressor genes such as *Retinoblastoma Protein 1(RB1)* and *Suppressor of Tumorigenicity 7(ST7)* [Wang, 2008; Pal, 2007]. Additionally, symmetric dimethylation of H2AR3 has been implicated in the silencing of differentiation genes in embryonic stem cells [Tee, 2010]. PRMT5 plays a critical role in the cell-cycle and pro-apoptotic effects of p53 via two mechanisms: direct inhibition of p53 activity via methylation of arginine residues on p53 itself and degradation of p53 via differential splicing of MDM4, a p53 ubiquitin ligase [Berger, 2008; Bezzi, 2013]. Finally, PRMT5 plays a role in cellular signaling through the methylation of epithelial growth factor receptor (EGFR) and phosphoinositol-3 kinase (PI3K) [Hsu, 2011; Wei, 2012].

PRMT5 has been implicated in the pathogenesis of AML and PRMT5 inhibition leads to cell growth inhibition in several preclinical models of AML (Serio, 2017; Kaushik, 2017; Tarighat, 2016). GSK3326595 is a potent, selective, reversible inhibitor of PRMT5 currently under investigation for use in multiple oncology indications. GSK3326595 and related PRMT5 inhibitor (GSK3203591) attenuate growth and induce cell death in preclinical models of AML (Figure 1). This suggests that PRMT5 is an appropriate novel target for therapy in AML and related diseases, including MDS.

The first-in-class clinical compound, GSK3326595, is currently in the first-in-human trial 204653 in solid tumors and non-Hodgkin's lymphoma. Study 208809 is the first evaluation of safety and efficacy of GSK3326595 in myeloid neoplasms.

Figure 1 Apoptosis and cell death evident in a panel of AML cell lines after treatment with PRMT5 inhibitor (GSK3203591)

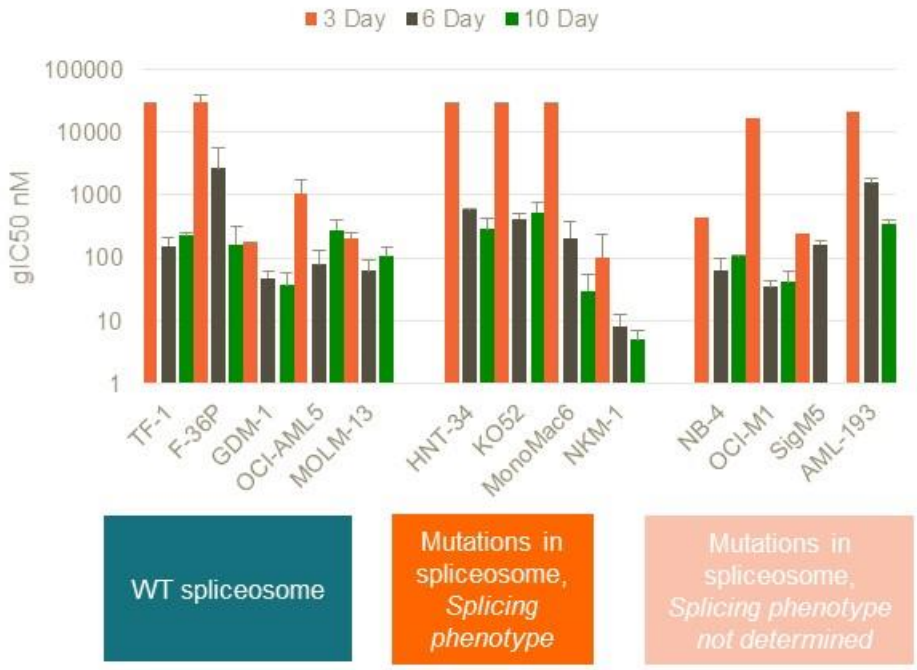


2.2.2.2. Spliceosomal Mutations and Potential Biomarkers for PRMT5 Inhibition in Myeloid Neoplasms

PRMT5 plays an important role in the splicing of messenger Ribonucleic Acid (mRNA) via methylation of proteins in the spliceosome [Prusty, 2017; Gonsalvez, 2007]. This leads to differential expression of multiple proteins, including p53, that are critical for cell growth and death and can lead to tumorigenesis if dysregulated [Bezzi, 2013]. Overall, PRMT5 is thought to be necessary for correct splicing, as conditional knockouts that are deficient for PRMT5 have selective retention of introns and skipping of exons with weak 5′ donor sites [Bezzi, 2013]. An identical splicing phenotype is observed in cancer cell lines treated with GSK3326595. Therefore, pharmacologic inhibition of PRMT5 (e.g., via GSK3326595) acts as a splicing inhibitor.

Mutations in genes (especially Splicing Factor 3B subunit 1 [SF3B1], Serine and Arginine Rich Splicing Factor 2 [SRSF2], U2 Small Nuclear RNA Auxiliary Factor 1 [U2AF1], and Zinc Finger CCCH-Type, RNA Binding Motif and Serine/Arginine Rich 2 (ZRSR2)) are relatively common in some myeloid malignancies. They are more common in MDS and CMML, where up to 60% of patient samples have been demonstrated to harbour a mutation in these genes [Dvinge, 2016]. Mutations are less commonly identified in *de novo* AML, though they still rank among the most common recurrent mutations identified [Dvinge, 2016; TCGA, 2013]. Spliceosomal mutations have been shown to confer a poor prognosis in both AML [Papaemmanuil, 2016] and MDS [Taskesen, 2014]. Intriguingly, mutations in the different genes are mutually exclusive. This has given rise to the hypothesis that cells may tolerate only a single 'hit' to the spliceosome, and therefore inhibiting mRNA splicing (e.g., via pharmacologic inhibition of the spliceosomal machinery) may confer therapeutic benefit to the subset of patients whose disease harbour underlying spliceosomal mutations. Recent work demonstrated increased sensitivity to PRMT5 inhibition in an *Srsf2*-mutant mouse AML tumor model compared to an isogenic *Srsf2*-wildtype control [Fong, 2019]. In-house preclinical studies have confirmed the sensitivity of splicing-factor mutant AML tumor models to inhibition of PRMT5. This research has shown increased growth inhibition and cell death in AML cell lines following treatment with a tool PRMT5 inhibitor GSK3203591. Interestingly, AML cell lines without splicing factor mutations were similarly sensitive, suggesting that, in addition to activity in splicing-factor mutant AML, PRMT5 activity in AML may also be more widespread (Figure 2).

Figure 2 Sensitivity of AML Cell Lines to PRMT5 Is Not Dependent on Spliceosome Mutational Status



Study 208809 will enroll participants in a mutation-agnostic fashion. Evaluation of the role of spliceosomal mutations will be performed retrospectively, and any changes in enrollment requirements will be made via protocol amendment.

2.2.3. Clinical Experience with PRMT5 inhibitors

PRMT5 inhibitors, including GSK3326595, are currently being evaluated in the treatment of both solid tumors and hematologic malignancies.

2.2.3.1. GSK3326595 - Study 204653

Phase I Study 204653 is a FTIH study in relapsed and/or refractory solid tumors and non-Hodgkin's lymphoma (NHL). In Part 1 (Dose Escalation Phase), participants have received doses up to 600 mg once daily (QD), or up to 200 mg twice daily (BID) and no maximum tolerated dose (MTD) has been established. In Part 2 of the study, disease-specific expansion cohorts are being evaluated to further explore clinical activity of GSK3326595 in participants with selected solid tumors and NHL. The starting dose in Part 2 in May 2018 was 400 mg QD; however, it was subsequently reduced to 300 mg QD after assessment of the safety and tolerability data in September 2019.

The most common adverse events observed with GSK3326595 in Study 204653 at a starting dose of 400 mg/day (seen in at least 10% of participants) were fatigue/asthenia, anemia, nausea, alopecia, dysgeusia, thrombocytopenia/decreased platelet count, decreased appetite, stomatitis, dry skin, vomiting and diarrhea. Further information can be found in the latest IB. In addition, within Study 204653, there have been two observations of optic neuropathy in participants treated with study drug over a prolonged period (>12 months exposure). Although no causal relationship has been established, in order to ensure appropriate ongoing monitoring of participants within this study, all those treated will undergo ophthalmic assessments as described in Section 8.4.6.

In addition to ophthalmic assessments, folate and selected vitamin levels will be monitored at baseline, Week 5, Week 9 and then every 8 weeks until EOT.

2.2.3.2. Other PRMT5 inhibitors

Apart from GSK3326595, four other PRMT5 inhibitors entered clinical trial development, including JNJ-64619178 (NCT03573310), PF-06939999 (NCT03854227), PRT543 (NCT03886831) and PRT 811 (NCT04089449). Top-line safety data reported from Phase I studies of JNJ-64619178 and PRT543 reveal a similar profile of adverse events (fatigue, hematologic, and gastrointestinal [GI] effects).

2.3. Benefit/Risk Assessment

A summary of single-agent toxicities of agents under investigation in this study are listed below. More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of GSK3326595 may be found in the latest Investigator's Brochure (IB) (GlaxoSmithKline Document Number 2017N314773_04). More detailed information about 5-Azacitidine may be found in the prescribing information (e.g., package insert). Section 2.3.2 outlines the risk assessment and mitigation strategy for this protocol.

2.3.1. Overlapping Toxicities (Part 2)

Based on the clinical evidence to date, participants in Part 2 receiving both GSK3326595 and 5-Azacitidine may be at increased risk of cytopenias compared to participants receiving either agent alone. Based on preclinical studies of GSK3326595 and preclinical and clinical experience with 5-Azacitidine, there is also the potential for overlapping gastrointestinal, hepatic, and reproductive toxicity. The potential for additive severity and incidence of these AEs exists. Refer to Section 7.1.2 for hepatic stopping criteria, to Section 11 for reproductive risk management guidelines, and to Appendix 12 for recommended toxicity management guidelines of GSK3326595. For toxicity management of 5- Azacitidine, refer to prescribing information.

In addition, risks and mitigation strategies related to the COVID-19 pandemic are included in Appendix 13.

2.3.2. Preclinical and Clinical Risk Assessment

Identified Risks of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
GSK3326595		
Bone marrow: hematologic/lymphoid effects	**Preclinical Effects:** Central and peripheral hematopoietic toxicity occurred in rats and dogs: Bone marrow - decreased cellularity, fibrosis (rats), asynchronous maturation and shift to immaturity with increased blasts; Peripheral - decreases in erythroid, myeloid and platelet counts; Lymphoid tissues - lymphoid depletion in thymus, gut associated lymphoid tissue (GALT), lymph nodes and spleen. Complete or ongoing recovery following cessation of dosing. **Clinical Effects:** Based on the review of safety data as of the IB update (cut off date 04 February 2020) [GlaxoSmithKline Document Number 2017N314773_04], hematologic adverse events of anemia, thrombocytopenia/ decreased platelet count and neutropenia/decreased neutrophil count have been reported across all GSK3326595 clinical trials to date. Some of these events were SAEs and led to treatment withdrawal.	ICF includes the risk of bone marrow/hematologic effects. Protocol includes exclusion criteria for recent bleeding events or uncontrolled thrombocytopenia. Protocol includes laboratory assessments (complete blood count [CBC], coagulation factors [international normalized ratio (INR), prothrombin time (PT), partial thromboplastin time (PTT)] and reticulocytes), monitoring for bruising/infection. Protocol includes dose stopping/modifications criteria for suspected Investigational Product (IP)-related hematologic toxicity.
Gastrointestinal (GI) effects	**Preclinical Effects:** Gastrointestinal toxicity was dose limiting in rats and dogs and included: decreased body weight and food consumption; emesis and abnormal stools (dogs: unformed, watery, mucoid, with red or black exudate); microscopic erosions, ulcers, hemorrhage, edema, inflammation, epithelial cell apoptosis/ degeneration/ regeneration, villous atrophy, decreased goblet cells, and crypt dilatation. Rats had epithelial hyperkeratosis/ hyperplasia of the tongue, esophagus and non-glandular stomach. These effects were reversible following discontinuation.	ICF includes the risk of gastrointestinal effects. Protocol includes medical history, physical examination (including weight) and clinical laboratory assessments to assess toxicity in the GI tract. Protocol includes specific dose adjustment/stopping safety criteria for gastrointestinal toxicity.

Identified Risks of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	Clinical Effects: Based on the review of safety data as of the IB update (cut off date 04 February 2020) [GlaxoSmithKline Document Number 2017N314773_04], GI adverse events of nausea, diarrhea, dysgeusia, vomiting and decreased appetite are among the most commonly reported treatment related adverse events in all GSK3326595 clinical trials to date.	
Fatigue/Asthenia	**Clinical data:** Based on the review of safety data as of the IB update (04 February 2020)[GlaxoSmithKline Document Number 2017N314773_04] among the 183 participants in Study 204653 of Part 2, the most frequent AE considered related to GSK3326595 was fatigue (42% of participants). Asthenia was noted in 21% of participants in Part 2. For Study 208809 of Part 1, fatigue was reported for 29% of 14 participants in 400 mg cohort and 0% of 8 participants in 300 mg cohort.	Informed Consent Form (ICF) includes the risk of fatigue/asthenia.
5-Azacitidine		
Hematologic Toxicity	5-Azacitidine causes anemia, neutropenia and thrombocytopenia.	Monitor complete blood counts frequently for response and/or toxicity, at a minimum, prior to each dosing cycle. After administration of the recommended dosage for the first cycle, adjust dosage for subsequent cycles based on nadir counts and hematologic response
Liver	Because 5-Azacitidine is potentially hepatotoxic in patients with severe pre-existing hepatic impairment, caution is needed in patients with liver disease. Patients with extensive tumor burden due to metastatic disease have been reported to experience progressive hepatic coma and death during 5-Azacitidine treatment, especially in such patients with baseline albumin <30 g/L. 5-Azacitidine is contraindicated in patients with advanced malignant hepatic tumors.	Monitor liver chemistries prior to initiation of therapy and with each cycle. Safety and effectiveness of 5-Azacitidine in patients with MDS and hepatic impairment have not been studied as these patients were excluded from the clinical trials.

Identified Risks of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Renal	Renal toxicity ranging from elevated serum creatinine to renal failure and death have been reported in patients treated with intravenous 5-Azacitidine in combination with other chemotherapeutic agents for non-MDS conditions. In addition, renal tubular acidosis, defined as a fall in serum bicarbonate to <20 mEq/L in association with an alkaline urine and hypokalemia (serum potassium <3 mEq/L) developed in 5 patients with CML treated with 5-Azacitidine and etoposide.	Monitor serum creatinine and electrolytes prior to initiation of therapy and with each cycle. If unexplained reductions in serum bicarbonate <20 mEq/L or elevations of Blood Urea Nitrogen (BUN) or serum creatinine occur, reduce or hold the dose. Patients with renal impairment may be at increased risk for renal toxicity. Also, 5-Azacitidine and its metabolites are primarily excreted by the kidney. Therefore, monitor these patients closely for toxicity. Patients with MDS and renal impairment were excluded from the clinical studies.
Tumor Lysis Syndrome	5-Azacitidine may cause fatal or serious tumor lysis syndrome, including in patients with MDS. Tumor lysis syndrome may occur despite concomitant use of allopurinol	Assess baseline risk and monitor and treat as appropriate.
Differentiation Syndrome	5-Azacitidine may cause life threatening or serious differentiation syndrome. Differentiation syndrome usually occurs within 1 to 2 weeks after starting treatment, but it can occur later. Signs and symptoms of differentiation syndrome include fever; cough; dyspnea; weight gain; edema; pericardial or pulmonary effusion; hypotension; and acute renal failure.	Assess baseline risk and monitor and treat as appropriate
Reproductive	Based on the mechanism of action and findings in animals, 5-Azacitidine can cause fetal harm when administered to a pregnant woman. 5-Azacitidine administered to pregnant rats via a single intraperitoneal (IP) dose approximating 8% of the recommended human daily dose caused fetal death and anomalies.	Advise females with reproductive potential to avoid pregnancy during treatment with 5-Azacitidine. Men should be advised to not father a child while receiving treatment with 5-Azacitidine. For male and female contraception and pregnancy guidelines, please refer to the local prescribing information for 5-Azacitidine.

Potential Risks of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
GSK3326595		
Hepatic events	**Preclinical Effects:** Hepatocellular single cell necrosis and Kupffer cell hyperplasia were present in rats but not dogs treated for 4 weeks; these changes were still present in animals held without dosing for 4-weeks after the dosing period ended. This did not correlate with transaminase activities as these values were decreased rather than increased. There was minimal to moderate centrilobular hepatocellular degeneration/necrosis in early decedent rats on the 13 week study that were generally consistent with hypoxia secondary to cardiac damage/insufficiency. There were no hepatic effects in rats at the end of the 17-week off dose period. **Clinical Effects:** Based on the overall review of hepatic events as of the latest IB update (cut-off date 04 February 2020) [GlaxoSmithKline Document Number 2017N314773_04], there is no clinical evidence of drug-induced hepatic toxicity.	ICF includes the risk of hepatic effects. Protocol includes hepatic eligibility criteria, laboratory assessments during the study, and dose stopping/modifications criteria for the management of hepatic events.
Damage to Exocrine Tissues	**Preclinical Effects:** Degeneration or apoptosis of acinar epithelial cells was present in rats treated for 4 or 13 weeks in pancreas, salivary gland, male mammary gland and/or Harderian gland. Degeneration of male mammary and Harderian glands were recovering in animals held without dosing for 4-weeks after the 4 week dosing period ended, but had fully recovered after a 17-week off dose period on the 13-week study. **Clinical Effects:** Based on the overall review of AE safety data as of the IB cut-off (4 February 2020) [GlaxoSmithKline Document	ICF includes the risk of damage to exocrine tissues. Protocol includes laboratory assessment of pancreatic enzymes.

Potential Risks of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	Number 2017N314773_04], there was no clinical evidence of drug induced pancreatic exocrine toxicity.	
Reproductive toxicity	**Preclinical Effects:** Male dogs and rats had testicular changes (degeneration of germ cells within seminiferous tubules or tubular epithelial degeneration) with associated epididymal changes (luminal cell debris and reduced luminal sperm); reversibility was observed in rats after a 17 week off dose period. Female rats had atrophy of ovaries, uterus, cervix and vagina. A single high-dose female dog had follicular atresia on the 4-week study. GSK3326595 may impact male and female fertility. In an embryofetal development study in rats, GSK3326595 was embryotoxic (increased pre- and post-implantation loss) and teratogenic (cardiac and skeletal malformations. Genotoxicity studies: in vivo rat micronucleus studies, Ames and mouse lymphoma studies (all GLP studies) were all negative. **Clinical Effects:** There have been no pregnancies reported as of the IB cut-off, 04 February 2020 [GlaxoSmithKline Document Number 2017N314773_04]. No reproductive toxicity has been reported, as of 04 February 2020.	ICF includes the risk of reproductive effects. Protocol requires pregnancy testing for women of childbearing potential. Male contraception for at least 5 half-lives plus 90 days (95 days) after the last dose of GSK3326595, as recommended by June 2015 Food and Drug Administration (FDA) draft guidance document. Female contraception for at least 5 half-lives (5 days) plus one menstrual cycle after the last dose of GSK3326595.
Bone and teeth effects	**Preclinical Effects:** Bone (rats): sternebrae and femur/tibia had intramedullary woven bone deposition and/or fibrosis, with decreased mature or lamellar bone manifested as variable loss of primary and secondary spongiosa, premature growth plate closure and marrow hematopoietic hypocellularity. These findings were reversible after a 17 week off-dose period. Similar bone changes were not observed in dogs.	Informed Consent Form (ICF) includes preclinical finding and the potential risk to humans. Protocol includes baseline and periodic dual energy x-ray absorptiometry (DEXA) for all participants on study

Potential Risks of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	Teeth (rats): pale, broken and/or missing incisors; ameloblast and odontoblast degeneration/necrosis and dental tubular degeneration. Rodent incisors grow continuously throughout their lifetime; currently only adults are included in ongoing clinical trials; potential concern for pediatric participants. **Clinical Effects:** A few participants were reported with bone adverse events (hypercalcemia, pathological fracture, osteoporosis) in Study 204653 as of the IB cut-off (04 February 2020) [GlaxoSmithKline Document Number 2017N314773_04]. and were attributable to underlying risk factors including bone metastasis (pathological fracture), advanced age and chronic renal failure. As there are insufficient data from participants previously treated or receiving ongoing GSK3326595 treatment, an association with these bone events and GSK3326595 cannot be determined. Evaluation of the non-clinical finding and any potential correlation to clinical studies continues.	
Ocular toxicity	**Preclinical data:** There have been no eye findings in rats and dogs treated up to 13 weeks. Procedures conducted include indirect ophthalmoscopy and slit lamp biomicroscopy and histologic evaluation of the eye including optic nerve. After a single dose of [14C]-GSK3326595, radioactivity (study method cannot determine parent vs. metabolite) was retained in the uveal tract of the eye in rats out to 14 days (last sampling timepoint). This is not unexpected since this indicates that drug-related material binds to melanin (radioactivity also detected in pigmented skin), a common property of many small molecule drugs.	ICF will include the risk for optic neuropathy Protocol requires the investigator to ask participants about any changes in vision at every visit and document responses. Ocular exams will be conducted at baseline and every 6 months, or sooner if a participant develops any new or evolving ophthalmic symptoms in the interval period (comprehensive ophthalmic exam with visual acuity, visual field assessment, OCT, and colour vision assessment). In addition, folate/B12 and selected vitamins level will be checked at Baseline, Week 5, Week 9 and then every 8 weeks until end of treatment (EOT).

Potential Risks of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	Clinical data: There have been reports of 2 participants in Study 204653 with optic neuropathy related to study treatment. Based on GSK's assessment of the overall data in these participants, there appears to be a link between GSK3326595 and optic neuropathy, as well as between low folate levels and the event. The events improved or fully resolved after discontinuation of GSK3326595 and with folic acid supplementation. At the present time there is insufficient evidence of a causal relationship between GSK3326595 and folate deficiency.	

2.3.3. Pharmacokinetic Risk Assessment

Currently limited information on metabolism and elimination of GSK3326595 exists. The isozymes catalyzing metabolism of GSK3326595 have not yet been identified. From *in vitro* microsome, hepatocyte data oxidation and deacetylation of GSK3326595 are the primary pathways of metabolism. Based on preclinical information of DDI potential of GSK3326595, it is not an inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6. GSK3326595 is also a potential P-glycoprotein (Pgp), MATE2-K, OAT3 and OCT2 substrate.

As per the prescribing information and product monograph of VIDAZA, the pharmacokinetics of 5-Azacitidine were studied in 6 MDS patients following a single 75 mg/m^2 intravenous (IV) dose and a single 75 mg/m^2 subcutaneous (SC) dose. 5-Azacitidine is rapidly absorbed after SC administration; the peak plasma 5-Azacitidine concentration of 750 ± 403 ng/mL occurred in 0.5 hour. The bioavailability of SC 5-Azacitidine relative to IV 5-Azacitidine is approximately 89% with mean half-life of 41± 8 minutes. Published studies indicate that urinary excretion is the primary route of elimination of 5-Azacitidine and its metabolites, with mean elimination half-life of total radioactivity (5-Azacitidine and its metabolites) of about 4 hours. Based on *in vitro* data, Azacitidine metabolism does not appear to be mediated by cytochrome P450 isoenzymes. Therefore, CYP inhibitors and inducers are unlikely to have any impact on the metabolism of 5-Azacitidine. Metabolism of 5-Azacitidine is by spontaneous hydrolysis and by deamination mediated by cytidine deaminase. Clinically significant inhibitory or inductive effects of 5-Azacitidine on cytochrome P450 enzymes are unlikely.

For participants enrolled in Part 2, the risk of a pharmacokinetic drug-drug interaction between GSK3326595 and 5-Azacitidine is low to moderate. Untested effect of 5-Azacitidine as a Pgp/BCRP/MATE2-K/OAT3/OCT2 inhibitor and unknown effects of GSK3326595 on cytosolic enzymes responsible for metabolism of 5-Azacitidine contribute to some of pharmacokinetic drug interaction risk. Therefore, Day1 and Day 8 PK sampling will be done to monitor levels of GSK3326595 and 5-Azacitidine following the start of combination therapy.

