Division	:	Worldwide Development
Information Type	:	Reporting and Analysis Plan (RAP)

Title	:	Reporting and Analysis Plan for A Phase I/II study to investigate the safety and clinical activity of GSK3326595 and other agents in subjects with myelodysplastic syndrome and acute myeloid leukaemia
Compound Number	:	GSK3326595
Effective Date	:	19-AUG-2022

Description:

- This RAP is intended to describe the detailed planned statistical analyses and outputs of Part 1, Part 2 interim and final analyses of primary, secondary and key exploratory endpoints required for the clinical study report. On 8 December 2021 Research Investment Board confirmed that enrolment into Part 2 of METEOR-2 (protocol amendment 3) investigating the combination of GSK3326595 and 5-Azacitidine will be closed. As a result, only Part 1 analysis will be performed and all analyses corresponding to Part 2, as well as the Exploratory Objectives will not be. Synoptic CSR will present baseline characteristics, exposure, full safety, primary and secondary (high level) endpoints for Part 1. PK, BM data will be deprioritized.

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1. INTRODUCTION

The purpose of this reporting and analysis plan (RAP) is to describe planned statistical analyses (interim and final) and outputs of primary, secondary and key exploratory endpoints required to be included in the Clinical Study Report (CSR) for study 208809. It is based on the protocol amendment 3 dated 15 FEB 2021. The main CSR will be a synoptic report including all primary and secondary endpoints.

2. SUMMARY OF KEY PROTOCOL INFORMATION

2.1. Changes to the Protocol Defined Statistical Analysis Plan

For Part 1 and Part 2A, the protocol version 1.0 defined the Clinical Benefit Rate (CBR) and Overall response rate (ORR) based on international working group (IWG) criteria for myelodysplastic syndrome (MDS). Since the protocol also allows acute myeloid leukaemia (AML) participants that have evolved from an antecedent MDS, for which the standard AML response criteria will be used, the RAP updated the CBR and ORR definition incorporating the AML responses. The same update was made in the subsequent protocol amendments. Protocol Amendment 3 discontinued 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 was amended to include intermittent dose schedules of GSK3326595 in relapsed / refractory MDS, chronic myelomonocytic leukaemia CMML and AML participants; and Part 2 Dose Expansion cohorts were to include treatment naïve MDS and CMML participants. On 8 December 2021 Research Investment Board confirmed that enrolment into Part 2 of METEOR-2 (protocol amendment 3) investigating the combination of GSK3326595 and 5-Azacitidine will be closed. As a result, only Part 1 analysis will be performed and all analyses corresponding to Part 2, as well as the Exploratory Objectives will not be. Synoptic CSR will present baseline characteristics, exposure, full safety, primary and secondary (high level) endpoints for Part 1. PK, BM (Pharmacokinetic, Biomarker) data will be deprioritized.

2.2. Study Objective(s) and Endpoint(s)

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.

Part 1	
Objectives	**Endpoints**
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 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
• 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 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 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]	

Part 2 (Dose Escalation)
CCI [redacted]

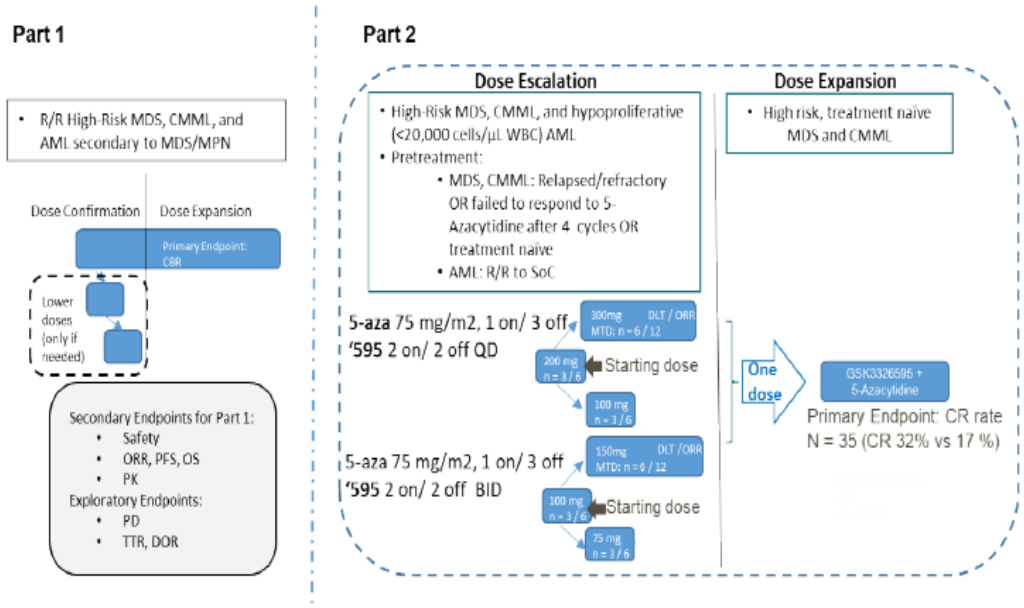
Part 2 (Dose Expansion)	
Objectives	**Endpoints**
Primary	
• To determine the clinical activity of GSK3326595 plus 5-Azacitidine in participants with high risk newly diagnosed MDS or CMML	• Complete Remission (CR) rate, defined as percentage of participants achieving a CR per IWG criteria
Secondary	
• 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

Part 2 (Dose Expansion)
Exploratory
CCI [redacted]

2.3. Study Design

Overview of Study Design and Key Features

Figure 1 Study Schematic



Design Features	• This is an open-label, multicentre, multi-part study of GSK3326595 as monotherapy and in combination with 5-Azacitidine in participants with myeloid malignancies. • A formal data analysis was performed with data cut off 30th June 2020 for participants in the Part 1 Dose Expansion cohort who have undergone at least two post-baseline disease assessments, have progressed or died, or permanently discontinued from study intervention. • It is estimated that a maximum of 113 participants will be enrolled in the study. • Participants may continue treatment in the study until disease progression, unacceptable toxicity, withdrawal of consent, or termination of the study by the sponsor.
	PART 1 • Part 1 is composed of a safety evaluation, followed by a single-arm dose expansion in participants with relapsed and/or refractory MDS and hypoproliferative AML that has evolved from an antecedent MDS. • 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. • The Neuenschwander continual reassessment method (N-CRM) will be utilized to guide dose escalation/de-escalation decisions based on the rate of dose-limiting toxicities (DLTs) observed in participants. • Six participants will initially be enrolled at the starting dose and up to 12 