2.3.4. Benefit Assessment

Study 208809 is an open-label study and the first to explore the clinical activity of PRMT5 inhibition in myeloid malignancies. As of the clinical data cut-off date of 30 June 2020, 30 participants have been treated with GSK3326595 in Part 1 of Study 208809 (n=13 at 400 mg and n=17 at 300 mg) and there were a total of 5 participants with clinical benefit events, 2 participants in 400 mg and 3 participants in 300 mg cohort. All participants enrolled in Part 1 have disease for which no standard of care therapy is available. These individuals are generally accepted as appropriate for clinical trials.

Participants enrolled in Part 2 Dose Escalation will have either AML, MDS, CMML which has relapsed or is refractory to the standard of care, MDS or CMML that have neither responded nor progressed on 5-Azacitidine after 4 cycles, or are treatment naïve MDS, CMML. For patients with R/R disease or patients who have not responded to 5-Azacitidine after 4 cycles, there is no standard of care established. While 5-Azacitidine is established as the front-line treatment for many patients with myeloid neoplasms,

response rates with 5-Azacitidine monotherapy are low (17% CR rate, Fenaux, 2009). There are many ongoing clinical trials investigating 5-Azacitidine in combination with other agents in treatment naïve patients, aiming to improve on 5-Azacitidine monotherapy. Participants enrolled in Part 2 Dose Expansion will be treatment naïve MDS or CMML. All participants in Part 2 will receive 5-Azacitidine, an active agent that is considered the appropriate front-line therapy for newly diagnosed MDS and CMML patients in combination with GSK3326595. In Part 2, the study will assess whether both agents in combination result in enhanced efficacy compared to historical responses to 5-Azacitidine alone. Refer to Appendix 12 for a full description of the response assumptions utilized in the study.

2.3.5. Overall Benefit: Risk Conclusion

Based on available data from preclinical and clinical development, these data indicate GSK3326595 inhibits PRMT5, and that this inhibition have some clinical utility in the treatment of myeloid malignancies. Taking into account the measures taken to minimize risk to participants in this clinical trial, the potential risks identified in association with GSK3326595 are justified by the anticipated benefits that may be afforded to participants in Part 1 (monotherapy) or in Part 2 in combination with an active standard-of-care therapy (5-Azacitidine).

3. OBJECTIVES AND ENDPOINTS

Part 1	
Objectives	**Endpoints**
Primary	
• To determine the clinical activity of GSK3326595 in participants with myeloid neoplasms	• Clinical Benefit Rate (CBR), as defined as the percentage of participants achieving a complete remission (CR), complete marrow remission (mCR), partial remission (PR), stable disease (SD) lasting at least 8 weeks, or hematologic improvement (HI), per International Working Group (IWG) criteria.
Secondary	
• To determine the safety, tolerability, and recommended myeloid monotherapy dose of orally-administered GSK3326595 in participants with relapsed and/or refractory myeloid neoplasms	• Frequency and severity of adverse events • Frequency of dose limiting toxicities (DLTs)
• To further describe the clinical activity of GSK3326595 in participants with relapsed and/or refractory myeloid neoplasms	• Overall response rate (ORR), defined as the percentage of participants achieving a CR, mCR, or PR, per IWG criteria. • Progression free survival (PFS), defined as time from first dose to disease

Part 1	
Objectives	**Endpoints**
	progression, as defined by IWG criteria, or death due to any cause, whichever occurs earlier • Overall survival (OS), defined as time from first dose to death due to any cause
• To characterize the pharmacokinetics (PK) of GSK3326595 in participants with relapsed and/or refractory myeloid neoplasms	• GSK3326595 PK parameters in plasma following single- (Day 1) and repeat-dose administration of GSK3326595
Exploratory	
CCI [redacted]	

Part 2 Dose Escalation	
Objectives	**Endpoints**
Primary	
• To determine the safety, tolerability, and recommended combination dose and regimen of orally-administered GSK3326595 when administered in combination with 5-Azacitidine in participants with myeloid neoplasms	• Frequency and severity of adverse events • Frequency of DLTs • Frequency of dose interruptions, dose reductions, and treatment discontinuation due to adverse events
Secondary	
• To determine the clinical activity of GSK3326595 plus 5-Azacitidine in participants with myeloid neoplasms	• Complete Remission (CR) rate, defined as the percentage of participants achieving a CR per IWG criteria
• To describe the pharmacokinetics (PK) of GSK3326595 and 5-Azacitidine after single- and repeat-dose administration	• GSK3326595 and 5-Azacitidine PK parameters in plasma following single- (Day 1) and repeat-dose administration of GSK3326595 in combination with 5-Azacitidine.
• To further describe the clinical activity of GSK3326595 plus 5-Azacitidine in participants with myeloid neoplasms	• ORR, defined as the percentage of participants achieving a CR, mCR, or PR, per IWG criteria.
Exploratory	
CCI [redacted]	

CCI [redacted]

Part 2 Dose Expansion	
Objectives	**Endpoints**
Primary	
• To determine the clinical activity of GSK3326595 plus 5-Azacitidine in participants with high risk newly diagnosed MDS and CMML	• Complete Remission (CR) rate, defined as the percentage of participants achieving a CR per IWG criteria
Secondary	
• To determine the safety and tolerability of orally-administered GSK3326595 when administered in combination with 5-Azacitidine in participants with high risk newly diagnosed MDS and CMML	• Frequency and severity of adverse events • Frequency of dose interruptions, dose reductions, and treatment discontinuation due to adverse events
• To describe the pharmacokinetics of GSK3326595 and 5-Azacitidine after single- and repeat-dose administration	• GSK3326595 and 5-Azacitidine PK parameters in plasma following single- (Day 1) and repeat-dose administration of GSK3326595 in combination with 5-Azacitidine.
• To further describe the clinical activity of GSK3326595 plus 5-Azacitidine in participants with high risk newly diagnosed MDS and CMML	• ORR, defined as the percentage of participants achieving a CR, mCR, or PR, per IWG criteria.
Exploratory	

CCI [redacted]

CCI

4. STUDY DESIGN

4.1. Overall Design

Study 208809 is an open-label, multicentre, multi-part study of GSK3326595 as monotherapy and in combination with 5-Azacitidine in participants with myeloid malignancies. Refer to Figure 3 for the overall study schematic.

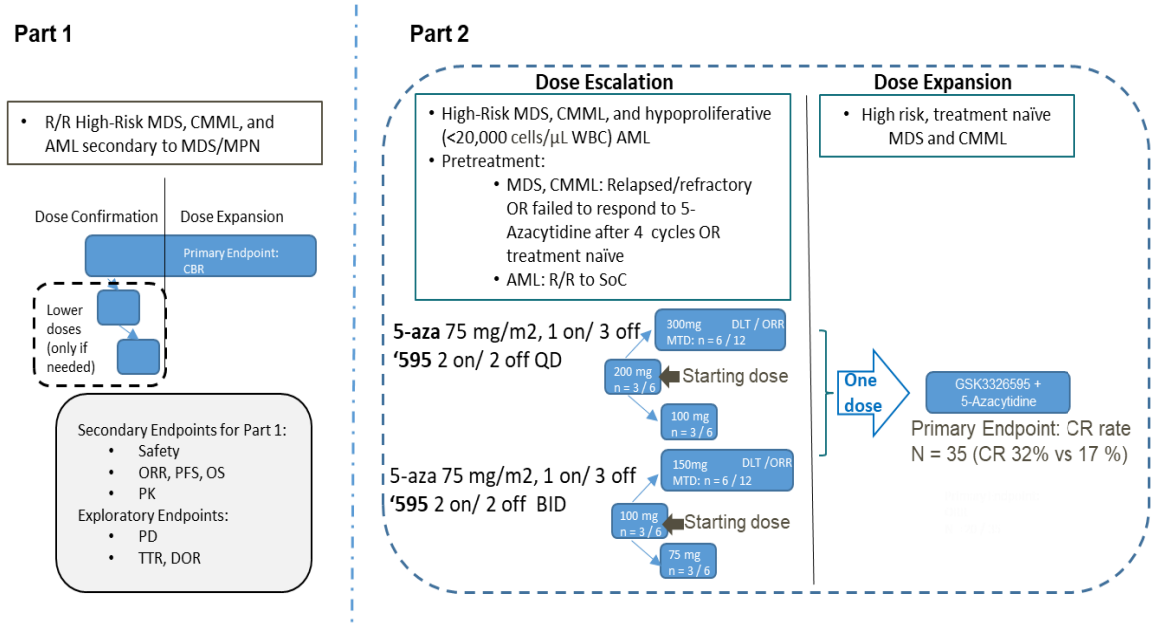
Additional agent(s) may be added, either as single agent or in combination, to any of the Parts of this study based on emerging clinical and preclinical data. A protocol amendment will be required to include the additional agents to be used in this study.

Part 1 (Section 4.1.1) is composed of a safety evaluation, followed by a single-arm dose expansion cohort to determine the CBR of GSK3326595 in participants relapsed and/or refractory MDS, CMML, and hypoproliferative AML that has evolved from an antecedent MDS. Part 2 is composed of two dose escalation cohorts of intermittent dosing of GSK3326595 (**Regimen 1**: 2 weeks on and 2 weeks off QD and Regimen 2: 2 weeks on and 2 weeks off BID) in combination with 5-Azacitidine followed by a single-arm dose expansion cohort to determine the CR rate of the combination of GSK3326595 plus 5-Azacitidine in high risk newly diagnosed MDS or CMML.

Participants may continue treatment in the study until disease progression, unacceptable toxicity, withdrawal of consent, or termination of the study by the sponsor (Section 7). Participants who continue to receive benefit upon termination of a cohort (e.g., for futility) may continue to remain on study provided that stopping criteria in Section 7 are not met.

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

Figure 3 Study Schematic



4.1.1. Part 1: Single Agent Activity in Relapsed/Refractory MDS and Hypoproliferative AML

The primary objective of Part 1 is to assess the clinical activity of GSK3326595 when administered as a single agent in participants with relapsed and/or refractory MDS (and related disorders) and hypoproliferative AML that has evolved from an antecedent MDS. Part 1 will consist of an abbreviated safety assessment to confirm a Recommended Myeloid Monotherapy Dose, followed by a single-arm dose expansion cohort to evaluate efficacy in this disease population. As described in Section 4.1.1.1.2, dosing will start at the solid tumor Part 2 Dose, as determined in Study 204653 (400 mg daily dose). Six participants will initially be enrolled, and the dose may be modified based on emerging toxicity in the myeloid population (in which case, additional participants will be enrolled at a different dose or schedule). Once the recommended dose for myeloid malignancies is determined, additional participants (for a total of up to 35 participants treated at the Recommended Myeloid Monotherapy Dose) will be enrolled to assess the clinical activity of GSK3326595 in relapsed and/or refractory MDS and hypoproliferative AML that has evolved from an antecedent MDS (please refer to Section 5 for definitions of the study population). Overall, up to 41 participants will be enrolled in Part 1: up to 12 participants during dose confirmation, and approximately 29 participants in dose expansion. If 6 participants will be enrolled during dose confirmation and treated at the Recommended Myeloid Monotherapy Dose, only 29 additional participants need be enrolled in expansion cohort for a total of 35 participants to be treated at the Recommended Myeloid Monotherapy Dose.

4.1.1.1. Part 1 Dose Confirmation

Part 1 will incorporate a safety run-in cohort in order to confirm that the solid tumor Part 2 Dose, as identified in study 204653 (400 mg QD), does not confer unacceptable toxicity in a population of participants with myeloid malignancies. The Neuenschwander

continual reassessment method (N-CRM) [Neuenschwander, 2009] will be utilized to guide dose escalation/de-escalation decisions, based on the rate of dose-limiting toxicities (DLTs) observed in participants. The dose of 300 mg QD was the starting dose for the dose expansion cohort due to tolerability issues (primarily fatigue) observed with the 400 mg dose in the dose confirmation cohort and in 204653 study.

4.1.1.1.1. Type and number of participants

It is estimated that at least 6 and up to 12 participants will be enrolled into Part 1 Dose Confirmation. The study population will be adults with a diagnosis of relapsed or refractory MDS, CMML, and hypoproliferative AML as described in Section 5.

If a participants fails to receive at least 75% of the planned doses within the 28-day DLT observation period for reasons other than toxicity (e.g., concurrent illness or disease progression), the participant will be replaced by additional participant(s) assigned to the same dose level.

4.1.1.1.2. Starting dose, planned dose levels, and alternative dosing schedules

The starting dose for Part 1 will be the dose and schedule identified as the solid tumor Part 2 Dose in the FTIH Study 204653. At the time of publication of the 208809 original protocol, this dose and schedule is 400 mg QD. No dose escalation is planned beyond this dose, unless emerging data (e.g., PK or PD data) indicate that a higher dose is appropriate for participants with myeloid malignancies.

In the possibility that the solid tumor Part 2 Dose is modified prior to initiation of the 208809 study, then the starting dose for 208809 may be modified without requiring protocol amendment. In this case, documentation (e.g., Note To File) will be provided detailing the change in dose, including the data and rationale for the dosing modification. The change will subsequently be reflected in the next scheduled 208809 protocol amendment. The solid tumor Part 2 dose was modified to 300 mg QD due to safety and tolerability during enrollment into Part 2 of Study 204653. Similarly in Study 208809 the starting dose was amended from 400 mg to 300 mg due to safety and tolerability issues.

If participant-to-participant dose modification is required (e.g. for emerging toxicity in the 208809 study) in Part 1 of the protocol, the following dose levels will be utilized: Note that if the starting dose is altered, a modified version of Table 4 will be provided for reference in the documentation provided.

Table 4 Pre-planned dose levels

DL+2	800 mg QD
DL+1	600 mg QD
DL0	400 mg QD
DL-1	300 mg QD
DL-2	200 mg QD

Alterations to the dosing schedule (including incorporation of intermittent dosing [e.g., 3 weeks on, 1 week off]) may be made to the schedule of administration based on the results of emerging PK and safety data. Any changes to the dosing schedule may be made only after review of all available data by the study team and investigators as described in the Dose Escalation Plan (Section 4.1.1.1.5), and clearance by the GSK medical monitor and an amendment submitted as required by national regulations. Any planned changes will apply to a cohort of participants and not an individual participant. Changes will be communicated to the site in writing along with justification and data supporting the change.

4.1.1.1.3. Dose confirmation

Approximately six participants will initially be enrolled at the dose described in Section 4.1.1.1.2. In the absence of DLTs, the dose escalation rules are deterministic. If DLTs are observed, an N-CRM model will be implemented to guide dose escalation/de-escalation decisions. A 28-day dose limiting toxicity window will be utilized as described in Section 4.1.1.1.4. Cohorts will be recruited in blocks of approximately three participants. The maximum number of participants assigned to any single dose will be at the discretion of the Sponsor in consultation with the investigators.

N-CRM is a Bayesian model-based adaptive dose finding approach. The design classifies the posterior distributions of probability DLT into four categories and makes dose recommendations:

- Under-dosing: DLT rate<16%
- Target toxicity: 16%<=DLT rate<33%
- Excessive toxicity: 33%<=DLT rate<60%
- Unacceptable toxicity: DLT rate>=60%

At the end of the DLT observation period for each dose level, the posterior distribution of DLT rate will be summarized by the posterior probability of the DLT rate falling into the interval of under-dosing, target toxicity, excessive toxicity, and unacceptable toxicity respectively. If the probability of excessive or unacceptable toxicity is more than 25%, a dose de-escalation will be required. Planned dose levels for escalation/de-escalation are described in Section 4.1.1.1.2.

4.1.1.1.4. Dose limiting toxicities

An event is considered to be a dose-limiting toxicity (DLT) if the event occurs within the first 28 days of treatment and meets the criteria listed in Table 5, unless it can be clearly established that the event is unrelated to treatment.

Table 5 Dose-Limiting Toxicity Criteria

Toxicity	DLT Definition
Non-hematologic	• Hepatic toxicity that meets Liver Stopping Criteria as defined in Section 7.1.2. • Grade 3 nausea, vomiting or diarrhea that does not improve within 72h despite appropriate supportive treatment(s) • Grade 4 or greater nausea, vomiting, or diarrhea of any duration • Any other Grade 3 or greater clinically significant non-hematologic toxicity[a]
Hematologic	• Grade 4 or greater treatment-emergent neutropenia, anemia, or thrombocytopenia, lasting for ≥14 days in the absence of IP, that cannot be attributed to underlying disease
Other	• Inability to receive all seven planned doses of 5-Azacitidine (in Part 2) as well as at least 75% of the planned doses of GSK3326595 (Part 1 and Part 2) within the 28-day DLT observation period due to toxicity • Dose interruption, starting at any time in the DLT observation period, due to toxicity[b], that lasts 7 days or prolongs scheduled interruption for 7 days or greater • Grade 2 or higher toxicity that occurs beyond 28 days which in the judgment of the investigator and GlaxoSmithKline (GSK) Medical Monitor is considered to be a DLT

Toxicity Grading based on National Cancer Institute – Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4

a. Except electrolyte imbalance or other laboratory abnormalities controlled without sequelae within 24h. Discuss with Medical Monitor if there is a question regarding "clinically significant"
b. Participants with prolonged dose interruption for reasons other than toxicity (e.g., acute illness, disease progression) will not be evaluable for DLT purposes and will be replaced in the cohort.

4.1.1.1.5. Dose escalation decisions

The GSK medical monitor, in joint discussion with the participating investigators, will be responsible for determining whether dose escalation or de-escalation during Part 1 should continue as recommended by the N-CRM approach. Prior to the dose escalation/de-escalation decision, the medical monitor, clinical scientist, safety physician, clinical pharmacologist, statistician and investigators will review critical safety data defined in the Dose Escalation Plan, including data on all adverse events including non-DLT toxicities, laboratory assessments and other safety evaluations, as well as any available PK and/or PD data. The quality review of critical safety data will be described in the Dose Escalation Plan, which includes ongoing study monitoring visits along with data review of the clinical database.

The dose-escalation/de-escalation decision and rationale for each cohort will be discussed with investigators during teleconference(s) and documented in writing with copies maintained at each study site and in the master study files at GlaxoSmithKline (GSK).

4.1.1.1.6. Intra-participant dose escalation

If the dose is escalated beyond the solid tumor Part 2 Dose, defined in study 204653, intra-participant dose escalations may be considered on a case-by-case basis, provided that the participant has completed the DLT observation period, that all participants at the

next higher dose level have completed the DLT observation period, and that prior approval has been obtained from the GSK Medical Monitor. Participants may be dose-escalated to the highest cleared dose. Individual participants may dose-escalate multiple times provided that the above criteria are met at each intra-participant dose escalation step.

Safety assessments from these participants will be included in the determination of the Recommended Myeloid Monotherapy Dose.

Participants approved for intra-participant dose escalation may require additional PK sampling on Day 15 at the higher dose, as specified in the SRM. Additional safety assessments may be specified at the time of dose escalation or schedule modification based on the safety profile in previous participants at the higher dose level. Intra-participant dose escalations or schedule modification will be discussed with investigators and approved by the GSK Medical Monitor and safety monitoring required will be specified in writing.

4.1.1.1.7. Identification of the recommended myeloid monotherapy dose

The Recommended Myeloid Monotherapy Dose will be confirmed only if the posterior probability of excessive or unacceptable toxicity is no more than 25%. The excessive or unacceptable toxicity is defined as DLT rate exceeding 33%.

Participants treated in dose confirmation cohort(s) at the Recommended Myeloid Monotherapy Dose will be included in the dose expansion cohort analysis.

4.1.1.2. Part 1 Dose Expansion: Clinical Efficacy in Relapsed/Refractory MDS and Hypoproliferative AML

Once the Recommended Myeloid Monotherapy Dose is identified, additional participants will be enrolled in a single-arm cohort (Part 1 Dose Expansion) at the Recommended Myeloid Monotherapy Dose to better characterize the clinical activity (as well as safety, PK, and PD profile) of GSK3326595 in relapsed and/or refractory MDS (and related diseases). Plasma samples for PK evaluation will be collected in all participants. PD and translational samples from blood and from bone marrow will be collected pre- and on-study drug treatment at timepoints as defined in the SoA. The primary endpoint will be CBR, defined as the percentage of participants with CR, PR, complete marrow response, SD lasting at least 8 weeks, or HI, per IWG criteria (Appendix 9: IWG Criteria for Response for Participants in Part 1 and Part 2).

4.1.1.2.1. Type and number of participants

In Part 1 Dose Expansion, the cohort may be composed of up to 35 participants with MDS, CMML or hypoproliferative AML that failed to respond to standard therapy, or that progressed after responding to standard therapy, as described in Section 5. The total number of participants enrolled in the expansion cohort will be smaller than 35, as participants enrolled in the dose confirmation cohort and treated at the Recommended Myeloid Monotherapy Dose will be included in dose expansion cohort analysis. If 6 participants are enrolled during dose confirmation and treated at the Recommended

Myeloid Monotherapy Dose, only 29 additional participants need be enrolled in expansion cohort for a total of 35 participants to be treated at the Recommended Myeloid Monotherapy Dose. Refer to Section 9.1.1 for the statistical rationale for the number of participants to be enrolled.

In Part 1 Dose Expansion, participants will not be replaced if they prematurely discontinue study intervention or withdraw from study.

4.1.1.3. Treatment Arms and Duration

All participants in Part 1 Dose Expansion will receive GSK3326595 as a single agent until progression, unacceptable toxicity, or withdrawal of consent.

4.1.1.4. Dose Selection

Participants will start dosing on Day 1 with the dose and schedule selected in Part 1 Dose Confirmation.

4.1.1.5. Statistical Design

Part 1 Dose Expansion will employ a Bayesian design that allows the trial to be monitored with the constraint of both Type I and Type II error rates. Clinical response will be assessed by bone marrow biopsy and defined per IWG criteria (see Appendix 9: IWG Criteria for Response for Participants in Part 1 and Part 2). The evaluation is designed to exclude a 30% CBR representing best available therapy in favour of a 50% CBR. The rational for the historical control assumption is provided in Appendix 12: Rationale for Response Assumptions. The first interim futility analysis will be conducted after a minimum of 8 evaluable participants have completed at least two post-baseline efficacy assessments, have progressed or died, or have permanently discontinued from study intervention. The subsequent interim futility analysis will be performed every 2-3 months depending on enrollment with minimum additional 5 evaluable participants. The decision rules, specifying the number of participants with a clinical response needed for continuing enrolment or, stopping for futility, are indicated in Table 6. The methodology is based on the predictive probability of success if enrolment continues to 35 [Lee, 2008].

Table 6 Part 1 Expansion Cohort Stopping Criteria for Futility

Number of Evaluable Participants	≤ This Number of CR, mCR, PR, SD ≥8 weeks or HI to Stop Early for Futility	Probability of continuing enrolling when Clinical Benefit Rate (CBR)=0.3	Probability of continuing enrolling when CBR=0.5
8	0	0.9424	0.9961
9	1	0.8040	0.9805
10	1	0.8040	0.9805
11	1	0.8040	0.9805
12	1	0.8040	0.9805
13	2	0.7399	0.9761
14	2	0.7399	0.9761
15	3	0.6547	0.9691
16	3	0.6547	0.9691
17	3	0.6547	0.9691
18	4	0.5924	0.9648
19	4	0.5924	0.9648
20	5	0.5202	0.9588
21	5	0.5202	0.9588
22	5	0.5202	0.9588
23	6	0.4702	0.9553
24	6	0.4702	0.9553
25	7	0.4134	0.9505
26	7	0.4134	0.9505
27	8	0.3578	0.9450
28	8	0.3578	0.9450
29	9	0.3064	0.9389
30	10	0.2407	0.9259
31	10	0.2407	0.9259
32	11	0.1968	0.9156
33	12	0.1468	0.8960
34	13	0.1035	0.8677
35	14	0	0

These rules are intended as a guideline. Actual decisions will depend on the totality of the data. The decision to terminate the cohort will not depend solely on the results of the statistical model but will take all factors into account, including the results of the model, safety, tolerability, PK, and PD data. In some cases (e.g., under-representation of a given predictive biomarker in the participants treated at the time of interim analysis), additional participants may be enrolled even if the model suggests a low likelihood of activity.

4.1.2. Decision Whether to Proceed to Part 2

A formal interim futility data analysis was performed with data cut off 30th June 2020 for participants who have undergone at least two post-baseline disease assessments, have progressed or died, or permanently discontinued from study intervention. As of data cut

off 30th June 2020, 30 participants have been enrolled to Part 1, 13 participants at 400 mg dose and 17 participants cohort at 300 mg dose. As per Protocol, the design recommends to stop early for futility if number of clinical benefit events is ≤ 3 out of 17 participants in the dose expansion cohort. Based on the interim analysis results reported of 300 mg cohort with data cut off 30th June 2020 further development in monotherapy setting is discontinued. Irrespective of the outcome of this analysis, any Part 1 participants still receiving therapy with GSK3326595 may continue receiving study drug until progression, death, withdrawal of consent, unacceptable toxicity, or termination of the study by the Sponsor, as described in Section 7.1. Clinic visits and efficacy analysis should continue as described in the SoA.

The decision to discontinue monotherapy development in myeloid malignancies is based on an evaluation of the efficacy (defined by the design in Table 6), and totality of safety, tolerability, PK, and PD data (including data from participants who prematurely discontinue therapy). The criteria to progress with monotherapy development required demonstrating single-agent efficacy in Part 1, during which both of the following criteria must have been met:

- GSK3326595 can be safely and tolerably administered to the study population at a dose expected to achieve therapeutic concentrations, **and**
- GSK3326595 demonstrated preliminary clinical activity based on clinical benefit rate, as defined by the design in Table 6.

4.1.3. Part 2: Further Exploration of Efficacy in Myeloid Neoplasms

Part 2 will be opened to

- determine a safe and tolerable combination dose and regimen of GSK3326595 in combination with standard-of-care therapy, 5-Azacitidine, in patients with myeloid neoplasms (Part 2 Dose Escalation phase); and
- to explore the clinical efficacy of the combination of GSK3326595 in combination with 5-Azacitidine, in treatment-naïve patients with MDS or CMML (Part 2 Dose Expansion phase)

4.1.3.1. Part 2: 5-Azacitidine plus GSK3326595

Part 2 will consist of two dose escalation cohorts with intermittent dosing (such as Regimen 1: 2 weeks on, 2 week off QD and Regimen 2: 2 weeks on, 2 weeks off BID) to select a safe and tolerable GSK3326595 dose and regimen in combination with 5-Azacitidine (the Recommended Combination Dose and Regimen). Dosing of GSK3326595 will start at 200 mg QD in cohort 1 and 100 mg BID in cohort 2 and escalate up to the Recommended Myeloid Combination Dose. Once the Recommended Combination Dose and Regimen is determined, additional participants (for a total of up to 35) will be enrolled to assess the clinical activity of GSK3326595 plus 5-Azacitidine in newly-diagnosed MDS and CMML participants. Overall, approximately 83 participants will be enrolled in Part 2: approximately 24 participants in each dose escalation cohort and up to 35 participants in Dose Expansion cohort.

4.1.3.1.1. Part 2 Dose Escalation

Part 2 will incorporate two dose escalation cohorts with intermittent dosing in order to select a safe and tolerable dose and regimen of GSK3326595 when administered in combination with 5-Azacitidine. An N-CRM model will be utilized to guide dose escalation decisions, based on the rate of dose-limiting toxicities (DLTs) observed in participants. The final dose and regimen for evaluation of efficacy will be decided based on all available data, including safety, tolerability, PK, PD, and efficacy.

Type and number of participants

It is estimated that approximately 48 participants will be enrolled into Part 2 Dose Escalation. The study population will be adults with a diagnosis of myeloid neoplasms as described in Section 5.

In order to be eligible for DLT determination, a participant must meet one of the following three criteria:

- Have received all seven planned doses of 5-Azacitidine as well as at least 75% of the planned doses of GSK3326595 within the 28-day DLT observation period, or
- Have received less than this minimum dose requirement due to toxicity in which case DLT should be recorded, or
- Have received less than this minimum dose requirement for reasons other than toxicity but already experienced a DLT

Any participant who does not meet this minimum dose requirement for reasons other than toxicity (e.g., concurrent illness or disease progression) will be replaced by additional participant(s) assigned to the same dose level.

Starting dose, planned dose levels, and alternative dosing schedules

Dose escalation will commence with the approved dose of 5-Azacitidine (75 mg/m^2 dose for seven days in a 28-day cycle, as detailed in the registered label in combination with GSK3326595 administered, at a starting dose of 200 mg QD (Regimen 1, cohort 1) and 100 mg BID (Regimen 2, cohort 1) at schedule of 2 weeks on, 2 weeks off.

Dosing will then escalate or de-escalate, using the dosing steps shown in Table 7. The dose of GSK3326595 administered in combination with 5-Azacitidine will not exceed the Recommended Myeloid Monotherapy Dose unless emerging data suggest that a therapeutic dose in combination requires a higher daily dose of GSK3326595 (e.g., if exposure is decreased due to drug-drug interaction). The 5-Azacitidine regimen will not be altered beyond the approved dose and schedule.

Table 7 Dose Escalation/De-escalation Dosing Steps in Part 2

Dose levels	QD dosing	BID dosing
D+1	300 mg	150 mg
D0	200 mg	100 mg
D-1	100 mg	75 mg

If a dose reduction is warranted for a specific participant, participants may have two dose reductions as follows: a) For the QD regimen dose reductions will happen by 100 mg increments down to a dose 100 mg QD and by 25 mg increments down to a dose of 50 mg for participants reducing below 100 mg QD. b) For the BID regimen, dose reductions will happen by 25 mg increments down to a dose level of 25 mg BID. Any further dose reductions (greater than two) will need to be discussed with the GSK medical monitor.

Based on relative bioavailability substudy in study 204653, comparable plasma exposures of GSK3326595 were observed between tablets and capsules. As a result, participants can be administered either tablets/capsules in Part 2. Alterations to the GSK3326595 dosing schedule (including intermittent dosing [e.g., 3 weeks on, 1 week off]) may be made to the schedule of administration based on the results of emerging PK and safety data. Any changes to the dosing schedule may be made only after review of all available data by the Study team and Investigators as described in the Dose Escalation Plan and clearance by the GSK medical monitor and an amendment submitted as required by national regulations. Any planned changes will apply to a cohort of participants and not an individual participant. Changes will be communicated to the site in writing along with justification and data supporting the change.

Dose Escalation, Dose-Limiting Toxicities, and the Determination of the Recommended Combination Dose

Participants will be enrolled in cohorts of approximately 3, starting at the dose level described in Section 4.1.3.1, using the dosing steps described in Section 4.1.3.1.1. Dose escalation will use the N-CRM method described in Section 4.1.1.1.3. Part 2 Dose Escalation will use the same DLT criteria described in Section 4.1.1.1.4. Dose escalation decisions will all be made as described in Section 4.1.1.1.5. Recommended Combination Dose will be the dose that maximizes the posterior probability of target toxicity interval as defined in Section 4.1.1.1.3 while controlling the posterior probability of excessive or unacceptable toxicity no more than 25%, or a lower dose that provides adequate PK exposure and biologic/clinical activity with superior tolerability. The Recommended Combination Dose and Regimen selection will be based on safety and tolerability and available PK and PD data.

4.1.3.1.2. Part 2, Dose Expansion: Clinical Efficacy in Newly Diagnosed MDS and CMML

Once the Recommended Combination Dose and Regimen is identified, additional participants will be enrolled in a single-arm, open-label, single cohort (Part 2 Dose Expansion) in order to better characterize the clinical activity (as well as safety, PK, and PD profile) of GSK3326595 in combination with 5-Azacitidine in newly diagnosed MDS and CMML participants. Plasma samples for PK evaluation will be collected in all participants. PD samples from plasma and from bone marrow will be collected pre- and on-study drug treatment at timepoints as defined in the SoA (Part 2 Dose Expansion). The primary endpoint will be CR rate, defined as the percentage of participants with CR per IWG criteria.

Type and Number of Participants

In Part 2 Dose Expansion, the cohort will be composed of approximately 35 participants with newly diagnosed MDS and CMML, as described in Section 5.1. Participants will not be replaced if they prematurely discontinue study intervention or withdraw from study.

Treatment Arms and Duration

All participants in Part 2 Dose Expansion will receive GSK3326595 plus 5-Azacitidine until progression, unacceptable toxicity, withdrawal of consent, or termination of the study by the Sponsor, as described in Section 7.

Dose Selection

Participants will start dosing on Day 1 with the dose and schedule selected as the Recommended Combination Dose and Regimen in Part 2 Dose Escalation (Section 4.1.3.1.1).

Statistical Design

A Bayesian approach has been designed to set up the decision-making framework for the study and is detailed in Section 9.1.2 including the operating characteristics of the overall trial design. The rational for the historical control assumption from 17% and the meaningful improvement to 32% is provided in Appendix 12. The first interim futility analysis will be conducted after 8 evaluable participants have had at least two post-baseline efficacy assessments, have progressed or died, or have permanently discontinued from study intervention. The subsequent interim futility analysis will be performed every additional 9 evaluable participants. The decision rules, specifying the number of participants with a complete remissions needed for continuing enrolment or, stopping for futility, are displayed in Table 8. For example, if in the first 17 participants there is one or fewer complete remissions observed, the study can be stopped for futility. The interim analysis will be for futility only, i.e., the Dose Expansion cohort will not stop early for efficacy. All evaluable population will be used for the interim futility analyses.

Table 8 Part 2 Expansion Cohort Stopping Criteria for Futility

Number of Evaluable Participants	≤This Number of Confirmed Complete Remissions to Stop Early for Futility	Probability of Continuing Enrolling When CR Rate=0.17	Probability of Continuing Enrolling When CR Rate=0.32
8	0	0.7753	0.9546
17	1	0.7059	0.9496
26	3	0.5733	0.9417
35	7	0.2151	0.8803

These rules are intended as a guideline. The decision to terminate the cohort will not depend solely on the Bayesian predictive probability of study failure but will take into account, safety, tolerability, available PK and PD data.

4.2. Number of Participants

It is estimated that a maximum of 113 participants will be enrolled in the study, divided as follows: 30 participants were enrolled in Part 1, 24 participants in each of the Part 2 Dose Escalation Cohorts and approximately 35 in Part 2 Dose Expansion. Further details of the type and number of participants are available in Section 4.1.1.1.1, Section 4.1.1.2.1, Section 4.1.3.1.1, Section 4.1.3.1, and Section 4.1.3.1.2.

4.3. Scientific Rationale for Study Design

Given the unmet medical need of myeloid malignancies, a Phase I/II study (208809) is proposed. The study comprises multiple Parts to efficiently evaluate the safety and efficacy of GSK3326595) in relapsed/refractory MDS, CMML and AML, and GSK3326595 and 5-Azacitidine in myeloid neoplasms as described in Section 5.

4.3.1. Part 1

Part 1 is a dose escalation/expansion study in participants with relapsed/refractory MDS (and low-grade AML that has evolved from an antecedent MDS) to determine the recommended myeloid monotherapy dose, as well as whether to proceed with monotherapy development. Decisions will be based on both efficacy as well as safety.

Efficacy will be monitored via interim analyses. A Bayesian design that allows the trial to be frequently monitored with the constraint of both Type I and Type II error rates will be used. Clinical response will be defined as CBR, per standard evaluation criteria (see Appendix 12 for definitions of response assessments and criteria). The design is based on a historical CBR of 30% versus a clinically meaningful CBR of 50%; the rationales for these response assumptions are described in Appendix 12.

Dose escalation/de-escalation decisions will be based primarily on the N-CRM, a well-validated method for identifying the maximum tolerated dose (MTD) of oncology therapeutics. Dose re-escalation after a de-escalation step may be permitted based on the results of the N-CRM model.

4.3.2. Part 2

Part 2 consists of a dose escalation and dose expansion cohorts in participants with myeloid neoplasms (See Section 5) treated with GSK3326595 in combination with 5-Azacitidine. The dose escalation part has been designed in order to explore a number of doses, intermittent schedule (2 weeks on, 2 weeks off) and regimens of GSK3326595 to determine the Recommended Combination dose and regimen. The Part 2 Dose Expansion cohort will explore clinical activity in newly diagnosed MDS or CMML.

5-Azacitidine was chosen as a combination partner as it is a widely-used epigenetic agent that demonstrates an OS benefit in first-line high-risk MDS (Fenaux, 2009). It is generally well-tolerated, with an acceptable incidence primarily of gastrointestinal and hematologic adverse events and can be administered to patients who would not otherwise be fit for intensive cytotoxic chemotherapy.

In Part 2, decisions will be based on both efficacy as well as safety. Safety and efficacy will be monitored as discussed in Section 4.3.1.

4.4. Justification for Dose

GSK3326595 has been previously administered to participants with myeloid malignancies and solid tumors, and GSK3326595 and 5-Azacitidine have not been previously administered in combination in any tumor type. 5-Azacitidine is currently approved as a single agent for use in MDS and CMML.

4.4.1. Starting Doses

4.4.1.1. GSK3326595

A Phase I study (204653) with GSK3326595 (as a single agent) is currently underway in participants with advanced solid tumors and non-Hodgkin's lymphoma. Doses of 12.5 to 600 mg once daily (QD) and doses of 50 mg to 200 mg BID have been evaluated. Based on safety, tolerability, PK, PD, and efficacy data, 400 mg QD was selected as the solid tumor Part 2 Dose, however, it was subsequently agreed to start participants at a dose of 300 mg daily due to safety and tolerability. Refer to Section 2.3.2 for a summary of key preclinical and clinical risks, as well as to the latest GSK3326595 Investigator's Brochure (GlaxoSmithKline Document Number 2017N314773_04) for full details of the clinical experience to date with GSK3326595.

The doses explored in Part 1 of this study were 400 mg and 300 mg.

Starting dose for the Part 2 combination with 5-Azacitidine has been lowered to 2 dose levels below 300 mg QD to manage overlapping toxicity with 5-Azacitidine, 100 mg QD continuous which is equivalent to 200 mg QD 2 weeks on/2 week off (same total dose of drug over a 4-week cycle). The equivalent dose for the BID regiment would be 100 mg BID 2 weeks on/ 2 week off.

The maximum QD dose that will be investigated in combination with 5-Azacitidine is 300 mg and for BID regimen it is 150 mg (2 weeks on, 2 weeks off).

The rationale for further exploration of BID regimen at 100 mg BID is supported by PK/PD modeling of plasma cfSDMA suppression (unpublished data), predicted to achieve more optimal cfSDMA suppression across participants than 300 mg QD. Similar decrease in plasma cfSDMA suppression was observed in patients treated with QD and BID regimen in Part 1 of study 204653. The maximum decrease observed to date is 74% and 80% at day 15 of dosing 200 mg BID or 600 mg QD, respectively. Similarly, analysis of plasma in 27 participants with MDS and AML revealed an average 77.7 % (±5 SD) and 75.6 % (±15 SD) decrease in cfSDMA after 15 days of treatment with 300 mg QD and 400 mg QD of GSK3326595, respectively (unpublished data).

The rationale for the intermittent dosing schedule (2 weeks on, 2 week off) was selected based on the available safety, tolerability, PK and PD data. More specifically: 1) the need to allow for sufficient bone marrow recovery as GSK3326595 and 5-Azacitidine can induce severe cytopenias, 2) data on time to achieve maximum reduction of cfSDMA in

plasma (nadir of cfSDMA achieved at day 14), 3) median time of onset of most common adverse events related to GSK3326595 (unpublished data).

4.4.1.2. 5-Azacitidine

The currently approved dose of 5-Azacitidine is 75 mg/m^2 daily for 7 days (either 7 continuous days or including 2-day interruptions to allow for weekends [e.g., Monday through Friday, then the following Monday and Tuesday]) to be administered by subcutaneous (SC) injection or intravenous (IV) infusion. Dose reductions (up to 50%, administered on the same schedule) are recommended for participants experiencing hematologic toxicity as well as for treatment-emergent renal impairment. While the inclusion/exclusion criteria (Section 5.1 and Section 5.2) exclude patients with significant kidney dysfunction at baseline, emerging toxicity may warrant a dose reduction as described in Appendix 11. For Part 2 of this study, 5-Azacitidine will be administered at the 75 mg/m^2 dose for seven days in a 28-day cycle, as detailed in the registered label. Refer to Section 6.1 of this protocol or Section 2 of the package insert for details of administration.

4.5. End of Study Definition

4.5.1. Participants Completion

In Part 1, a participant is considered to have completed the study if he/she has been followed until death or completed Part 1 of the study.

In Part 2 dose escalation a participant is considered to have completed the study if they have discontinued study treatment (either due to disease progression or reasons listed in Section 7) and completed the EoT visit and 30-day AE/SAE follow up after last dose of study drug, or withdrawn consent to further treatment/study participation.

In Part 2 dose expansion a participant is considered to have completed the study if they have discontinued study treatment for reasons listed in Section 7, if they die while receiving study treatment, or are receiving ongoing study treatment at the time of the Sponsor's decision to close the study.

Participants who have not died and are no longer being followed up for survival are considered to have discontinued the study

4.5.2. Study completion

The study will be considered completed for purposes of a final analysis for Part 1 or Part 2 when participants have completed treatment as outlined in Section 4.5.2 and 70% of the participants enrolled in Part 1 have died and 70% of the participants enrolled in Part 2 dose expansion have died. Survival follow up for remaining participants may not be needed. However, the study or a particular part of the study may be stopped prior to completion (e.g., for toxicity or futility) as described in Section 4.1.

5. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

1. Males and females ≥18 years of age (at the time consent is obtained)
2. Capable of giving signed informed consent as described in Appendix 1: Regulatory, Ethical, and Study Oversight Considerations which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.
3. Able to swallow, retain, orally-administered medication
4. Eastern cooperative oncology group (ECOG) performance status (defined in Appendix 10) of 0, 1, or 2
5. Diagnosis of one of the following:

- Part 1:
  - MDS classified as intermediate, high, or very high risk by International Prognostic Scoring System-Revised [IPSS-R] criteria, as described in Appendix 7: IPSS-R Scoring System for MDS [Greenberg, 2012]), OR
  - CMML classified as intermediate-2 or high risk per CMML-specific prognostic scoring system (CPSS) or clinical/molecular CPSS (CPSS-mol) criteria, as described in Appendix 8: CMML Scoring System (Such, 2013; Elena, 2016), OR
  - MDS/CMML secondary to prior anti-neoplastic therapy, of any risk score, OR
  - AML, which has evolved from an antecedent MDS/Myeloproliferative neoplasms (MPN) of any risk score, provided that the myeloblast percentage in the marrow is ≤ 30% or the peripheral white blood cell count is less than 20,000 cells/µL in the absence of leukoreducing therapy (e.g., hydroxyurea, leukapheresis)
    - NOTE: Participants without a documented history of antecedent MDS/MPN must have AML with myelodysplasia-related changes or recurrent cytogenetic abnormalities per World Health Organization (WHO) criteria
- Part 2 Dose Escalation:
  - MDS classified as intermediate, high, or very high risk by International Prognostic Scoring System-Revised [IPSS-R] criteria, as described in Appendix 7: IPSS-R Scoring System for MDS [Greenberg, 2012]), OR
  - CMML classified as intermediate-2 or high risk per CMML-specific prognostic scoring system (CPSS) or clinical/molecular CPSS (CPSS-mol) criteria, as described in Appendix 8: CMML Scoring System (Such, 2013; Elena, 2016), OR

  - MDS/CMML secondary to prior anti-neoplastic therapy, of any risk score, OR
  - AML, with relapsed or refractory disease and ineligible for or have exhausted standard therapeutic options, provided the peripheral white blood cell count is less than 20,000 cells/µL in the absence of leukoreducing therapy (e.g., hydroxyurea, leukapheresis)

- Part 2 Dose Expansion:
  - MDS Treatment naïve classified as high/very high by IPSS-Revised [IPSS-R] criteria, as described in Appendix 7: IPSS-R Scoring System for MDS [Greenberg, 2012]), OR
  - CMML Treatment naïve classified as intermediate-2 or high risk per CMML-specific prognostic scoring system (CPSS) or clinical/molecular CPSS (CPSS-mol) criteria, as described in Appendix 8: CMML Scoring System

6. Prior therapy
   - Part 1: Participants must have disease that failed to respond to, or progressed despite, treatment at least one systemic therapy
   - Part 2 Dose Escalation:
     - Participants with **MDS or CMML** may:
       - have disease that failed to respond to, or progressed despite, treatment at least one systemic therapy

         OR
       - be treatment naïve;

         OR
       - have completed minimum 4 cycles of 5-Azacitidine and have not reported response or progression 5-Azacitidine
     - Participants with **AML** must have disease that failed to respond to, or progressed, despite treatment with at least one systemic therapy

   - Part 2 Dose Expansion Participants must have received no prior therapy for their disease of MDS or CMML, OR have completed no more than one cycle of a hypomethylating agent

7. Molecular markers
   - Part 1: At least 12 participants must have documented loss-of-function mutation(s) at least one of the following genes/proteins: SF3B1, SRSF2, U2AF1, or ZRSR2; in addition, at least 12 participants must have documented wild type status of all of these genes/proteins. While enrolment will initially proceed without consideration of mutational status, enrolment may be limited to one group

or the other as the study proceeds based on the enrolment rates in each group, in order to ensure this minimum number of mutated and wild type participants.

- Part 2: 30% of total participants in Dose Escalation on MTD for each Regimen and at least 14 participants in the Dose Expansion should have documented mutation(s) at least one of the following genes/proteins: SF3B1, SRSF2, U2AF1, or ZRSR2. While enrolment will initially proceed without consideration of mutational status, enrolment may be limited to one group or the other as the study proceeds based on the enrolment rates in each group, in order to ensure this minimum number of mutated participants.

8. Participants with a prior history of stem cell transplant (autologous and/or allogeneic) are allowed if:
   - At least 3 months has elapsed from the time of transplant *and*
   - the participant has recovered from transplant-associated toxicities prior to the first dose of GSK3326595 *and*
   - For participants with a prior history of allogeneic transplant,
     - the participant has been off systemic immunosuppressive medications (including but not limited to: cyclosporine, tacrolimus, mycophenolate mofetil, or corticosteroids) for at least 1 month prior to the first dose of GSK3326595. Topical steroids are permitted
     - there are no signs or symptoms of acute graft versus host disease, other than Grade 1 skin involvement.
     - there are no signs or symptoms of chronic graft versus host disease requiring systemic therapy

9. All prior treatment-related toxicities must be NCI-CTCAE v4 ≤ Grade 1 (except alopecia [permissible at any Grade] and peripheral neuropathy [which must be ≤ Grade 2]) at the time of treatment allocation.
   - Note: Participants with treatment-related toxicities that are unlikely to resolve per the investigator may be enrolled on a case-by-case basis after discussion with the medical monitor

10. Adequate organ system functions (at both screening and where applicable pre-first dose) as defined in Table 9.

Table 9 Definitions for Adequate Organ Function

System	Laboratory Values
Hematologic	
Platelets	≥10 X 10^9/L (participants may receive transfusion to ensure adequate platelet counts)
PT/INR and PTT	≤1.5 X upper limit of normal (ULN), unless participant is receiving systemic anticoagulation
Hepatic	
Albumin	≥2 g/dL
Total bilirubin	≤1.5 x ULN **NOTE**: Isolated bilirubin >1.5 X ULN is acceptable if: • bilirubin is fractionated and direct bilirubin <35% OR • participant has a diagnosis of Gilbert's syndrome
Alanine aminotransferase (ALT)	≤2.5 x ULN
Renal	
Estimated glomerular filtration rate (eGFR)[a]	≥ 50 mL/min/1.73 m^2 **NOTE:** Participants with eGFR of <60 mL/min/1.73 m^2 will require additional monitoring as described in Appendix 2: Clinical Laboratory Tests.

a. EGFR should be calculated using the Chronic Kidney Disease Epidemiology Collaborative (CKD-Epi) method:-

Females, serum creatinine >62 µmol/L: $144 \times (\text{serum creatinine} \times 0.0113/0.7)^{-1.209} \times 0.993^{age}$
Females, serum creatinine ≤62 µmol/L: $144 \times (\text{serum creatinine} \times 0.0113/0.7)^{-0.329} \times 0.993^{age}$
Males, serum creatinine >80 µmol/L: $141 \times (\text{serum creatinine} \times 0.0113/0.9)^{-1.209} \times 0.993^{age}$
Males, serum creatinine ≤80 µmol/L: $141 \times (\text{serum creatinine} \times 0.0113/0.9)^{-0.411} \times 0.993^{age}$
[Levey, 2009]

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

11. Agree to abide by the gender-specific contraceptive requirements described in Section 5.3.1.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

1. History of prior solid organ transplant
2. History of a second malignancy, excluding non-melanoma skin cell cancer, within the last three years
   - Participants with second malignancies that were indolent, *in situ* or definitively treated may be enrolled even if less than three years have elapsed since treatment. Participants with a recent history of ductal carcinoma in situ (DCIS) that has been definitively treated may be enrolled irrespective of the time since diagnosis. Consult the GSK Medical Monitor if second malignancies meet the requirements specified above.

3. Active severe or uncontrolled infection. Controlled infections are permitted.
4. Symptomatic or untreated Central Nervous System (CNS) disease
   - Note that lumbar puncture (LP) is not required for study enrollment unless there is clinical suspicion for CNS disease
   - Participants with a history of CNS disease are permitted to enroll if they have previously received appropriate therapy *and* CNS remission has been documented. Participants on maintenance intrathecal chemotherapy may be enrolled and continue to receive therapy.
5. Recent prior therapy, defined as follows:
   - Any non-monoclonal anti-cancer therapy within 14 days or 5 half-lives, whichever is longer, prior to the first dose of IP.
     - Participants in Part 2 may enroll during the first cycle of 5-Azacitidine and continue cycle 1 in combination with IP, after discussion between the investigator and the medical monitor
   - Prior therapy with biologic agents (including monoclonal antibodies) within 28 days prior to the first dose of IP
   - Any radiotherapy within 14 days or major surgery within 28 days prior to the first dose of IP.
   - Note: participants receiving hormonal therapy for a definitively-treated malignancy (e.g., adjuvant therapy of localized breast or prostate cancer) may continue to receive adjuvant therapy during study, after discussion with the medical monitor
6. Prior therapy with any PRMT5 inhibitor
7. Current use of a prohibited medication or planned use of any forbidden medications during treatment with study drug(s) (see Section 6.6.1.3 for the list of medications).
8. History of known human immunodeficiency virus (HIV) infection, or positive HIV test result at screening. NOTE: HIV – Patients may be eligible if they fullfill all of the requirements below: Have started on antiviral therapy for at least 4 weeks prior to start of study drug treatment, Not be taking HIV related therapy (antivirals, antibiotics) that is on the prohibited list per protocol, Have a CD4 count ≥350 cells/uL, Have a HIV viral load <400 copies/ml
9. Presence of hepatitis B surface antigen (HBsAg) or positive hepatitis C antibody test result at screening.

   Note: Participants with chronic HBV infection, who meet the criteria for anti HBV therapy may be eligible if patient is on a suppressive antiviral therapy prior to initiation of cancer therapy.

   Note: Participants with positive hepatitis C antibody due to prior resolved disease can be enrolled only if a confirmatory negative Hepatitis C RNA polymerase chain reaction (PCR) is obtained. Also Hep C - Patients may be eligible if they have both: completed curative antiviral therapy, have a HCV viral load <quantifiable limit

10. Any of the following cardiac abnormalities:
    - History, within the past 6 months prior to first dose of study drug(s), of acute coronary syndromes (including myocardial infarction and unstable angina), coronary angioplasty, or stenting
    - Baseline Corrected QT (Fridericia's formula) interval (QTcF) ≥480 msec
    - Uncontrolled arrhythmias. Participants with rate-controlled atrial fibrillation prior to first dose of study drug(s) may be eligible.
    - Class II, III or IV heart failure as defined by the New York Heart Association (NYHA) functional classification system.
11. History of sensitivity to any of the study medications, or components thereof, or a history of drug or other allergy that, in the opinion of the investigator or Medical Monitor, contraindicates their participation
12. History of optic nerve neuropathy or neuritis.

5.3. Lifestyle Considerations

5.3.1. Gender-Specific Restrictions

Contraceptive use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

5.3.1.1. Female Participants of Childbearing Potential

A female participant of childbearing potential (woman of childbearing potential [WOCBP]) is eligible to participate if:

- She is not pregnant, and
- Not breastfeeding, and
- Agrees to follow the contraceptive guidance in Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information from the first dose of study intervention until at least 5 days plus one menstrual cycle after the last dose of GSK3326595 and at least the time period described in the current prescribing information after the last dose of 5-Azacitidine, whichever is longer (in Part 2). The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

A WOCBP must have a negative highly sensitive serum pregnancy test within 7 days before the first dose of study intervention.

- Additional requirements for pregnancy testing during and after study intervention are located in Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information.
- The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy

5.3.1.2. Female Participants of Non-Childbearing Potential

Refer to Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information for definitions of "non-childbearing potential". Female participants of non-childbearing potential have no requirements for contraception. If there is any question by the investigator and/or medical monitor regarding the child-bearing potential of a female participant, then an FSH and estradiol may be required at screening.

5.3.1.3. Male Participants

A male participant with a female partner of childbearing potential must agree to use contraception as detailed in Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information of this protocol from the first dose of study intervention of GSK3326595 until at least 95 days after the last dose of study intervention and at least the time period described in the current prescribing information after the last dose of 5-Azacitidine, whichever is longer (in Part 2).

All male participants must refrain from donating sperm from the first dose of study intervention until at least 95 days after the last dose of study intervention.

5.3.2. Meals and Dietary Restrictions

- Participants should be instructed to refrain from consumption of Seville oranges, grapefruit or grapefruit juice, pomelos, exotic citrus fruits, grapefruit hybrids, or fruit juices for at least 24 hours before the start of study intervention until after the final dose.
- During each serial PK sampling day (e.g., Days 1 and 15 in Part 1, Day 1 and Day 8 in Part 2), participants should be instructed to abstain from ingesting alcohol, tobacco products, caffeine- or xanthine-containing products (e.g., coffee, tea, cola drinks, and chocolate) for 24 hours before the start of dosing until after collection of the final PK sample.

5.4. Screen Failures

Screen failures are defined as patients who consent to participate in the clinical study but who are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse events (SAEs).

Individuals identified as Screen Failures may be rescreened if the failure was based on elements of eligibility that may change, e.g., laboratory test results.

6. STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, intended to be administered to a study participant according to the study protocol.

6.1. Study Intervention(s) Administered

Study Intervention Name:	**GSK3326595**		**5-Azacitidine**
Dosage formulation:	Hydroxypropyl methylcellulose (HPMC) Capsules	Tablets	Lyophilized powder in 100 mg single-dose vials
Unit dose strength(s)/ Dosage level(s):	25 and 100 mg strengths as free-base drug substance	100 mg	75 mg/m^2
Route of Administration	Oral		Subcutaneous or intravenous
Dosing instructions:	GSK3326595 is to be administered orally with water (approximately 200 mL) at approximately the same time of day (±4 hours for QD dosing and ±1 hours for BID dosing) with no food or antacids for 2 h before and 1 h after each dose. Only for cycle 1 day 8 visit in Part 2 Dose escalation participants should take the drug with food within 30 minutes (if BID, dosing cohort, both doses taken with food). If a dose is delayed by more than 4 hours, the participant should not take that dose and should mark the dose as "not taken". On serial PK days and for two days prior, participants should attempt to take GSK3326595 within a 1 h window (i.e., 23-25 hours after the last dose). Capsules/tablets should not be chewed or crushed. If dose regimen requires more than one capsule/tablet per dose, the capsules/tablets should be taken one at a time. Based on relative bioavailability substudy in study 204653, comparable plasma exposures of GSK3326595 were observed between tablets and capsules. As a result, participants can be administered either tablets or capsules in Part 2. Participants who started on capsules may be switched to tablets for		Administer 75 mg/m^2 subcutaneously or intravenously for 7 days out of a 28 day cycle, as per prescribed information in registered label

Study Intervention Name:	**GSK3326595**		**5-Azacitidine**
	the remainder of the study, once they have been notified by the Sponsor.		
Physical description	Capsules of Opaque White (size 00) for 100 mg, capsules of Opaque Light Green (size 1) for 25 mg	White to almost white film coated tablets with no markings	See dosage formulation
Packaging and Labelling	Study intervention will be provided in bottles. Each bottle will be labelled as required per country requirement.		5-Azacitidine will be commercially available and will be stored, packaged, prepared, and labelled as per local standard.
Manufacturer	GSK		Celgene or other manufacturers registered

NOTE: These formulation details are current at the time of protocol finalization and may be updated in other documents (e.g., SRM and/or informed consent form) without requiring protocol amendment

6.2. Method of Treatment Assignment

Part 1, Part 2	Upon signing informed consent, participants will be assigned a unique number in ascending numerical order at each study site. This number will remain consistent for the duration of the study.

For all participants enrolled in the study, study intervention will be dispensed/administered at the study visits summarized in the SOA. Returned study intervention should not be re-dispensed to the participants.

6.3. Blinding

This is an open-label study. Investigators and study team will have direct access to individual participant's study intervention

6.4. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored

(manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

3. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
4. Further guidance and information for the final disposition of unused study intervention are provided in the SRM.
5. Precautionary action to limit exposure (example: wearing gloves, washing hands post exposure) should be taken by site staff during dispensing GSK3326595. A Material Safety Data Sheet (MSDS) describing occupational hazards and recommended handling precautions will be provided to the investigator. In the case of unintentional occupational exposure notify the monitor, Medical Monitor and/or GSK study contact.

6.5. Study Intervention Compliance

- When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention
- When participants self-administer study intervention(s) at home, compliance with GSK3326595 will be assessed through review of dosing diaries during site visits and documented in the source documents and Case Report Form (CRF). A record of the number of GSK3326595 capsules/tablets dispensed to and taken by each participant must be maintained and reconciled with study intervention and compliance records. Treatment start and stop dates, including dates for treatment delays and/or dose reductions will also be recorded in the CRF.
- 5-Azacitidine will be subcutaneously or intravenously administered to participants at the site. Administration will be documented in the source documents and reported in the CRF.

6.6. Concomitant Therapy

6.6.1. Concomitant Medications

Participants will be instructed to inform the investigator prior to starting any new medications from the Screening Visit until the end of the study (Final Study Visit). Any concomitant medication(s), including herbal preparations, taken during the study will be recorded in the eCRF. The minimum requirement is that drug name, route of administration, dose and frequency of dosing, along with start and stop dates of administration should be recorded. Additionally, a complete list of all prior cancer therapies will be recorded in the eCRF.

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

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

6.6.1.1. Permitted Medications

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

Erythropoiesis-stimulating agents and colony-stimulating factors like filgrastim and pegfilgrastim may be used as clinically indicated for treatment of cytopenias. If used, these agents should be held for a period prior to disease assessment, per local institutional practice or guidelines.

Hydroxyurea may be used as per local practice for control of leukocytosis, except as prohibited at time of enrollment in Part 1 and Part 2 (Section 5.1).

6.6.1.2. Cautionary Medications

The following paragraphs describe potential interactions between GSK3326595 and other medications. While co-administration is not prohibited, these medications should be used with caution and additional monitoring for adverse effects should be utilized.

Perpetrator risk of GSK3326595 has been identified as a CYP1A2 inducer. Co-administration of GSK3326595 and substrates of CYP1A2 (e.g., alosetron, duloxetine, melatonin, ramelteon, tasimelteon, tizanidine) should be avoided in order to prevent inadvertent under-exposure to these agents. GSK3326595 is a substrate for P-gp. Other P-gp substrates include medications such as 3-hydroxy-3-methylglutaryl-coenzyme A (HMGCoA) reductase inhibitors (statins) and digoxin, which may have a narrow therapeutic index. While co-administration of other P-gp substrates with GSK3326595 is not prohibited, they should be used with caution and additional monitoring for adverse effects should be utilized.

Though QT prolongation was not identified in pre-clinical animal studies of GSK3326595, medications that are associated with a risk of torsades de pointes (as per crediblemeds.org or similar database) should be used with caution. If co-administration with GSK3326595 is necessary, additional ECG monitoring should be implemented until the medication is at steady state, as per standard clinical practice.

6.6.1.3. Prohibited Medications

Participants should not receive other systemic anti-cancer therapy for their myeloid disorder while on treatment in this study. Any participant requiring new therapy for their myeloid neoplasm (e.g., chemotherapy, targeted therapy, immunotherapy, etc.) must be discontinued from study. Participants previously on adjuvant hormonal therapy for

definitively-treated tumors (e.g., localized breast or prostate carcinoma) may continue to receive their hormone therapy after discussion with the investigator and medical monitor.

Note: with the exception of other systemic anti-cancer therapies, any medication (including antibacterials, antifungals, or antivirals) which are necessary for the health, well-being, and standard clinical care of participants with myeloid neoplasms are exempt from the restrictions below.

No *in vitro* CYP phenotyping data are available for GSK3326595. In the absence of these data, strong and moderate inhibitors or inducers of CYP isoenzymes should not be coadministered with GSK3326595, except for those medications necessary for the health of the participant as noted in the paragraph above. If administered (e.g., azole antifungals for treatment and/or prophylaxis of systemic fungal infection), then the date, dose, and duration of therapy with these concomitant medications should be recorded in the CRF.

GSK3326595 was found to be a substrate for P-gp in bidirectional permeability assays using Continuous cell of heterogeneous human epithelial colorectal adenocarcinoma cells (Caco-2) and Madine-Darby canine kidney (MDCK)-II monolayers. GSK3326595 should not be co-administered with strong and moderate inhibitors of Pgp Such inhibitors include cyclosporine, tacrolimus, and ketoconazole.

In addition, GSK3326595 is a substrate of MATE2-K, OAT3 and OCT2 uptake transporters; therefore, GSK3326595 should not be co-administered with strong and moderate inhibitors or inducers of MATE2-K, OAT3 and OCT2. Such inhibitors include, but are not limited to, cimetidine, probeneacid, metformin, pyrimethamine, and benzylpenicillin (penicillin G).

6.6.2. Concomitant Non-Drug Therapies

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

> **NOTE**: Participants may receive focal palliative intervention during this study (e.g., radiation therapy for local management of leukemia cutis). Any proposed focal therapy must be approved by the investigator and the medical monitor prior to intervention.

Participants will abstain from using herbal preparations/medications 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, ginseng, and marijuana.

6.7. Dose Modification

In the dose escalation cohorts of Part 1 and Part 2, participants will be assigned to a dose level as described in Section 4.1.1.1.2 and Section 4.1.3.1.1, respectively. The participant's dose may be escalated as described in Section 4.1.1.1.3 and Section 4.1.3.1.1.

Dose modifications will be permitted on a case-by-case basis for management of toxicity or other adverse events. Toxicity management guidelines for GSK3326595 may be found in Appendix 11. Toxicity management guidelines for 5-Azacitidine may be found in the package insert.

6.8. Intervention after the End of the Study

The investigator is responsible for ensuring that consideration has been given to the post-study care of the participant's medical condition.

Refer to Section 8.3.2 and the Schedule of Assessments for follow-up assessments of participants who are to be followed for disease progression and/or survival after they permanently discontinue from study intervention.

If available, participants continuing on treatment at the time of final analysis may be offered the option to continue in a separate rollover trial, if available, based on the investigators' discretion.

For participants who discontinue on study treatment, any post study treatment will not be provided as part of the protocol. Upon discontinuation from assigned study treatment, participants may receive additional (non-protocol) therapy at the discretion of the treating physician. New therapy should be documented on the eCRF. Every effort should be made to complete the required withdrawal and follow up evaluations prior to initiating further therapy or dosing of an investigational agent (see Section 7 for follow-up assessments and procedures).

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

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

Participants will receive study intervention until disease progression, death or unacceptable adverse event. In addition, study intervention may be permanently discontinued for any of the following reasons:

- Deviation(s) from the protocol
- Request of the participant or proxy
- Investigator's discretion
- Participant is lost to follow-up
- Study is closed or terminated.

In all cohort(s), unless the cohort is closed early, survival follow-up will continue until the study is completed. At such time, the cohort will be closed and any further follow-up on participants enrolled in that cohort will cease. Participants with lack of disease progression who are still receiving study intervention at the time of study completion may continue treatment through a separate mechanism (e.g., roll-over protocol).

7.1. Discontinuation of Study Intervention

The primary reason study intervention was permanently discontinued must be documented in the participant's medical records and electronic case report form (eCRF). If the participant voluntarily discontinues from intervention due to toxicity, 'adverse event' will be recorded as the primary reason for permanent discontinuation on the eCRF.

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

All participants who discontinue from study intervention will have safety assessments at the time of discontinuation and during post study intervention follow-up as specified in the Schedule of Activities (Section 1.3).

Participants who discontinue study intervention without disease progression should continue to be followed for disease assessment until disease progression or initiation of new anti-cancer therapy. All participants who permanently discontinue study intervention will be followed for survival and new anti-cancer therapy (including radiotherapy) every 6 months until death or termination of the study by the sponsor. If participants are unable or unwilling to attend clinic visits during follow-up, contact to assess survival may be made via another form of communication (e.g., telephone, email, etc.).

7.1.1. Disease Progression

Participants with equivocal progression (e.g., mild increase in myeloblast content in the marrow without significant change in hematologic parameters in the periphery) may continue on study therapy provided that safety-related stopping criteria are not met.

Participants whose disease assessment demonstrates progressive disease (PD) per standard criteria may continue to receive study intervention until progression is confirmed at a follow-up assessment at least 4 weeks after the first assessment demonstrating PD. These considerations should be balanced by clinical judgment (e.g., whether the participant is clinically deteriorating and unlikely to receive any benefit from continued treatment).

If confirmed at least 4 weeks later, participants with PD should discontinue therapy with study drug(s). However, participants with confirmed PD may remain on study on a case-by-case basis (e.g., as long as the Investigator and the GSK Medical Monitor concur that the participant could continue to receive benefit, the participant is not experiencing serious toxicity, and there is no alternative treatment that is likely to benefit the participant). Discussion between the Investigator and the Medical Monitor must occur in order for a participant to continue study intervention once PD has been confirmed. Participants who continue on study beyond confirmed progression should continue to undergo all assessments described in the Schedule of Activities tables (Section 1.3). Participants who demonstrate continued progression at subsequent scheduled disease assessments may be required to discontinue therapy at the discretion of the Investigator and the Medical Monitor.

7.1.2. Liver Chemistry Stopping Criteria

Liver chemistry stopping and increased monitoring criteria have been designed to assure participant safety and evaluate liver event etiology.

Discontinuation of study intervention for abnormal liver tests is required when:

- a participant meets one of the conditions outlined in Figure 4 or Figure 5 , OR
- when in the presence of abnormal liver chemistries not meeting protocol-specified stopping rules, the investigator believes study intervention discontinuation is in the best interest of the participant.

Figure 4 Liver Chemistry Stopping and Increased Monitoring

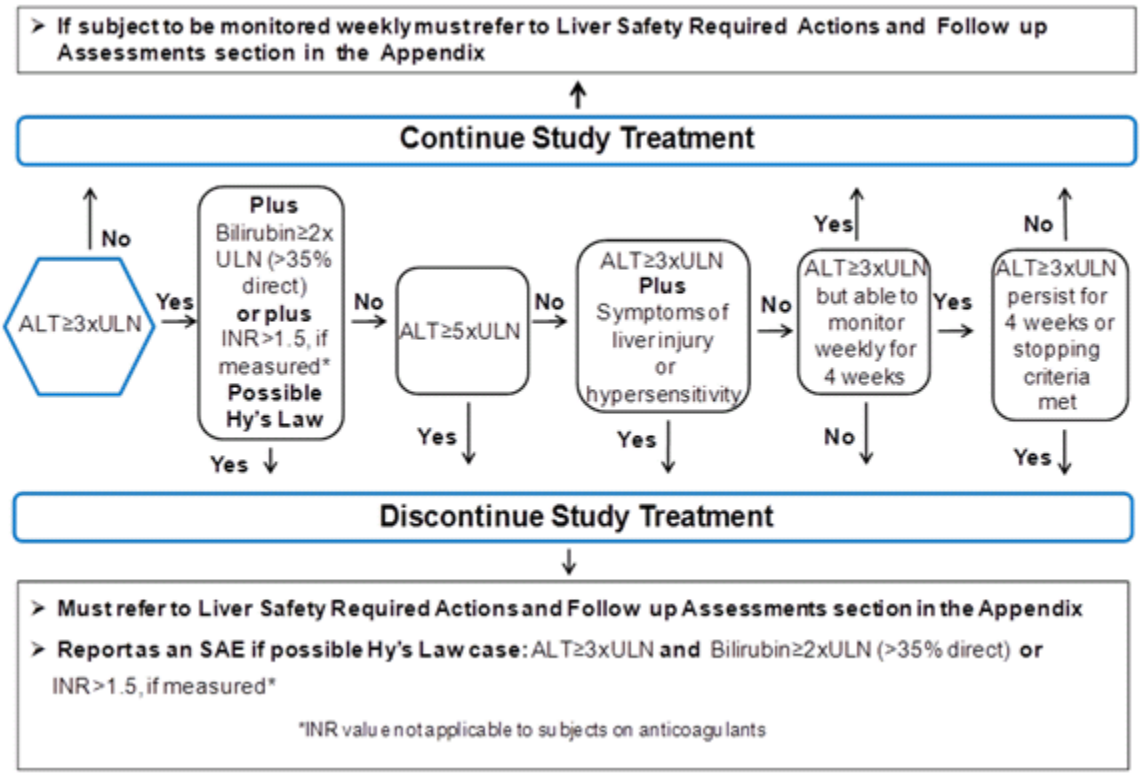
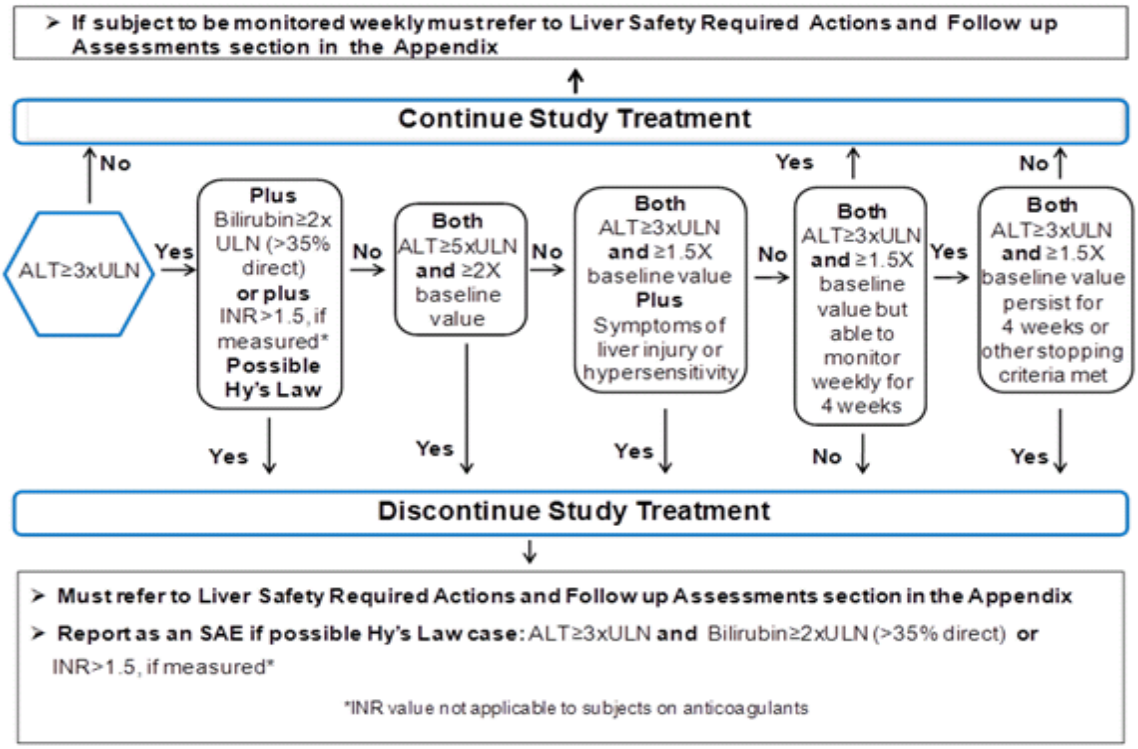


Figure 5 Phase I/II Liver Chemistry Stopping and Increased Monitoring Algorithm including Participants WITH documented liver metastases/tumor infiltration at baseline AND entry criteria ALT>2.5xULN but ≤5xULN



Liver Safety Required Actions and Follow up Assessments Section can be found in Appendix 6: Liver Safety: Required Actions and Follow-up Assessments and Study Intervention Rechallenge Guidelines.

Refer to Section 7.1.6 for rechallenge guidelines after a liver safety event.

7.1.3. QTc Stopping Criteria

If a participant meets the corrected QT (QTc) interval duration criteria below, study intervention(s) will be withheld.

- QTcF interval ≥500 msec OR interval increase from baseline ≥60 msec: Study drug(s) will be permanently discontinued unless the benefits of therapy outweigh the risk of rechallenge in the opinion of the investigator, the GSK Medical Monitor, as well as the GSK medical governance. In this situation, rechallenge may be permitted (see Section 7.1.6 for rechallenge guidelines).

  NOTE: QT interval duration criteria should be based on the 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 2 minutes apart from each other), and then use the

averaged QTc values of the 3 ECGs to determine whether the participants should have study intervention discontinued.

The QTc is the QT interval corrected for heart rate according to Fridericia's formula (QTcF; defined as [QT/(RR1/3)]).

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

See the SoA for data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that need to be completed.

7.1.4. Other Stopping Criteria

Stopping criteria for other toxicities (including nausea, diarrhea, and thrombocytopenia unable to be rescued by platelet transfusion) are detailed in Table 20.

Safety will be reviewed on an ongoing basis by the Safety Review Team (SRT) which will be compromised of, at a minimum, a GSK medical monitor, GSK Global Safety representative, and GSK clinical study representative (including a representative from Biostatistics). Deaths, SAEs, and Grade 3/4 adverse events will be carefully evaluated for the possibility of causality.

If clinically significant adverse events or toxicities are observed in more than one third of the participants, and/or if deaths related to study drug are observed, enrollment may be terminated, and/or a lower-dose cohort may be opened or expanded.

7.1.5. Temporary Discontinuation

Participants who require temporary withdrawal of study intervention s) (e.g., for toxicity), may be permitted to restart therapy as described in Table 20.

7.1.6. Rechallenge

7.1.6.1. Study Intervention Restart or Re-challenge

If participant meets liver chemistry or QTc stopping criteria, do not restart/rechallenge participant with study intervention unless:

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

Refer to Appendix 6: Liver Safety: Required Actions and Follow-up Assessments and Study Intervention Rechallenge Guidelines for full guidance.

7.2. Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioural, compliance or administrative reasons.
- An end of treatment (EOT) visit should be performed as detailed in the SoA
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records and report to the sponsor.
- Refer to the SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

7.3. Lost to Follow Up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of lost to follow up.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix 1: Regulatory, Ethical, and Study Oversight Considerations.

8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA
- Protocol waivers or exemptions are not allowed
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.

- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and was performed within the time frame defined in the SoA.
- The maximum amount of blood collected from each participant during any 12 month period, including any extra assessments that may be required, will not usually exceed 650 mL.
- Whenever vital signs, 12-lead ECG, and blood draws are scheduled for the same nominal time, the assessments should occur in the following order: 12-lead ECG, vital signs, and blood draws. Whenever vital signs and blood draws are scheduled for the same nominal time, vital signs should be performed prior to blood draws. The timing of the assessments should allow the blood draw to occur at the exact nominal time. Detailed procedures for obtaining each assessment are provided in the SRM.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1. Visit Windows

Screening (baseline to pre-dose):

- Informed consent must be obtained prior to any study-specific evaluations or procedures. However, there is no maximum time after which informed consent must be re-obtained. If a participant is re-screened, the informed consent does not need to be re-signed.
- All other screening assessments should be completed within 14 days prior to first dose.
- For females of childbearing potential, pregnancy testing should be performed within 7 days prior to first dose.

Week 1: Visits during Week 1 must be performed on the day indicated. All subsequent visits following Week 1 Day 1 (first day of dosing) must refer back to the Week 1 Day 1 visit (i.e. all time windows that are allowed around each visit are relative to the Week 1 Day 1 visit).

Week 2 Day 1 (Day 8) to Week 9:

- Based on participant and clinic schedule, assessments can be ± 2 days.
- The Day 15 PK collection (for Part 1) and the Day 8 PK collection (for Part 2) is timed to permit evaluation of PK at steady-state dosing. Part 1 will evaluate PK of

GSK3326595 alone; Part 2 will evaluate PK of both GSK3326595 as well as 5-Azacitidine. If a participant is not receiving drug on the steady state collection date (either as a consequence of a planned drug holiday or due to toxicity), then this PK collection should be rescheduled for a later timepoint when the participant is again being dosed at steady state, and the alternate collection date noted in the eCRF. If a participant in Part 2 is receiving 5-Azacitidine in a fashion that does not administer dose on Day 8, then the steady-state PK collection should be obtained on the last day of 5-Azacitidine dosing.

- The bone marrow biopsy at week 5 (for tumor PD and efficacy) should be performed ± 2 days.

Every 4-week, 8-week, and 12-week visits after Week 9 until Week 49:

- Based on participant and clinic schedule, assessments (including efficacy assessments at Weeks 13, 25, 26, 37, and 49) can be ± 5 days.

Every 4-week, 8-week, 12-week and 26-week visits after Week 49:

- After week 49, the every 4-week visits will change frequency to every 8 weeks. 5 Azacitidine administration will remain on a 4 week cycle
- For the every 8-12 and 26 -week visits, clinic visits can be scheduled ± 7 days.
- After week 49, bone marrow biopsies are only required as clinically indicated (e.g., for changing blood counts or other signs of clinical progression)

End of treatment visit:

- Should be within 30 days from last dose of study drug. If a participant is unable to return to the clinic due to hospitalization, site staffs are encouraged to telephone the participant for assessment of adverse events.

Long term survival follow-up (not applicable to Part 2 dose escalation):

- All participants who discontinue therapy should be followed for survival as described in Section 8.3.2. Contact should be attempted every 6 months ± 2 weeks.

8.2. Critical Baseline Assessments

8.2.1. Disease Characteristics

The following information, as available, should be provided for all participants:

- Cytogenetic and mutational evaluation of tumor sample at screening and/or following the most recent prior line of therapy
- Information regarding prior lines of therapy, best response, duration of response (if any)

8.2.2. Tumor Sample

For all participants enrolled on study, a fresh baseline bone marrow biopsy (or biopsy of extramedullary disease, if bone marrow biopsy is not feasible or likely to be negative) is required and should be obtained within 14 days prior to the first dose of study drug(s).

8.3. Efficacy Assessments

8.3.1. Disease Assessment

Bone marrow biopsies for response assessments will be performed as outlined in the Schedule of Assessments. Participants enrolled in Part 1 (including those with AML, CMML and MDS), and Part 2 will have responses graded per IWG criteria, as described in Appendix 9: IWG Criteria for Response for Participants in Part 1 and Part 2. Note that for clear-cut cases of progression (e.g., new-onset leukemia cutis or emergence of myeloblasts in the peripheral blood) that bone marrow biopsy may not be necessary to document progression.

8.3.2. Survival Assessments

For the Part 2 dose expansion, all participants who discontinue therapy will be followed for survival every 6 months as outlined in the Schedule of Assessments. Follow-up should be made by telephone, email, or other appropriate form of communications.

8.4. Safety Assessments

Planned time points for all safety assessments are provided in the SoA.

8.4.1. Physical Examinations

Each physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal (including abdominal examination), and neurological systems as well as the skin. Height should be measured and recorded at screening. Weight should be measured and recorded at screening and at each visit as detailed in the SoA.

Investigators should pay special attention to clinical signs related to previous serious illnesses or abnormal physical examinations.

8.4.2. Performance Status

The performance status will be assessed using the ECOG scale (Appendix 10) as specified in the SoA.

8.4.3. Vital Signs

- Vital sign measurements to be measured, in a consistent fashion, per institutional standard (e.g., in a seated or semi-supine position after 5 minutes rest), will include temperature, systolic and diastolic blood pressure, pulse rate, and respiratory rate.

- In case of an abnormal first reading, three readings of blood pressure and pulse rate should be taken and averaged to give the measurement to be recorded in the CRF.
- Vital signs will be measured more frequently if warranted by clinical condition of the participant. On days where vital signs are measured multiple times, temperature does not need to be repeated unless clinically indicated.

Refer to the SRM for further details.

8.4.4. Electrocardiograms

- Triplicate 12-lead ECG will be obtained prior to dosing and single 12-lead ECG on days outlined in the SoA using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTcF intervals. Refer to Section 7.1.3 for QTc withdrawal criteria and to Table 20 for management strategies for QTcF prolongation. Local ECG may be collected and read centrally.

8.4.5. Bone Mineral Density

In order to assess the clinical bone safety of GSK3326595, DEXA scans will be performed on all participants at baseline and approximately every 8 weeks thereafter (Section 1.3). This evaluation has been deemed most relevant as it is the clinical gold standard to detect any unexpected changes in bone mineral density (BMD), which may suggest an increased risk of fracture. Locally collected scans may be read centrally.

For consistency in the assessment, wherever possible, DEXA scans should be performed on the same machine for all evaluations on a particular participant, if this is not possible, it should be discussed with the GSK Medical Monitor DEXA scans should be performed prior to CT scans, as both examinations are to be done every 8 weeks.

DEXA scheduling should allow for a 7 day washout of CT IV and/or oral contrast agents, as these can interfere with the results of the analysis. Please refer to the SRM for more details.

8.4.6. Ophthalmic Assessment

Study sites must establish a close collaboration with an appropriately qualified eye-care specialist (ophthalmologist/optometrist) who in conjunction with the Investigator will be responsible for carrying out the schedule of ophthalmic assessments, and managing / referring any participant who develops visual symptoms and / or signs potentially associated with GSK3326595 exposure.

Management of participants with potential treatment-related changes in vision must be performed in close collaboration with the Investigator, appropriately qualified eye-care specialist, and the GSK Medical Monitor.

Participants will have listed below assessments performed by a qualified eye-care specialist at screening/baseline, then every 6 months and at EOT. The assessments may be expedited in the event that a participant develops any new or evolving ophthalmic

symptoms and / or signs in the interval period between assessments. If an abnormal result is recorded at the EOT visit, additional assessment will be required as deemed necessary by the Investigator, appropriately qualified eye-care specialist and the GSK Medical Monitor.

- Full comprehensive exam with best corrected visual acuity (BCVA) at distance for each eye
- Humphrey Visual field assessment (or equivalent as agreed with the Sponsor)
- Optical coherence tomography (OCT) of the optic nerve retinal nerve fibre layer (RNFL) with ganglion complex analysis
- OCT of the macula
- Assessment of color vision by Ishihara method

Primary outputs of the Humphrey Visual Field and OCT assessments will be held centrally by GSK in the event that central or independent evaluation of these is deemed beneficial to support on-going safety evaluation.

Additional examinations, if deemed necessary, may be performed at the discretion of the treating eye-care specialist, and in discussion with the Investigator and Medical Monitor. Further details can be found in the Ocular Manual.

8.4.7. Clinical Safety Laboratory Assessments

- Refer to Appendix 2: Clinical Laboratory Tests for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.
- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 30 days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered significantly abnormal by the investigator or medical monitor.
- If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.
- All protocol-required laboratory assessments, as defined in Appendix 2: Clinical Laboratory Tests must be conducted in accordance with the laboratory manual and the SoA.

8.4.7.1. Urine and Serum Safety Studies

All participants with eGFR at baseline of <60 mL/min/1.73 m^2 should have additional urinary and serum tests performed as part of the clinical safety assessments. These additional tests are included in Appendix 2: Clinical Laboratory Tests.

8.4.8. Adverse Events and Serious Adverse Events

The definitions of an AE or SAE can be found in Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

The investigator and any qualified designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or the study, or that caused the participant to discontinue the study intervention(s) (see Section 7).

8.4.8.1. Time Period and Frequency for Collecting AE and SAE Information

- All SAEs will be collected from the signing of the ICF until 30 days post last dose at the time points specified in the SoA (Section 1.3).
- All AEs will be collected from start of study treatment until 30 days post last dose at the time points specified in the SoA (Section 1.3).
- Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the CRF not the AE section.
- All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.
- Investigators are not obligated to actively seek AEs or SAEs after the conclusion of the study participation. However, if the investigator learns of any AE or SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.
- The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

8.4.8.2. Method of Detecting AEs and SAEs

- Care will be taken not to introduce bias when detecting AE and/or SAE. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrence.
- One line of solicited questioning will be followed for the vision symptom review. At each visit, the investigator should ask the participant “Have you had any changes in your vision since your last visit/contact?”.

8.4.8.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is given in Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

8.4.8.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information e.g., summary or listing of SAE) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

8.4.8.5. Pregnancy

- Details of all pregnancies in female participants and, if indicated, female partners of male participants will be collected after the start of study intervention and until 90 days after the last dose of GSK3326595 or as otherwise specified in package insert of 5-Azacitidine.
- If a pregnancy is reported, the investigator should inform GSK within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.4.8.6. Cardiovascular and Death Events

For any cardiovascular events detailed in Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting and all deaths, whether or not they are considered SAEs, specific Cardiovascular (CV) and Death sections of the CRF will be required to be completed. These sections include questions regarding cardiovascular (including sudden cardiac death) and non-cardiovascular death.

The CV CRFs are presented as queries in response to reporting of certain CV Medical Dictionary for Regulatory Activities Medical Dictionary for Regulatory Activities (MedDRA) terms. The CV information should be recorded in the specific cardiovascular section of the CRF within one week of receipt of a CV Event data query prompting its completion.

The Death CRF is provided immediately after the occurrence or outcome of death is reported. Initial and follow-up reports regarding death must be completed within one week of when the death is reported.

8.4.9. Treatment of Overdose

For this study, any dose of study drug(s) greater than the protocol-specified dose within a 24-hour time period ± 4 hours will be considered an overdose.

GSK does not recommend specific treatment for an overdose of GSK3326595.

In the event of a 5-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 5-Azacitidine overdose.

In the event of any overdose, the investigator (or treating physician) should:

1. Contact the Medical Monitor immediately.
2. Closely monitor the participant for AE/SAE and laboratory abnormalities until study drug(s) can no longer be detected systemically and the duration of effect has been exceeded (at least 28 days).
3. Obtain a plasma sample for PK analysis within 3 days from the date of the last dose of study intervention if requested by the Medical Monitor (determined on a case-by-case basis).
4. Document the quantity of the excess dose as well as the duration of the overdosing in the CRF.

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 participant.

8.5. Pharmacokinetics

- Blood samples of approximately 2 mL will be collected for measurement of GSK3326595 (in all Parts). In Part 2, an additional 2 mL will be collected to characterize 5-Azacitidine as specified in the SoA. A maximum of 6 additional samples may be collected at additional time points during the study if warranted and agreed upon between the investigator and the sponsor. Instructions for the collection and handling of biological samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded. Details of PK blood sample collection, processing, storage and shipping procedures will be provided in the Lab Manual.

- Genetic analyses will not be performed on these whole blood samples unless consent for this was included in the informed consent. Participant confidentiality will be maintained.
- Once the plasma has been analyzed for GSK3326595 any remaining plasma may be analyzed for other compound-related metabolites and the results reported under a separate protocol.

8.6. 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 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 5: Genetics for information regarding genetic research. Details on processes for collection and shipment and destruction of these samples can be found in the Lab Manual

8.7. Pharmacodynamics and Biomarkers

All participants will have PD and biomarker sampling performed on the days indicated in the SoA. Additional PD and/or biomarker assessments may be requested on a case-by-case basis in an unscheduled fashion as deemed appropriate based on emerging clinical data (e.g., at time of response).

CCI [redacted]. Change from baseline levels will be measured. Whole blood samples may be utilized for the identification and/or validation of a single gene or group of genes indicative of modulation in response to GSK3326595. This gene or genes may serve as a novel PD biomarker of PRMT5 inhibition by GSK3326595. The PD outcome may be correlated to clinical outcome. Blood or tumor samples may also be used to discover and validate biomarkers indicative of resistance or sensitivity to the study drug, GSK3326595.

While samples collected for this study will be primarily used to assess MDS, CMML, AML, and the activity of the study intervention, samples may also be used for research to develop methods, assays, prognostics and/or companion diagnostics related to PRMT5 inhibition, disease process, pathways associated with disease state, and/or mechanism of action of the study intervention or other treatments currently under investigation.

Blood Sample Collection

Plasma samples will be collected from all participants in Part 1 according to the SRM for the purpose of assessing pharmacodynamic, predictive, and/or disease-related biomarkers.

Peripheral whole blood samples will be collected as described in the Schedule of Activities (Section 1.3) and according to the SRM for the purpose of transcriptomic studies to assess pharmacodynamic, predictive, and/or disease-related biomarkers.

Serum samples will be collected according to the SRM for the purpose of proteomics studies to assess pharmacodynamic, predictive, and/or disease-related biomarkers.

Tumor Biopsy Collection

A fresh bone marrow biopsy (or biopsy of extramedullary disease, if bone marrow biopsy is not feasible or likely to be negative) is required from all participants at screening and on the days indicated in the SoA. When possible, bone marrow biopsy for PD and biomarker evaluation should be collected 6 hours (± 3 hours) after dosing with GSK3326595. If genomic testing (eg splicing factor mutations) of bone marrow biopsies was performed prior to enrollment, results and type of test used should be provided.

Samples may also be used for research to develop methods, assays, prognostics and/or companion diagnostics related to PRMT5 inhibition, disease process, pathways associated with disease state, and/or mechanism of action of the study intervention or other treatments currently under investigation.

8.7.1. Immunogenicity Assessments

Immunogenicity or immunophenotyping studies may be conducted using multiplex Immunohistochemistry (IHC), gene expression, and/or alternative equivalent technologies. This assessment may help identify possible combinations with immune therapies.

8.7.2. RNA Transcriptome Research

Transcriptome studies will be conducted using microarray, RNAseq, and/or alternative equivalent technologies, which facilitates the simultaneous measurement of the relative abundances of thousands of Ribonucleic Acid (RNA) species resulting in a transcriptome profile for a subset of blood and/or tumor biopsy samples. This will enable the evaluation of changes in transcriptome profiles that may correlate with biological response relating to MDS, CMML, AML, or the action of GSK3326595. The same samples may also be used to confirm findings by application of alternative technologies.

8.7.3. RNA Expression Research of a Subset of RNA Species

RNA expression studies may be conducted using quantitative reverse transcription polymerase chain reaction (RT-PCR), and/or alternative equivalent technologies, which can facilitate the simultaneous measurement of the relative abundances of hundreds of RNA species resulting in a RNA expression profile for a subset of blood and tumor biopsy samples. The RNAs assayed may be those involved with the pathogenesis of MDS, CMML, AML, and/or the absorption, distribution, metabolism, or excretion of GSK3326595, or in the participant's response to GSK3326595. In addition, continuing research may identify other proteins or regulatory RNAs that may be involved in response to GSK3326595 or the pathogenesis of MDS, CMML or AML. The RNAs that

code for these proteins and/or regulatory RNAs may also be studied. This will enable the evaluation of changes in RNA expression profiles that may correlate with biological response relating to MDS, CMML, AML, or the action of GSK3326595.

8.7.4. Circulating Cell Free DNA (cfDNA) Analysis

Tumor-specific circulating nucleic acid (cfDNA) levels detected in plasma or serum have been found to correlate with increasing tumor burden. Furthermore, cfDNA in cancer participants can harbor many genetic alterations (mutations, microsatellite alterations, aberrant methylation), which are generally consistent with the tumor. Thus, tumor specific circulating cfDNA has the potential to be a useful biomarker of therapeutic response as well as offering a less invasive blood based technique for identifying and selecting participants for certain treatments. Given the promise of cfDNA blood based test for participant selection, this test will be explored to determine whether mutations in cfDNA correlate with that in the tumor tissue from which it is derived. This test may also be explored to correlate increasing cfDNA levels with increasing tumor burden.

8.7.5. Proteome Research

Proteomic studies will be conducted using any of a variety of mass spectrometry methods and/or alternative equivalent technologies which facilitates the simultaneous measurement of the relative abundances of hundreds to thousands of protein species resulting in a proteome profile for a subset of blood and/or tumor biopsy samples. This will enable the evaluation of changes in proteome profiles that may correlate with biological response relating to MDS, CMML, AML, or the action of GSK3326595. The same samples may also be used to confirm findings by application of alternative technologies.

8.8. Patient Reported Outcomes

Patient Reported Outcomes (PROs) are not evaluated in this study.

8.9. Health Economics OR Medical Resource Utilization and Health Economics

Health Economics/Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

9.1. Sample Size Determination

The sample size for each part of the trial was chosen to adequately characterize the safety, clinical activity, PK, and pharmacodynamic marker data based on the objectives of each part of the study. The references for the control assumption and rationale for meaningful improvement over the historical control are provided in the Appendix 12: Rationale for Response Assumptions.

9.1.1. Part 1

Part 1 will evaluate safety and clinical activity of GSK3326595 in participants with relapsed or refractory MDS and low-grade AML that has evolved from an antecedent MDS.

The Part 1 dose confirmation will be guided by the N-CRM model. No formal statistical hypotheses will be tested. The design classifies the DLT rate into four categories and makes dose recommendations based on posterior distribution of the four categories detailed in the Section 4.1.1.1.3.

CRM model may not be employed until the first DLT occurs. It is estimated that at least 6 and up to 12 participants will be enrolled into Part 1 dose escalation. The prior distribution assumptions will use the information from the GSK3326595 first time in human study 204653. Details on the model will be provided in the Reporting and Analysis Plan (RAP).

The Part 1 expansion cohort will employ a Bayesian design that allows the trial to be monitored frequently with the constraint of both Type I and Type II error rates. The evaluation is designed to exclude a 30% clinical benefit rate (CBR) representing best available therapy in favour of a 50% clinical benefit rate. A close to non-informative prior will be used. Let p denote the CBR, the prior distribution used is p ~ Beta (0.05, 0.05). The cohort will be stopped early due to futility if the predictive probability of success is less than 1%. The success is defined as posterior probability of CBR > 30% at the end of the cohort is larger than 89.1%. The first interim analysis will be performed when at least 8 participants become evaluable. The maximum sample size is 35 participants, and the design will have type I error of 0.07 and power of 83%.

9.1.2. Part 2

Part 2 will evaluate safety and clinical activity of GSK3326595 in combination with 5-Azacitidine in newly diagnosed MDS, CMML.

9.1.2.1. Dose escalation

The Part 2 dose escalation will employ N-CRM design, similar to what is used for Part 1 dose escalation. The goal is to identify the MTD of GSK3326595 when combined with approved dose of 5-Azacitidine for each Regimen. It is estimated that approximately 24 participants will be enrolled in each Part 2 dose escalation cohorts. The MTD is defined in Section 4.1.3.1.1.

For each Regimen, simulations were conducted to determine the average sample size and percentage of times each dose would be selected as an MTD under different scenarios, assuming the N-CRM dose recommendations are followed. The simulations assume 3 dose levels starting at the second dose level, recruiting in cohort size of approximately 3 DLT evaluable participants, with maximum of 6 participants at each dose level (6 needed to declare an MTD) with further 6 for MTD confirmation, resulting in approximately 24 participants per dose escalation. The prior distribution assumptions for the combination treatment incorporates the information from the GSK3326595

monotherapy first time in human study 204653 and results from Part 1 of this study. The minimally informative prior for each parameter (α, β) for the N-CRM two parameter logistic model are specified via a bivariate normal distribution with a separate mean and standard deviation (SD) for α and ln(β) and a correlation term, ρ, using reference dose level 2. The parameters of the model are:

QD schedule: α= -1.7681 (2.5018), ln(β) = -5.7972 (0.0012), ρ = -0.9975

BID schedule: α= -1.4373 (2.2972), ln(β) = -0.1725 (0.4273), ρ = -0.9964

Further details on the model will be provided in the RAP. The simulation results are shown in Table 10. For each scenario a dose with a true DLT rate falling in the target toxicity interval are highlighted. The average sample sizes over the 1000 clinical trials simulated under the four simulation scenarios were 10.4, 9.4, 8.0 and 7.1 for QD and it is 10.1, 8.6, 7.5 and 6.8 for BID schedule. The percent of trials with all toxic dose were 6%, 23% 60% and 72% for QD and these were 9%, 38%, 65% and 75% for BID schedule.

Table 10 Operating Characteristics

GSK3326595 Dose and Regimen in combination with 5-Azacitidine	Scenario 1: Low Toxicity		Scenario 2: Target Toxicity		Scenario 3: Two Target Toxicity		Scenario 4: High Toxicity	
	True DLT Rate (%)	Percent of Times Selecting Dose as MTD (%)	True DLT Rate (%)	Percent of Times Selecting Dose as MTD (%)	True DLT Rate (%)	Percent of Times Selecting Dose as MTD (%)	True DLT Rate (%)	Percent of Times Selecting Dose as MTD (%)
300 mg QD	20	81.3	20	65.0	40	20.7	45	12.2
200 mg QD	10	12.0	15	10.8	30	15.2	35	13.0
100 mg QD	0	6.7	10	24.2	20	64.1	25	74.8
150 mg BID	20	78.5	25	47.5	40	19.7	45	11.5
100 mg BID	10	12.3	20	14.3	30	15.3	35	13.5
50 mg BID	0	9.2	15	38.2	20	65.0	25	75.0

9.1.2.2. Dose Expansion

Part 2 Dose Expansion will treat approximately 35 participants and will employ a Bayesian approach that allows the trial to be monitored frequently as detailed in Table 8. The evaluation is designed to exclude a 17% CR rate for 5-Azacitidine in favour of a 32% CR rate. The decision making framework was set up based on the positive and negative guideline. Positive guideline is set as at least 90% probability that the true CR rate with combination treatment is > 17%, or Pr (true CR rate > 17% | data) > 90%, and

the negative guideline is set as at least 90% probability that the true CR rate is < 32%, or Pr(true CR rate < 32% | data) > 90%; if neither guidelines are met, ORR and safety will be taken in the decision making. A vague prior was used to assess the operating characteristics of the design with the prior distribution for the CR rate of Beta (0.017, 0.036). The minimum observed value that meets the criteria for the positive guideline is 10 or more CR out of 35 participants, the maximum observed value that meets the criteria for the negative guidelines is 7 or less CR out of 35 participants. Predictive probability (which is the probability of achieving failure at the end of study with 35 participants given the data observed) will be used to guide the interim decision-making, starting with 8 evaluable participants. The futility threshold is the predictive probability of negative guideline is more than 95%. With such decision making framework, taking into account the interim analyses the operating characteristics are presented in Table 11.

Table 11 Operating Characteristics

True CR Rate (%)	Probability of continuing (%)	Probability of stopping (%)	Probability of making a decision based on other endpoints (%)
17%	5.9	78.5	15.6
25%	36.5	36.1	27.4
32%	71.2	12.0	16.8

9.2. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants who sign the ICF
DLT Evaluable	For DLT assessment (Part 1 Dose Confirmation and Part 2 Dose Escalation): defined as participants who received at least 75% of the planned doses of GSK3326595 and all seven planned doses of 5-Azacitidine (Part 2) within the 28-day DLT observation period or those who have had a DLT.
Response Evaluable	Defined as participants who have had two post baseline disease assessments, have progressed or died, or permanently discontinued from the study intervention
All Treated	Participants who receive at least one dose of GSK3326595 as monotherapy or at least one dose of both combination drugs as combination treatment.
PK	Participants from the All Treated Population for whom a PK sample is obtained and analyzed.

9.3. Statistical Analyses

9.3.1. Efficacy Analyses

9.3.1.1. Efficacy Endpoints

Clinical benefit rate (CBR):

- Part 1 and Part 2: defined as the percentage of participants with CR, mCR, PR, SD lasting at least 8 weeks, and HI, as per IWG criteria (Appendix 9: IWG Criteria for Response for Participants in Part 1 and Part 2). Participants with unknown or missing response will be included in the denominator when calculating the percentage.

Complete remission rate (CR):

- Part 2: defined as the percentage of participants with CR as per IWG criteria (Appendix 9: IWG Criteria for Response for Participants in Part 1 and Part 2). Participants with unknown or missing response will be included in the denominator when calculating the percentage.

Overall Response Rate (ORR):

- Part 1 and Part 2: defined as the percentage of participants with CR, mCR, or PR as per IWG criteria (Appendix 9: IWG Criteria for Response for Participants in Part 1 and Part 2). Participants with unknown or missing response will be included in the denominator when calculating the percentage.

Progression Free Survival (PFS):

- Part 1 and Part 2 Dose Expansion: defined as the time from the first dose of study intervention to disease progression per IWG criteria or death due to any cause, whichever occurs earlier. Participants who have not progressed or died at the time of the PFS analysis, will be censored at the date of last adequate disease assessment. In addition, participants with an extended time without adequate assessment or who start a new anti-cancer therapy prior to a PFS event will be censored at the date of last adequate disease assessment (assessment where visit level response is CR, mCR, PR, HI, or SD) prior to the extended time without adequate assessment or initiation of new anti-cancer therapy, respectively. Further details on rules for censoring will be provided in the RAP.

Overall Survival (OS):

- Part 1 and Part 2 Dose Expansion: defined as the time from the first dose of study intervention to the death due to any cause. Participants who are alive at the time of OS analysis will be censored at the last date of known contact.

CCI [redacted]:

- CCI [redacted] (Appendix 9: IWG Criteria for Response for Participants in Part 1 and Part 2).

CCI [redacted]

- CCI [redacted] (Appendix 9: IWG Criteria for Response for Participants in Part 1 and Part 2). For participants who have not progressed or died at the time of the DOR analysis, the same censoring rule as for PFS analysis will be used.

9.3.1.2. Part 1

All efficacy analyses in Part 1 will be performed based on All Treated population unless otherwise specified. Participants enrolled in Part 1 dose escalation will be included in the dose expansion cohort analysis given the participant was treated at the same dose as the dose expansion cohort.

Primary Efficacy Endpoint – CBR

The estimate of CBR along with 95% exact CI will be provided. The interim futility analyses for the dose expansion cohorts will be based on the All Evaluable population and primary/final efficacy analysis will be based on the All Treated population.

Secondary Efficacy Endpoint - ORR

The estimate of ORR along with 95% exact CI will be provided.

Secondary Efficacy Endpoint - PFS

PFS will be summarized using Kaplan-Meier quantile estimates along with 95% CIs, if data warrant.

Secondary Efficacy Endpoint - OS

If data warrant, OS will be summarized using Kaplan-Meier quantile estimates along with 95% CIs.

Exploratory Efficacy Endpoint - CCI [redacted]

CCI [redacted]

Exploratory Efficacy Endpoint - CCI [redacted]

CCI [redacted]

CCI

9.3.2. Safety Analyses

All safety analyses will be performed on the All Treated Population. Unless otherwise specified, safety summaries will be conducted by dose for Part 1 and Part 2 dose escalation cohorts respectively.

9.3.2.1. Extent of Exposure

The treatment exposure will be summarized with treatment duration and dose intensity (daily dose for oral daily dosing) as well as the dose modifications including dose reductions, dose interruptions/delays and dose escalations. The summaries will be provided for GSK3326595 and 5-Azacitidine separately in Part 2A analyses. Details will be specified in the RAP.

9.3.2.2. Adverse Events

Adverse events will be coded using the standard MedDRA and grouped by system organ class. Adverse events will be graded by the investigator according to the NCI-CTCAE v4.

Events will be summarized with frequency and percentage by preferred term. Separate summaries will be provided for all AEs regardless of grade, treatment-related AEs, treatment-related AEs by maximum grade, SAEs, treatment-related SAEs, AEs leading to discontinuation of study intervention, AEs leading to dose reductions and AEs leading to dose interruptions/delays. Details will be provided in the RAP.

DLTs will be listed and summarized by dose cohort for Part 1 dose escalation and Part 2 dose escalation based on DLT Evaluable Population.

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

9.3.2.3. Clinical Laboratory Evaluations

Hematology and clinical chemistry data will be summarized using frequencies and proportions according to NCI-CTCAE v4. Laboratory test results outside the reference ranges that do not have an associated NCI-CTCAE criterion will be summarized using proportions. Summaries by visit will include data from scheduled assessments only, and all data will be reported according to the nominal visit date for which it was recorded (i.e., no visit windows will be applied). Unscheduled data will be included in 'worse case post baseline' summaries which will capture a worst case across all scheduled and unscheduled visits after the first dose of study intervention. Further details will be provided in the RAP.

9.3.2.4. Other Safety Measures

Data for vital signs, ECGs, and cardiac output evaluation (e.g., echocardiogram) will be summarized based on predetermined criteria identified to be of potential clinical concern. Further details will be provided in the RAP.

9.3.3. Other Analyses

9.3.3.1. Pharmacokinetic Analyses

The plasma concentrations for individual participants will be determined using a validated analytical method for GSK3326595. For participants participating in serial sampling, plasma GSK3326595 concentration-time data will be analyzed by non-compartmental methods with Phoenix WinNonlin. The following pharmacokinetic parameters will be determined, as data permit:

- maximum observed plasma concentration (Cmax)
- time to Cmax (tmax)
- area under the plasma concentration-time curve (AUC(0-t), AUC(0-∞) and AUC(0-τ))
- apparent terminal phase half-life (t½).
- oral clearance (CL/F)

- time invariance (TI) and accumulation ratio (AR) as calculated by the following equations:

$$TI = \frac{AUC(0-\tau), Day15}{AUC(0-\infty), Day1}$$

$$AR = \frac{AUC(0-\tau), Day15}{AUC(0-\tau), Day1}$$

$$TI = \frac{AUC(0-\tau), Day15}{AUC(0-\infty), Day1}$$

$$AR = \frac{AUC(0-\tau), Day15}{AUC(0-\tau), Day1}$$

For Part 2, additionally plasma concentration of 5-Azacitidine will be determined using a validated analytical method. Plasma 5-Azacitidine concentration-time data will be analyzed by non-compartmental methods with Phoenix WinNonlin and similar pharmacokinetic parameters as above will be determined, as data permit.

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

Cmax and AUC (AUC(0-∞), single dose; and AUC(0-τ), steady state) will be plotted as a function of the dose administered. If more than 2 dose cohorts are required to reach MTD (or the recommended dose based on available safety, PK and response data),dose proportionality of AUC and Cmax for GSK3326595 following single dose administration and AUC(0-τ) and Cmax following repeat dose administration will be assessed graphically and using the power model as described below:

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

where a is the intercept and b is the slope.

The power model will be fitted by restricted maximum likelihood (REML) using Statistical Analysis System (SAS) Proc Mixed. Both the intercept and slope will be fitted as fixed effects. If there is sufficient data, the model may also be fit with the intercept and/or slope as random effects depending on the ability of the model to converge and on estimation of variance-covariance matrix. The mean slope and corresponding 90% CI will be estimated from the power model.

A nonlinear mixed effects model may be used to determine population pharmacokinetic parameters and identify important covariates (e.g., age, weight, or disease related

covariates). Further details of population PK analysis will be described in the RAP; results of such an analysis may be included in a report separate from the clinical study report.

9.3.3.2. Pharmacokinetic/Pharmacodynamic Analyses

CCI [redacted] Initially, the relationships will be explored graphically. If these graphical analyses suggest a relationship between safety/efficacy/PD endpoints and GSK3326595 PK parameters, PK/PD models may be derived and evaluated using the nonlinear mixed effect modeling approach. Further details of PK/PD analyses will be described in the RAP; results of these analyses may be included in a report separate from the clinical study report.

9.3.3.3. Pharmacodynamic/Biomarker Analyses

If data permit, the relationships between various PD endpoints and biomarkers will be explored similarly to Section 9.3.3.2.

9.3.4. Interim Analyses

Full details of the interim analyses will be specified in the RAP.

9.3.4.1. Part 1

The primary driver for the dose-escalation decision(s) will be safety and tolerability of each dose cohort.

For Part 1 dose escalation and de-escalation decisions will be guided by an N-CRM model. Predicted DLT rates will be provided with the aim of escalating to doses with small probability of excessive or unacceptable toxicity.

For Part 1 dose expansion cohort, the first interim analysis will be performed when at least 8 participants become evaluable. Participants who were enrolled during dose escalation but treated at the same dose as expansion cohort will be included in the analysis. The cohort will be stopped early due to futility if the predictive probability of success is less than 1%. The interim futility analysis will be performed every 2-3 months depending on enrollment with minimum additional 5 evaluable participants. All evaluable population will be used for the interim futility analyses. The cohort may be stopped early for futility but not for efficacy.

9.3.4.2. Part 2

The interim analyses for the Dose Expansion are specified in Section 4.1.3.1.2.

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11. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

11.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

11.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with:
- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations
    - The protocol, protocol amendments, ICF, IB, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
    - Any amendments to the protocol will require IEC/IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

- The investigator will be responsible for the following:
    - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC
    - Notifying the IRB/IEC of SAE or other significant safety findings as required by IRB/IEC procedures
    - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

11.1.2. Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

11.1.3. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.
- Participants who are rescreened are required to sign a new ICF.

The ICF may contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research in accordance with Standard Operating Procedure (SOP)-GSKF-410. The investigator or authorized designee will explain to each participant the objectives of the exploratory research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a participant's agreement to allow any remaining specimens to be used for exploratory research. Participants who decline to participate will not provide this separate signature.

11.1.4. Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

11.1.5. Dissemination of Clinical Study Data

- 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 participants, 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.
- GSK may make anonymized participant-level data from this trial available to external researchers for scientific analyses or to conduct further research that can help advance medical science or improve participant care. This helps ensure the data provided by the trial participants are used to maximum effect in the creation of knowledge and understanding.

11.1.6. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (e.g., Contract Research Organizations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 25 years from the issue of the final Clinical Study Report (CSR)/ equivalent summary unless local regulations or institutional policies require a longer retention period. No records may be

destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

11.1.7. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in the SRM

11.1.8. Study and Site Closure

GSK or its designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of GSK. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development

11.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 12 will be performed by a local laboratory, with the following exceptions: The additional urine and serum renal biomarker testing, will be performed at the central laboratory. Testing for homocysteine and methylmalonic acid levels may be performed either locally or centrally.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 12 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit	RBC Indices: Mean Corpuscular Volume (MCV) Mean Corpuscular Haemoglobin (MCH) % Reticulocytes	White Blood Cell (WBC) count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils Myeloblasts (if present)	
Clinical Chemistry[1]	BUN	Potassium	Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total and direct bilirubin
	Creatinine	Sodium	Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT)	Total Protein
	Glucose (fasting)	Calcium	Alkaline phosphatase	Albumin
	Amylase	Lipase	Serum bicarbonate	

Laboratory Assessments	Parameters
Folate and selected vitamins	Serum B12 and Folate. For borderline results of B12 and/or folate, the following 2 additional tests will be performed within 2 weeks of the borderline result: Methylmalonic acid (serum or plasma) and Homocysteine (serum or plasma). **B12:** • >300 pg/mL (above 221 pmol/L) – Normal • 200 to 300 pg/mL (148 to 221 pmol/L) – Borderline • <200 pg/mL (below 148 pmol/L) – Low; consistent with deficiency **Folate:** • >4 ng/mL (above 9.1 nmol/L) – Normal. • From 2 to 4 ng/mL (from 4.5 to 9.1 nmol/L) – Borderline. • <2 ng/mL (below 4.5 nmol/L) – Low; consistent with folate deficiency.
Thyroid Function	Thyroid stimulating hormone (TSH), free Tri-iodothyronine (T3), Free thyroxine (T4) – Screening, Week 5 Day 1, and Week 9 Day 1 and every 8 weeks thereafter and EOT.
Coagulation	Partial Thromboplastin Time (PTT), Prothromin time/International Normalized Ration (PT/INR)
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase, by dipstick • Microscopic examination (if blood or protein is abnormal)
Additional Urine and serum renal biomarkers (Only participants with baseline eGFR <60 ml/min/1.73 m^2)	• NGAL, KIM-1, and albumin/creatinine ratio (urine) • Cystatin C (serum)
Pregnancy testing	• Human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)[2]
Screening Tests	• Follicle-stimulating hormone and estradiol (as needed in women of non-childbearing potential only) • Serology: HIV antibody, hepatitis B surface antigen [HBsAg], and hepatitis C virus [HCV] antibody. A positive HCV antibody must be confirmed via second study (e.g., HCV RNA or comparable test) The results of each test must be entered into the CRF.

NOTES :
1. Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 7 and Appendix 6. All events of ALT ≥3 × upper limit of normal (ULN) and bilirubin ≥2 × ULN (>35% direct bilirubin) or ALT ≥3 × ULN and international normalized ratio (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).
2. Serum testing is required at screening. For all other pregnancy tests specified in the SoA, either serum or urine testing may be used.

From the first dose of GSK3326595 until 30 days after the last dose of study treatment, all laboratory tests with abnormal values that are considered clinically significant should be repeated as clinically indicated until the values return to normal (per institutional guidelines) or back to the pre-study 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.

11.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

11.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of a study intervention, whether or not considered related to the study intervention. • 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 study intervention.

Events <u>Meeting</u> the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease). • 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 intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses 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. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

Events <u>NOT</u> Meeting the AE Definition
• 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 participant'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 participant's condition.
- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which 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.

11.3.2. Definition of SAE

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).

A SAE is defined as any untoward medical occurrence that, at any dose:
Results in death
Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant 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.
Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant 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 outpatient setting. Complications that occur during hospitalization are AE. If a complication prolongs hospitalization or fulfils 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.
Results in persistent disability/incapacity • 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 (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

Is a congenital anomaly/birth defect
Other situations: • Medical or scientific judgment should be exercised in deciding whether SAE 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 participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. Examples of such events include 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.

11.3.3. 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

11.3.4. Recording and Follow-Up of AE and SAE

AE and SAE Recording
• When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event. • The investigator will then record all relevant AE/SAE information in the CRF.

- It is **not** acceptable for the investigator to send photocopies of the participant'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 case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to GSK.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

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.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/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 underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the IB and/or Product Information, for marketed products, in 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 in which 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 before the initial transmission of the SAE data to** GSK**.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by GSK to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to GSK within 24 hours of receipt of the information.

11.3.5. Reporting of SAE to GSK

SAE Reporting to GSK via Electronic Data Collection Tool

- The primary mechanism for reporting SAE to GSK will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next Section) in order to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool 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 participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next Section) or to the medical monitor by telephone.
- Contacts for SAE reporting can be found in SRM.

SAE Reporting to GSK via Paper CRF

- Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the **medical monitor**
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts for SAE reporting can be found in SRM.

11.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

11.4.1. Definitions:

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

If fertility is unclear (e.g., amenorrhea in athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with one (or more) of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

   For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

   Note: Documentation can come from the site personnel's: review of the participant's medical records, medical examination, or medical history interview.
3. Postmenopausal female
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
   - A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement consistent with the local laboratory's reference range for postmenopausal females is required. Females on Hormonal Replacement Therapy (HRT) and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

11.4.2. Contraception Guidance:

Female Participants

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in Table 13. Female participants of non-childbearing potential have no requirements for contraception.

Table 13 Highly Effective Contraceptive Methods

• **CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:**
• **Highly Effective Methods[b] That Have Low User Dependency**
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)[c]
• Bilateral tubal occlusion
• Vasectomized partner   • *Note: Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.*
• **Highly Effective Methods[b] That Are User Dependent**

• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c]
  • oral
  • intravaginal
  • transdermal
  • injectable

• Progestogen-only hormone contraception associated with inhibition of ovulation[c]
  • oral
  • injectable

• Sexual abstinence   • *Note: Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant*

a. Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies. b. Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly. c. If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action. Note: Periodic abstinence (calendar, sympto-thermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception for this study. Male condom and female condom should not be used together (due to risk of failure with friction)

Pregnancy Testing

- WOCBP should only be included after a confirmed menstrual period and a negative highly sensitive serum pregnancy test
- Additional pregnancy testing (either serum or urine) must be performed every four weeks during the treatment period and at the EOT visit.
- Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected

Male participants

- Male participants with female partners of child-bearing potential are eligible to participate if they agree to ONE of the following during the protocol-defined time frame in Section 5.1:
  - Are abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent
  - Agree to use a male condom plus an additional method of contraception with a failure rate of <1% per year as described in Table 13 when having penile-vaginal intercourse with a woman of childbearing potential
- Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration during the protocol-defined time frame
- In addition male participants must refrain from donating sperm for duration of study and for 95 days after the last dose of GSK3326595 or as indicated in package insert for 5-Azacitidine.

11.4.3. Collection of Pregnancy Information:

Male participants with partners who become pregnant

- Investigator will attempt to collect pregnancy information on any male participant's female partner of a male study participant who becomes pregnant while participating in this study. This applies only to male participants who receive GSK3326595.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the

appropriate form and submit it to GSK within 24 hours of learning of the partner's pregnancy.

- The female 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.

Female Participants who become pregnant

- Investigator will collect pregnancy information on any female participant, who becomes pregnant while participating in this study.
- Information will be recorded on the appropriate form and submitted to GSK within 24 hours of learning of a participant's pregnancy.
- Participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow up information on participant and neonate, 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 intervention by the investigator, will be reported to GSK as described in Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting. 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 participant who becomes pregnant while participating will be withdrawn from the study

11.5. Appendix 5: Genetics

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 GSK3326595 or MDS, CMML and AML, and related diseases. They may also be used to develop tests/assays including diagnostic tests) related to GSK3326595 or study interventions of this drug class, and MDS, CMML and AML. 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 for relationships between genetic variants and response after treatment with GSK3326595, e.g. safety/tolerability, and/or efficacy. Additional analyses may be conducted if it is hypothesised 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 GSK3326595 or study interventions 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 GSK3326595 or study interventions of this class) or MDS, CMML and AML continues but no longer than 15 years after the last participant's last visit or other period as per local requirements.

11.6. Appendix 6: Liver Safety: Required Actions and Follow-up Assessments and Study Intervention Rechallenge Guidelines

Liver Safety: Required Actions and Follow-up Assessments

Phase I/II liver chemistry stopping and increased monitoring criteria have been designed to assure participant 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 **Participant with entry criteria ALT≤ 2.5 x ULN**	
ALT-absolute	ALT ≥ 5xULN
ALT Increase	ALT ≥ 3xULN persists for ≥4 weeks
Bilirubin[1, 2]	ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin)
INR[2]	ALT ≥ 3xULN **and** INR>1.5, if INR measured
Cannot Monitor	ALT ≥ 3xULN **and** cannot be monitored weekly for 4 weeks
Symptomatic[3]	ALT ≥ 3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity

Required Actions and Follow up Assessments following ANY Liver Stopping Event	
Actions	**Follow Up Assessments**
• **Immediately** discontinue study treatment • Report the event to GSK **within 24 hours** • Complete the liver event 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 participant until liver chemistries resolve, stabilize, or return to within baseline (see **MONITORING** below) • **Do not restart/rechallenge** participant with study treatment unless allowed per protocol and GSK Medical Governance approval **is granted**	• Viral hepatitis serology[4] • Only in those with underlying chronic hepatitis B at study entry (identified by positive hepatitis B surface antigen) quantitative hepatitis B DNA and hepatitis delta antibody[5]. • Blood sample for pharmacokinetic (PK) analysis, obtained 2 days after last dose[6] • Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH). • Fractionate bilirubin, if total bilirubin ≥2xULN • Obtain complete blood count with differential to assess eosinophilia

• If restart/rechallenge **not allowed per protocol or not granted**, permanently discontinue study treatment and may continue participant in the study for any protocol specified follow up **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 participants 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 participants weekly until liver chemistries resolve, stabilize or return to within baseline	• Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form • Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications • Record alcohol use on the liver event alcohol intake case report form **For bilirubin or INR criteria:** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG or gamma globulins). • Serum acetaminophen adduct HPLC assay (quantifies potential acetaminophen contribution to liver injury in participants with definite or likely acetaminophen use in the preceding week [James, 2009]). **NOTE: not required in China** • 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 participant 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 participants 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. If hepatitis delta antibody assay cannot be performed, it can be replaced with a PCR of hepatitis D RNA virus (where needed) [Le Gal, 2005].
6. PK sample may not be required for participants known to be receiving placebo or non-GSK comparator treatments.) 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 participant'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**
Participant <u>with</u> entry criteria ALT≤2.5x ULN ALT ≥3xULN **but** <5xULN **and** bilirubin <2xULN, **without** symptoms believed to be related to liver injury or hypersensitivity **and** who can be monitored weekly for 4 weeks **Participant <u>with documented</u> liver metastases/tumor infiltration at baseline AND entry criteria ALT>2.5 x ULN but ≤5 x ULN** ALT ≥3x ULN and 1.5x baseline value **but** ALT <5x ULN and 2x baseline value **and** bilirubin <2xULN**, without** symptoms believed to be related to liver injury, or hypersensitivity **and** who can be monitored weekly for 4 weeks	• Notify the GSK medical monitor **within 24 hours** of learning of the abnormality to discuss participant safety. • Participant can continue study treatment • Participant must return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) until they resolve, stabilise or return to within baseline • If at any time participant meets the liver chemistry stopping criteria, proceed as described above **For participants with entry criteria ALT≤2.5 x ULN** • If, after 4 weeks of monitoring, ALT <3xULN and bilirubin <2xULN, monitor participants twice monthly until liver chemistries normalize or return to within baseline.

References

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Le Gal F, Gordien E, Affolabi D, Hanslik T, Alloui C, Dény P, Gault E. Quantification of Hepatitis Delta Virus RNA in Serum by Consensus Real-Time PCR Indicates Different Patterns of Virological Response to Interferon Therapy in Chronically Infected Patients. J Clin Microbiol. 2005;43(5):2363–2369.

Liver Safety – Study Treatment Restart or Rechallenge Guidelines

If participant meets liver chemistry stopping criteria do not restart/rechallenge participant with study intervention 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 participant

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

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

Following drug-induced liver injury, **drug rechallenge is associated with a 13% mortality across all drugs in prospective studies**.[1] 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)
- participant 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[2,3]
- evidence of drug-related preclinical liability (e.g. reactive metabolites; mitochondrial impairment[3])

Rechallenge refers to resuming study intervention following drug induced liver injury (DILI). Because of the risks associated with rechallenge after DILI this should only be considered for a participant 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 intervention can be considered where:

- Investigator requests consideration of rechallenge with study intervention for a participant who is receiving compelling benefit with study intervention that exceeds risk, and no effective alternative therapy is available.

- Ethics Committee or Institutional Review Board approval for rechallenge with study intervention must be obtained, as required.
- If the rechallenge is approved by GSK Medical Governance in writing, the participant must be provided with a clear description of the possible benefits and risks of study intervention administration, including the possibility of recurrent, more severe liver injury or death.
- The participant must also provide signed informed consent specifically for the rechallenge with study intervention. Documentation of informed consent must be recorded in the study chart.
- Study intervention must be administered at the dose specified by GSK.
- Participants approved by GSK Medical Governance for rechallenge with study intervention 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 intervention rechallenge, participant meets protocol-defined liver chemistry stopping criteria, study intervention should be permanently discontinued.
- GSK Medical Monitor, and the Ethics Committee or Institutional Review Board as required, must be informed of the participant's outcome following study intervention rechallenge.
- GSK to be notified of any adverse events, as per Section 8.4.

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

Restart refers to resuming study intervention 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 intervention should not be associated with Human Leukocyte Antigen (HLA) markers of liver injury.

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

- Investigator requests consideration for study intervention 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 intervention-induced liver injury or study intervention 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 intervention restart must be obtained, as required.

- If restart of study intervention is approved by GSK Medical Governance in writing, the participant must be provided with a clear description of the possible benefits and risks of study intervention administration, including the possibility of recurrent, more severe liver injury or death.
- The participant must also provide signed informed consent specifically for the study intervention restart. Documentation of informed consent must be recorded in the study chart.
- Study intervention must be administered at the dose specified by GSK.
- Participants approved by GSK Medical Governance for restarting study intervention 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 intervention re-start, participant 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 participant's outcome following study intervention restart.
- GSK to be notified of any adverse events, as per Section 8.5.

References:

- [1]Andrade RJ, Robles M, Lucena MI. Rechallenge in drug-induced liver injury: the attractive hazard. Expert Opin Drug Saf. 2009;8:709-714.
- [2]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.
- [3]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.

11.7. Appendix 7: IPSS-R Scoring System for MDS

Table 14 IPSS-R prognostic score values

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.

Table 15 IPSS-R prognostic risk categories/scores

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.

11.8. Appendix 8: CMML Scoring System

11.8.1. CPSS Scoring System (Such, 2013)

Table 16 CPSS: Variables and scores used for predicting likelihood of survival and leukemic evolution in the individual patient with CMML

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.

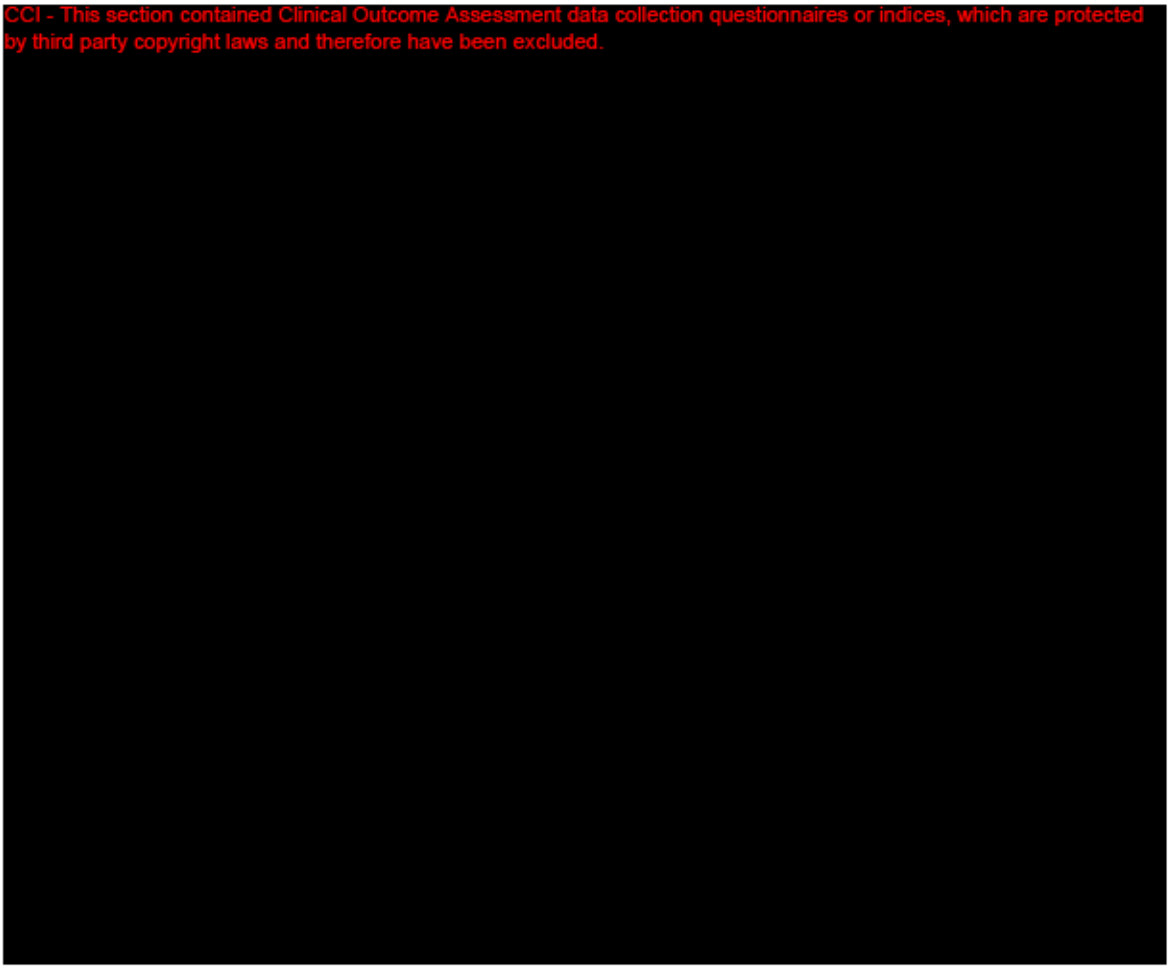
Table 17 CPSS: Variables and scores used for predicting likelihood of survival and leukemic evolution in the individual patient with CMML

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.

11.8.2. CPSS-mol Scoring System (Elena, 2016)

Table 18 Variables and prognostic score values of the CMML genetic score

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.



- —, Not applicable.
- ↵* Cytogenetic risk groups are defined according to Such13: low, normal, and isolated –Y; intermediate, other abnormalities; and high, trisomy 8, complex karyotype (≥3 abnormalities), and abnormalities of chromosome 7.

Table 19 Variables and prognostic score values of the CPSS-Mol

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.

- — , Not applicable.
- ↲* Genetic risk groups are defined as reported in Table 18.
- ↲† RBC transfusion dependency is defined according to Elena and Such.

References

Elena C, Galli A, Such E, Meggendorfer M, Ulrich G, Rizzo E. Integrating clinical features and genetic lesion in the risk assessment of patients with chronic myelomonocytic leukemia. Blood. 2016;128(10):1408-1417

Such E, Germing U, Malcovati L, Cervera J, Kuendgen A, Della Porta MG. Development and validation of a prognostic scoring system for patients with chronic myelomonocytic leukemia. Blood, 2013 ;121(15) :3005-15.

11.9. Appendix 9: IWG Criteria for Response for Participants in Part 1 and Part 2

Category	Response Criteria
Complete Remission	Bone marrow: ≤5% myeloblasts with normal maturation of all cell lines[a] Persistent dysplasia will be noted[a,b] Peripheral blood (Response must be maintained for at least 4 weeks) Hgb ≥11 g/dL Platelets ≥100 Gi/L Neutrophils ≥ 1.0 Gi/L[b] 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]
Hematologic improvement (HI)	Erythroid (HI-E): Hgb increase of > 1.5 g/dL relevant reduction of units of RBC transfusions by an absolute number of at least 4 RBC transfusions/8wk compared with the pretreatment transfusion number in the previous 8 wk ; 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 participants 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	Participant 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 for MDS [Cheson, 2006].

References

Cheson BD, Greenberg PL, Bennett JM, Lowenberg R, Wijermans PW, Nimer SD, Pinto A, Beran M, de Witte TM, Stone RM, Mittelman M, Sanz GF, Gore SD, Schiffer CA, and Kantarjian H. Clinical application and proposal for modification of the International Working Group (IWG) response criteria in myelodysplasia. Blood. 2006 July 15;108, Number 2: 419-425.
http://www.bloodjournal.org/content/bloodjournal/108/2/419.full.pdf?sso-checked=true

11.10. Appendix 10: ECOG Performance Status

The performance status assessment is based on the ECOG scale [Oken, 1982]

0 = Fully active, able to carry on all pre-disease performance without restriction.

1 = Restricted in physically strenuous activity but ambulatory and able to carry out work

of a light or sedentary nature (e.g., light house work, office work).

2 = Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.

3 = Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.

4 = Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.

5 = Dead

References

Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET. Toxicity and response criteria of the Eastern Cooperative Oncology Group. American Journal of Clinical Oncology. 1982 Dec; 5(6):649-55

11.11. Appendix 11: Guidelines for Management of Toxicity

The following dose modification criteria for GSK3326595 should provide guidance for, but not act as a replacement for sound clinical judgment. The investigator should use clinical judgment to determine which drug may be contributing to the toxicity necessitating dose adjustment, and make the appropriate change for that drug. Dose modifications should be made after discussion with the GSK medical monitor. 5-Azacitidine dose adjustments shall be made in accordance with FDA package insert registered label.

Table 20 Dose Adjustment/Stopping Safety Criteria for GSK3326595

Toxicity	Dose Adjustment/Stopping Criteria	Management Guidelines
Thrombocytopenia	Grade 1 & 2 (platelet count above 50,000)	Continue dosing at same dose level with weekly or more frequent monitoring as necessary
	Grade 3 (platelet count between 25,000-50,000)	After discussion with medical monitor and using sound clinical judgement, continue at same dose. Monitor complete blood count (CBC) at least twice weekly, more frequently if clinically indicated.
	Grade 4 (platelet count below 25,000)	If platelet count <25,000 but ≥10,000 • Continue at same dose or at a reduced dose • Monitor CBC at least twice weekly • Transfuse platelets as per institutional standards If platelet count <10,000 • Continue at same dose or at a reduced dose • Monitor CBC at least twice weekly • Transfuse platelets as per institutional standard with subsequent CBC post-transfusion to ensure appropriate improvement in platelet counts. • If transfusion is unable to rescue platelet counts, then study intervention(s) should be interrupted until platelet counts recover to > 20,000 (either spontaneously or via transfusion).
Anemia, Neutropenia, and other Hematologic Toxicity	Grades 1 & 2	Continue dosing at same dose level with weekly or more frequent monitoring as necessary
	Grades 3 & 4	• Implement supportive measures (e.g., transfusion, growth factor support, prophylactic antimicrobials) per institutional standard • Continue dosing at same dose or consider reducing dose • Monitor CBC at least twice weekly, more frequently as necessary

Toxicity	Dose Adjustment/Stopping Criteria	Management Guidelines
QTcF	If >30 msec and <60 msec change from baseline AND manual QTcF <500 (average of three ECGs)	• Continue current dose of study intervention(s) • Supplement electrolytes, particularly potassium and magnesium, to recommended levels: (1) Maintain serum potassium > 4 mol/L (2) Maintain serum magnesium levels >0.85 mmol/L • Discontinue any concomitant medications with potential for QTcF prolongation. • Consider 24 hour or longer telemetry monitoring if clinically indicated.
	If ≥ 60 msec change from baseline occurs OR QTcF ≥500 (average of three ECGs)	• Discontinue study intervention(s) and notify the GSK Medical Monitor. (1) Supplement electrolytes to recommended levels: a. Maintain serum potassium > 4 mol/L b. Maintain serum magnesium levels >0.85 mmol/L (2) Rule out other potential etiologies for prolonged QTcF such as cardiac ischemia (3) Discontinue any concomitant medications with potential for QTcF prolongation. (4) Consider telemetry monitoring if clinically indicated. • This participant may consider restarting study intervention at a previous dose level if the following criteria for QTcF rechallenge are met : • QTcF Rechallenge Procedures: Do not rechallenge with study intervention unless under the following conditions: (1) QTcF event reduced to <450 msec, (2) potassium and magnesium levels are within institutional normal range, (3) a favorable risk/benefit profile (in the medical judgement of the Investigator and the GSK Medical Monitor), (4) approval within GSK medical governance: a. agreement with Safety Evaluation Medical Director and the Project Physician Lead, b. review with Chair or co-Chair of the GSK QT panel, c. Safety Evaluation Vice President (VP) and Clinical VP approval d. Head Unit Physician approval (5) Institutional IRB (or equivalent) approval, and

Toxicity	Dose Adjustment/Stopping Criteria	Management Guidelines
		(6) The participant is re-consented regarding the possible increased risk of QTc prolongation. • If approval for re-challenge is granted, the participant must be re-consented (with a separate informed consent specific to QTc prolongation) • Discontinuation procedures: If the participant is withdrawn due to QTcF event, the participant should complete the following activities post-dose: (1) Evaluation by cardiologist. (2) Weekly assessments for QTcF should be monitored weekly for two weeks, and then next assessment at 4 weeks post-dose. (3) If QTcF results have not resolved to baseline by 4 weeks post-dose, then continue every 4-5 weeks until resolution
Liver		• Refer to procedures outlined in Section 7.1.2 Liver Safety Required Actions and Follow up Assessments
Diarrhea	Grade 1	• Initiate supportive care including loperamide.
	Grade 2	• Initiate supportive care including loperamide. • Consider temporary discontinuation of study drug(s) and discuss with GSK Medical Monitor.
	Grade 3	• Above plus consider intravenous (IV) hydration, hospital admission and prophylactic antibiotics as appropriate. • Hold study drug(s) and discuss with GSK Medical Monitor. • If diarrhea recovers to Grade 1, discuss with medical monitor; consider resuming treatment at the same or lower dose based on clinical judgement.
	Grade 4	• Above plus consider intravenous (IV) hydration, hospital admission and prophylactic antibiotics as appropriate. • Discontinue study drug(s) permanently
Nausea/Vomiting	Grade 1	• Initiate supportive care with antiemetics as necessary.

Toxicity	Dose Adjustment/Stopping Criteria	Management Guidelines
	Grade 2	• Initiate supportive care with antiemetics as necessary • Consider temporary discontinuation of study drug(s) and discuss with GSK medical monitor. If drug is held, participant may resume therapy at same level once nausea/vomiting has resolved to ≤Grade 1.
	Grade 3	• Supportive care as above, plus consider intravenous (IV) hydration, hospital admission and IV nutrition as appropriate. • Hold study drug(s) and discuss with GSK Medical Monitor. • If nausea/vomiting recovers to less than Grade 2, discuss with medical monitor; consider resuming treatment at lower dose based on clinical judgement.
	Grade 4	• Supportive care as above, plus consider intravenous (IV) hydration, hospital admission and IV nutrition as appropriate • Discontinue study intervention(s) permanently
All Other Non-Hematologic Toxicity*	Grade 1	• Continue dosing with no change
	Grade 2	• Continue dosing with no change OR • Hold study drug(s) for up to 1 week for toxicity to be < Grade 2, then continue at the same dose (dose reduction is required if the grade 2 toxicity is considered a DLT)
	Grade 3	• 1st episode: Hold dose for one week intervals until≤ Grade 2, then restart study drug(s) at the same or reduced dose. • 2nd episode: Utilize an alternative, less frequent schedule or reduce by one dose level. If no recovery to ≤Grade 1* after a 21 day delay, participant should discontinue therapy.
	Grade 4	• Discontinue study drug(s) OR • In rare situations, based on discussion and written agreement between GSK medical monitor and investigator, if the participant is receiving benefit then the episode may be managed as per Grade 3 toxicity.

11.12. Appendix 12: Rationale for Response Assumptions

The statistical design for each Part of the study will test the hypothesis that GSK3326595 (either as a single agent or in combination with 5-Azacitidine, depending on the Part) will achieve a clinically meaningful result, versus the null hypothesis that the combination will achieve a response that is no better than historical controls. For each Part, the hypotheses were determined based on historical response rates in a comparable patient population. When determining appropriate efficacy hurdles, the following factors were taken into account:

Part 1:

For participants enrolled in Part 1, efficacy is defined as a clinical benefit rate (the percentage of participants that have achieved a CR, marrow CR, PR, HI, or SD lasting at least 8 weeks, by IWG criteria) of 50% relative to a 30% CBR. This was based, in part, on the study of rigosertib in a similar population of relapsed and refractory MDS (Garcia-Manero, 2016). This study demonstrated a CBR of approximately 60% with rigosertib, compared to a 30% CBR with best available care. Of note, this publication did not specify the duration of stable disease. Furthermore, a Phase I/II study of risogertib in relapsed/refractory MDS and AML that progressed from MDS (a similar population to the one in study 208809), demonstrated a 53% CBR (Navada, 2018). Taken together, 30% is a reasonable estimate for an ineffective therapy, and a CBR of 50% (which takes into account a durable stable disease in addition to complete and partial responses) is the threshold for further evaluation of GSK3326595 in this population.

Part 2:

In the pivotal AZA001 study in treatment-naïve participants, 5-Azacitidine demonstrated a significant improvement in OS compared to conventional care (Fenaux, 2009). In addition to the significant improvement in OS, 5-Azacitidine yielded an improved ORR (29% versus 12%) including a significant improvement in CR rate (17% versus 8%); on the other hand, the stable disease rate was not significantly different between the two arms. As treatment with 5-Azacitidine yielded an improved OS, as well as improved ORR and CR, CR rate was selected as the surrogate endpoint to evaluate in Part 2 of the current study. In a study that was conducted to validate the IWG criteria in higher-risk MDS patients using AZA001 study data, patients that achieved CR had a longer OS (median OS of 41 months), compared to patients who achieved PR (median OS of 26 months), marrow CR (median OS of 12 months) or heamatologic improvement (median OS of 13 months) (Komrokji, 2015). Based on this data CR was chosen as a surrogate endpoint for OS in this population.

As 5-Azacitidine alone in the AZA001 study yielded a 17% CR rate, this was selected as an assumption that any CR rate observed with the combination of 5-Azacitidine plus GSK3326595 was due to the effects of 5-Azacitidine alone. 32% was selected as an assumption for the combination, in order to demonstrate a benefit for the two agents in combination over 5-Azacitidine alone.

References

Fenaux P, Mufti GJ, Hellstrom-Lindberg E, Santini V, Finelli C, Giagounidis A. Efficacy of azacitidine compared with that of conventional care regimens in the treatment of higher-risk myelodysplatic syndromes : a randomised, open-label, phase III study. Lancet Oncology. 2009 Mar;10(3):223-32

Garcia-Manero G, Fenaux P, Al-Kali A, Baer MR, Sekeres MA, Roboz GJ. Rigosertib versus best supportive care for patients with high-risk myelodysplastic syndromes after failure of hypomethylating drugs (ONTIME): a randomised, controlled, phase 3 trial. Lancet Oncology 2016; 17: 496–508

Navada SC, Fruchtman SM, Odchimar-Ressig R, Dermakis EP, Petrone ME, Zbyszewski PS. A phase ½ study of rigosertib in patients with myelodysplastic syndromes (MDS) and MDS progressed to acute myeloid leukemia. Leukemia Research 2018; 64: 10-16

Perl A, Altman J, Cortes J, Smith C, Litzow M, Baer M. Selective inhibition of FLT3 by gilteritinib in relapsed or refractory acute myeloid leukaemia: a multicentre, first in human, open label, phase 1-2 study. Lancet Oncology, 2017. 18 (8) p1061–1075

11.13. Appendix 13: Overall Rationale for this Appendix

COVID-19 pandemic may impact the conduct of clinical studies. Challenges may arise from quarantines, site closures, travel limitations, interruptions to the supply chain for the investigational product or other considerations if site personnel or study participants become infected with COVID-19. These challenges may lead to difficulties in meeting protocol-specified procedures, including administering or using the investigational product or adhering to protocol-mandated visits and laboratory/diagnostic testing.

This protocol appendix outlines measures that may be applicable for any site impacted by the COVID-19 pandemic. The purpose of the appendix is to provide information on the measures to be taken to protect participants' safety, welfare and rights, and promote data integrity.

These measures will remain in place until the site is able to resume normal working activities.

Study Procedures During COVID-19 Pandemic

During the special circumstances caused by the current COVID-19 pandemic, the following considerations should be taken into account: specific public health guidance, the impact of any travel restrictions implemented by local/regional health authorities and local institutions, and individual benefit /risk when making enrollment and treatment decisions for trial participants.

Every effort should be made to adhere to protocol-specified assessments for participants on study intervention, including follow up however when not possible, for the duration of these special circumstances, the following measures may be implemented for enrolled participants where applicable country and local regulations and infrastructure allow.

- Clinical investigators should document in site files and in participant notes/Electronic Heath Records as appropriate how restrictions related to COVID-19 led to the changes in study conduct and duration of those changes and indicate which trial participants were impacted and how those trial participants were impacted (as per the current local COVID-19 related regulatory guidance).
- Missing protocol required data/visits due to COVID-19 must be noted in participant notes and recorded as a COVID-19-related protocol deviation.

Protocol Defined Procedures/Visits:

- Where applicable country and local regulations and infrastructure for home healthcare allow, home healthcare may take place at a location other than the clinical trial site to perform study assessments, which may include collection of blood and urine samples, measurement of vital signs and weight, and preparation and administration of study drug (at the discretion of the Investigator, based on safety and tolerability). It is the responsibility of the investigator to inform GSK when this occurs and to document in source notes. The participant should be informed of the plan and any potential risks associated with this approach and sign a revised

Informed Consent Form if required. IRB/Ethics committee should be informed and/or approve of this change in approach and the process documented in study files.

- Additional unscheduled safety assessments such as routine blood sampling may be performed at the discretion of the Investigator including in the participant's home, if deemed necessary. Biological samples may be collected at a different location, other than the study site (e.g., at participant's home) by qualified study personnel or at a local medical facility according to standard operating procedures and applicable regulations (see note). Biological samples should not be collected if they cannot be processed in a timely manner or appropriately stored until the intended use.
- Where applicable country and local regulations allow for telemedicine, and if visits to a site/home are not feasible, then the medical evaluation of the participant may take place by telemedicine. Telemedicine will use secure video conferences, phone calls, and a web portal and/or mobile application as a way of communicating with and monitoring the participant's progress. Details of telemedicine will be included in the SRM. The study investigator is responsible for ensuring that the identification, management, and reporting of AEs and SAEs are completed in accordance with the protocol and applicable regulations. AEs are first reported by participants to the investigator/study team or may be identified by the study team during interactions with the participants via telemedicine encounters. In addition, mobile nurses may identify AEs as well and report them to the investigator for evaluation. Additionally, AEs may be identified from lab reports, and other records. As determined by the investigator, the appropriate medical intervention, therapeutic intervention, and/or support measures are instituted, as necessary. The participant should be informed of the plan and any potential risks associated with the virtual medium and sign a revised Informed Consent Form if required. IRB/Ethics committee should be informed and/or approve of this change in approach and the process documented in study files.

Note: If the Investigator wishes to conduct a trial visit at a location that has not been previously assessed by GSK, it is the investigator's responsibility to identify an adequate alternate location and to notify GSK of the alternate location. The investigator should ensure that this alternate location meets ICH GCP requirements, is well-equipped to perform study procedures and covered by an adequate insurance. Furthermore, the investigator should have sufficient oversight to ensure that the staff at the alternate location are trained to perform study procedures.

Study Intervention(s)

- If despite best efforts it is not possible to administer the dose of study intervention as defined in the protocol (see Section 6 Study Interventions and Concomitant Therapy), the participant may still continue in the trial at Investigator discretion and advice of the Medical Monitor may be sought as appropriate. If allowed by country regulation/ethics, then GSK3326595 can be shipped direct-to-participant (DTP) from the investigational site to the participant's home address. The process for this shipment must be agreed with GSK who will provide the relevant documentation and links to courier sites required to ensure shipments are adequately temperature controlled (if required) throughout transportation.

- Any study participant in Part 2 who cannot attend a clinical site, or local medical facility where possible, will not be able to receive 5-Azacitidine at home. The participant may continue to receive GSK3326595 at home, if applicable, or withdraw from the study, whichever the Investigator and participant decide.
- No special procedures for the safe handling of GSK3326595 are required. Caution should be exercised when handling 5-Azacitidine; see package insert for more details.
- The Principal Investigator assumes GCP responsibilities for IMP handling and the medical control for dispensing to participants. Site Staff should document the dispensing in the Dispensing/Accountability Logs adding a comment that this was a DTP dispensing.
- Compliance with study intervention administration will be verified through observation by study staff or trained home healthcare professionals.
- In some cases, trial participants who no longer have access to investigational product or the investigational site may need additional safety monitoring (e.g., on withdrawal of an active investigational treatment).

Data Management/Monitoring:

- Diary cards may be transmitted from and to the investigator by electronic mail and or conventional mail. If copies/scans of completed diaries are sent to the investigator by electronic mail, the participant should be instructed to maintain the original documents and to return them to the site when a visit to the site will be allowed.
- If on-site monitoring is no longer permitted, GSK will consider remote Source Data Verification/Source Document Review (SDV/SDR) where permitted by the clinical site/institution. Remote SDV/SDR will be proposed to study sites to meet a participant and/or critical quality need, e.g., to assess participant safety or to ensure data integrity. In case of remote SDV/SDR, GSK will work with the site to ensure participant privacy.
- eCRF/CRF Final or Interim Sign off Process: The Principal Investigator (PI) is responsible for ensuring that the data within the eCRF casebook and any other data sources utilized during the study for each study participant is complete and consistent with source documents throughout the study (ICH GCP 4.9.1 4.9.2). The PI may sign/re-sign the eCRF from any computer/location by accessing InForm (or other electronic data capture [eDC] platform) using his/her unique eCRF log-in credentials. The PI may delegate this activity to another medically qualified and trained sub-investigator and this must be documented on the Delegation of Responsibilities (DoR) Log. It is recommended that the PI identifies a sub-investigator as a back-up for eCRF signatures. The sub-investigator must be appropriately trained on the protocol and eCRF requirements (with training documented), and the DoR log updated accordingly.
- Essential Document Sign Off Process: If an investigator is unable to print and sign essential documents such as Protocol /Amendment signature page then Email approval can be accepted by replying to the relevant email that is sent by GSK.

11.14. Appendix 14: Abbreviations and Trademarks

µL	Microlitre
µmol	Micromole
ABCG2	ATP-binding cassette sub-family G member 2
AE	Adverse Event
ALT	Alanine aminotransferase
AML	Acute myeloid leukaemia
ANC	Absolute neutrophil count
AR	Accumulation ratio
AST	Aspartate aminotransferase
AUC	Area under concentration time curve
$AUC_{(0-t)}$	Area under the Concentration-time Curve from time zero (pre-dose) to last time of quantifiable concentration within a participant across all treatments
$AUC_{(0-\tau)}$	AUC from 0 hours to the time of next dosing.
$AUC_{(0-\infty)}$	Area under the Concentration-time Curve from time zero to infinity
BAC	Best available care
BCRP	Breast cancer resistance protein
BID	Twice a day
BM	Bone marrow
BMD	Bone mineral density
BUN	Blood urea nitrogen
CBC	Complete blood count
CBR	Clinical benefit rate
cfDNA	Circulating cell free deoxyribonucleic acid
CI	Confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CKD-Epi	Chronic Kidney Disease Epidemiology Collaborative
CL/F	Oral clearance
C_{max}	Maximum observed serum concentration
cm	Centimeter
CMML	Chronic myelomonocytic leukaemia
CNS	Central Nervous System
Caco-2	heterogeneous human epithelial colorectal adenocarcinoma cell line
CONSORT	Consolidated Standards of Reporting Trials
CPSS (mol)	CMML-specific prognostic scoring system (molecular)
CR	Complete remission
CRi	Marrow response as per CR but platelet count <100 x 10^9/L or neutrophil count <1 x 10^9/L.
CRp	Marrow response as per CR but platelet count <100 x 10^9/L.
CRF	Case Report Form
CV	Cardiovascular
D	Day
DCIS	Ductal carcinoma in situ
del	Deletion
DEXA	Dual-energy X-ray absorptiometry

DHEA	Dehydroepiandrosterone
DILI	Drug induced liver injury
DL	Dose level
dL	Decilitres
DLTs	Dose limiting toxicities
DOR	Duration of response
DoR	Delegation of Responsibilities
DTP	Direct-to-participant
ECG	Electrocardiogram
ECHOs	Echocardiogram
ECOG	Eastern cooperative oncology group
eDC	Electronic data capture
eCRF	Electronic case report form
EGFR	Epithelial growth factor receptor
EOT	End of treatment
ePRO	Electronic Patient Reported Outcome
FACIT	Functional Assessment of Chronic Illness Therapy
FDA	Food and Drug Administration
FSH	Follicle stimulating hormone
g	Gram
GALT	Gut associated lymphoid tissue
GCP	Good Clinical Practice
GI	Gastrointestinal
Gi	Giga
g/L	Grams per litre
GSK	GlaxoSmithKline
H0	Null hypothesis
HA	Alternative hypothesis
HBsAg	Hepatitis B surface antigen
hCG	Human chorionic gonadotropin
HCV	Hepatitis C virus
Hgb	Hemoglobin
HI	Hematologic improvement
HI-E	Hematologic improvement Erythroid
HI-N	Hematologic improvement Neutrophil
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency virus
HLA	Human leukocyte antigen
HMGCoA	3-hydroxy-3-methylglutaryl-coenzyme A
HR	Hazard Ratio
HRQL	Health related quality of life
HRT	Hormonal replacement therapy
h	Hour
HPMC	Hydroxcypropyl methylcellulose
IB	Investigator's Brochure
ICF	Informed consent form

ICH	International Council for Harmonisation
IEC	Independent ethics committee
IHC	Immunohistochemistry
INDSRs	Investigational New Drug Safety Reports
INR	International normalized ratio
IP	Intraperitoneal
IP	Investigational product
IPSS-R	International Prognostic Scoring System Revised
IRB	Institutional review board
ITT	Intent-to-treat
IUD	Intrauterine devices
IUS	Intrauterine hormone release system
IV	Intravenous
IVRS/IWRS	Interactive voice/web response system
IWG	International Working Group
L	Liter
LLN	Lower limit of normal
LLS	Leukemia and Lymphoma Society
LP	Lumbar puncture
LV	Left ventricle
LVEF	Left Ventricular Ejection Fraction
MATE	Multidrug and Toxin Extrusion
mCR	Complete marrow remission
MCH	Mean corpuscular hemoglobin
MCV	Mean corpuscular volume
MDCK	Madine Darby canine kidney
MD	Myelodysplastic
MDS	Myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities Medical Dictionary for Regulatory Activities
MEP50	Methylosome protein 50
mEq/L	Milliequivalents per Litre
mg	Milligram
mg/m²	milligrams per meter squared
min	Minute
mIU	milli international unit
mL	milliliter
mmol	Millimoles
MP	Myeloproliferative
MPN	Myeloproliferative neoplasms
mRNA	Messenger ribonucleic acid
MSDS	Material Safety Data Sheet
msec	Millisecond
MTD	Maximum tolerated dose
n	Number

NCI-CTCAE	National Cancer Institute – Common Terminology Criteria for Adverse Events
N-CRM	Neuenschwander continual reassessment method
NHL	Non-Hodgkin's lymphoma
Ng	Nanogram
nm	Nanometers
NYHA	New York Heart Association
OAT	Organic Anionic Transporter
OCT	Organic Cationic Transporter
ORR	Overall response rate
OS	Overall survival
PCR	Polymerase chain reaction
PD	Pharmacodynamics
PD	Progressive disease
PFS	Progression free survival
pg	Picogram
Pgp	P-glycoprotein
PGx	Pharmacogenetics
PI	Principal Investigator
PI3K	phosphoinositol-3 kinase
PK	Pharmacokinetic
pmol	Picomole
PP	Per protocol
PR	Partial response
pre-mRNA	Precursor messenger ribonucleic acid
PRMT5	Protein arginine methyltransferase 5
PRMT5i	Protein arginine methyltransferase 5 inhibitor
PRO	Patient Reported Outcome
PT	Prothromin time
PTT	Partial Thromboplastin Time
Q	Every
QD	Once a day
QLQ-C30	Quality of Life Questionnaire Core-30
QoL	Quality of life
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate according to Fridericia's formula
RAP	Reporting and Analysis Plan
RB1	Retinoblastoma protein 1
RBC	Red Blood cells
R/R	Relapsed/Refractory
REML	Restricted maximum likelihood
RNA	Ribonucleic acid
RT-PCR	Reverse transcriptase polymerase chain reaction
SAE	Serious Adverse Event
SAS	Statistical analysis system
SC	Subcutaneous
SD	Stable disease

CCI	[redacted]
SDV/SDR	Source Data Verification/Source Document Review
SEER	Surveillance, Epidemiology and End Results
SF3B1	Splicing factor 3B subunit 1
SGPT	Serum glutamic pyruvic transaminase
SOA	Schedule of Activities
SOP	Standard operating procedure
SRM	Study Reference Manual
SRT	Safety Review Team
SRSF2	Serine and arginine rich splicing factor 2
SS	Steady state
ST7	Suppressor of Tumorigenicity 7
SUSAR	Suspected Unexpected Serious Adverse Events
$t_{1/2}$	Half life
T3	Triiodothyronine
T4	Thyroxine
TI	Time invariance
TSH	Thyroid stimulating hormone
T_{max}	Time of maximum concentration observed
CCI	[redacted]
U2AF1	U2 Small Nuclear RNA Auxiliary Factor 1
µL	Microliter
ULN	Upper limit of normal
UK	United Kingdom
v	Version
VP	Vice President
W	Week
WBC	White blood cell
WHO	World Health Organization
WOCBP	Woman of childbearing potential
ZRSR2	Zinc Finger CCCH-Type, RNA Binding Motif and Serine/Arginine Rich 2

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
NONE

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11.15. Appendix 15: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

Amendment 1

Overall Rationale for the Amendment:

The primary driver for the protocol amendment is to provide a change to the inclusion criterion for the renal function. The estimated glomerular filtration rate (eGFR) has been lowered to ≥50 mL/min/1.73m^2). The risk, rationale for risk and risk mitigation for this change has been added to the preclinical and clinical risk assessment table in Section 2.3.2.

Other changes are detailed below.

Further additions to the pre-clinical and clinical risk assessment table following the IB update and data cut of 4th February 2019.

Details of a new tablet formulation (that is still in development) for the compound GSK3326595 has been added.

Revised nomenclature around the classification of inhibitors and inducers of CYP isoenzymes and inhibitors of BCRP and PgP has been made.

Clarification around time windows and visits has been added.

Clarification around the timings of interim analysis and the definition of evaluable participants has been added for each Part of the study.

Removal of text of AEs of special interest in the statistical analysis section.

Some additional clarifications in the Schedule of Activities tables.

Typographical errors have been corrected and minor editorial changes have been made.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis, rationale Section and Section 2.1 study rationale	Removal of some text about possible curative therapy for the diseases MDS and AML	This statement has been removed for clarity
1.3.1 Schedule of Activities tables	Addition of a row detailing when study drug (GSK3326595) is dispensed and when the diary cards are reviewed	To add clarity

Section # and Name	**Description of Change**	**Brief Rationale**
2.3.2 Preclinical and clinical risk assessment	The clinical effects listed in the bone marrow/hematologic/lymphoid, gastro-intestinal, heart, liver and renal sections of the table have been updated. The pre-clinical effects in the renal section have also been updated.	Following the recent IB update to version 03, and the recent data cut of 4th February 2019, these sections have been updated based on the current available clinical data on the compound. This Section has also been updated to provide rationale for the change in the inclusion criterion 10 (eGFR has been lowered to ≥50 mL/min/1.73m2 from ≥60 mL/min/1.73m2).
4.1.1.5 and 4.1.3.3.4 Statistical design	Minor editorial revision around the wording of the interim analysis.	To provide clarity
5.1 Inclusion criteria, number 10	Change in the renal function criteria. eGFR has been lowered to ≥50 mL/min/1.73m2 from ≥60 mL/min/1.73m2). Participants with eGFR of <60 mL/min/1.73m2 will require additional monitoring as described in Appendix 2.	To aid recruitment on the study, the renal function has been lowered, the rationale for this change has been given in Section 2.3.2.
6.1 Study Intervention administered	Addition of tablet formulation.	To provide more detail on the tablet formulation of GSK3326595.
6.6.1.3 Prohibited medications	Revised nomenclature around the classification of inhibitors and inducers of CYP isoenzymes and inhibitors of BCRP and PgP has been made. The word ‘potent’ has been replaced with ‘strong and moderate’.	To provide an update on the most current terminology.

Section # and Name	Description of Change	Brief Rationale
8.1 Visit Windows	Additional text on screening/re-screening and visit windows has been provided.	To add more clarity and to confirm that all visit windows on the study should refer to the Week 1 Day 1 (first day of dosing) date.
8.4.6.2 Additional urine and serum safety studies	Additional text placed here to confirm that participants with eGFR of <60 mL/min/1.73m2 will require additional monitoring as described in Appendix 2 of the protocol. Additional urine and serum renal biomarkers will be tested in these participants.	The rationale is given in Section 2.3.2 of the protocol.
9.3.2.2 Safety Analyses, Adverse events	Removal of text referring to AEs of special interest.	There are no AEs of special interest at this time.
References, Section 10	Update to the IB reference (to provide details of the current version, 03). Also to provide a reference to another clinical study with GSK3326595 that is mentioned in Section 2.3.2 of the protocol.	Updated/additional reference added in the text of the protocol.
11.2 Appendix 2	Additional urine and serum renal biomarker tests have been added to the clinical laboratory tests.	Rationale for these additional tests is given in Section 2.3.2 of the protocol.

Amendment 2:

Overall Rationale for the Amendment:

The primary driver for the protocol amendment is the addition of non-clinical bone findings and the related risk mitigation strategy, with a DEXA scan procedure being added to assess bone density at periodic intervals throughout the study.

The other main driver for this protocol amendment is the reduction in cardiac monitoring: LVEF stopping criteria have been removed; echocardiogram and troponin collection have been removed; cardiac risk and mitigation strategy have been updated; and select cardiac criteria from the inclusion criterion (number 10) on adequate organ system function have been removed.

The non-clinical and clinical risk assessment and mitigation strategies (Section 2.3.2) for GSK3326595 have been updated, based on review of safety data as of the IB cut off date (04th February 2020). Also, some of the non-clinical and clinical risk assessment and mitigation strategies for 5-Azacitidine have been updated. Other minor changes are detailed below.

Updates to Section 8.3.1, Section 9.3.1 and Appendix 9 and Appendix 10: to add clarity that the IWG disease response criteria (detailed in Appendix 9) will be used for all participants enrolled into Part 1 (whether AML, CMML or MDS), Parts 2A and 2B; the standard disease response criteria for participants with AML (detailed in Appendix 10) will be used for all participants enrolled in Part 2C.

Removal of 25mg capsule/strength as this is no longer being used going forward.

Typographical errors have been corrected and minor editorial changes have been made.

Section # and Name	Description of Change	Brief Rationale
Section 1.1, Synopsis, and Section 2.1, Study Rationale	Correction of "demethylation" to "dimethylation" in the text "PRMT5 is responsible for the majority of symmetric dimethylation of arginine *in vivo"*	Correction of error.
Section 1.3, Schedule of Activities (SOA) tables	Removal of Left Ventricle Ejection Fraction (LVEF) evaluation	A recent cardiac data review has shown no evidence of cardiotoxicity. Therefore, specific cardiac monitoring of troponin, LVEF and cardiac valves are no longer required in this protocol.
Section 1.3, Schedule of Activities (SOA) tables	Addition of DEXA bone densitometry	Pre-clinical bone findings have been observed. Therefore, DEXA scans at baseline and periodically during the study have been added to this protocol as part of the risk/mitigation strategy,
Section 2.3.2, Preclinical and Clinical Risk Assessment (GSK3326595)	Addition of a new potential risk of bone effects from an ongoing 13 week rat toxicity study. The mitigation strategy for this new risk has also been added (DEXA scans to be conducted; update to the Informed Consent Form).	Due to the recent bone findings in the 13 week rat toxicity study, DEXA scans at baseline and periodically during the study have been added to this protocol as part of the risk/mitigation strategy. The Informed Consent Form will also be updated with this information.
	Updated wording on cardiac risk and removal of the mitigation strategy.	A recent cardiac data review has shown no evidence of cardiotoxicity in human subjects. Therefore, specific cardiac monitoring of troponin, LVEF and cardiac valves are no longer required.
	Updated wording to the risks/mitigation strategies for gastro-intestinal (GI), bone marrow/hematologic/lymphoid, liver, exocrine tissues and reproductive effects	This wording has been updated, based on review of safety data as of the IB cut off date (04th February 2020).
	Removal of renal effects from the risk assessment table.	A review of AEs and SAEs as of 19 February 2020 showed no notable safety concerns with regard to direct nephrotoxicity. Therefore this section has been removed from the table.

Section # and Name	Description of Change	Brief Rationale
Section 2.3.2 Preclinical and Clinical Risk Assessment (5-Azacitidine)	Addition of a new potential risk, differentiation syndrome. Also, updated text has been added to the mitigation strategy for reproductive effects.	To provide an update regarding the latest known information about 5-Azacitidine.
Section 5.1, Inclusion Criteria, criterion 10, Table 10	Table 10, Definitions of adequate organ function, removal of cardiac parameters, ejection fraction and troponin.	A recent cardiac data review has shown no evidence of cardiotoxicity. Therefore, specific cardiac monitoring of troponin, LVEF and cardiac valves are no longer required.
Section 6.1, Study Intervention(s) administered	Removal of 25 mg strength of capsule	25mg strength will no longer be used in this study.
Section 7.1.1 Discontinuation of study intervention, disease progression	Updated text from “Time and Events Table” to “Section 1.3, Schedule of Activities (SOA)	Text corrected.
Section 7.1.4, LVEF Stopping Criteria	Removal of this section.	A recent cardiac data review has shown no evidence of cardiotoxicity in human subjects. Therefore, specific cardiac monitoring of troponin, LVEF and cardiac valves are no longer required.
Section 8.1, Visit Windows	Removal of text “Baseline Left Ventricular function evaluation must be performed within 35 days of first dose”.	A recent cardiac data review has shown no evidence of cardiotoxicity. Therefore, specific cardiac monitoring of troponin, LVEF and cardiac valves are no longer required.
Section 8.3.1, Efficacy assessments, disease assessment	Additional text to state that “Participants enrolled in Part 1 (including those with AML, CMML and MDS) will have responses graded per IWG criteria”.	To add clarity
Section 8.4.5, Safety Assessments	New section added “Bone Mineral Density”	Pre-clinical bone findings have been observed. Therefore, DEXA scans at baseline and periodically during the study have been added to this protocol.
Section 8.4.5, Cardiac Output Assessments	Section removed.	A recent cardiac data review has shown no evidence of cardiotoxicity. Therefore, specific cardiac monitoring of troponin, LVEF and cardiac valves are no longer required.

Section # and Name	Description of Change	Brief Rationale
Section 8.4.6.1, Clinical Safety Laboratory Assessments	Removal of section on troponins.	A recent cardiac data review has shown no evidence of cardiotoxicity. Therefore, specific cardiac monitoring of troponin, LVEF and cardiac valves are no longer required.
Section 9.3.1.1, Statistical Analysis, Efficacy Analyses, Efficacy Endpoints	Removal of text “MDS” and “AML”, and just referring Parts 1, 2A and 2B to the IWG criteria (in Appendix 9), and referring Part 2C to the response criteria (Appendix 10).	To add clarity.
Section 10, References	Update to the IB reference for 2020, Version 04	To add the latest reference for the 2020 IB, Version 04.
Section 11.2, Appendix 2, Clinical lab tests Table 11	Addition of text stating that the additional renal markers will be analysed at a central lab. Removal of cardiac safety markers (central and local troponin)	To add clarity A recent cardiac data review has shown no evidence of cardiotoxicity. Therefore, specific cardiac monitoring of troponin, LVEF and cardiac valves are no longer required.
Section 11.9, Appendix 9, IWG Criteria for Response for Participants with MDS	Title changed to “IWG Criteria for Response for Participants in Part 1, Part 2A and Part 2B”	To add clarity
Section 11.10, Appendix 10, Response Criteria for Participants with AML	Title changed to “Response Criteria for Participants in Part 2C”.	To add clarity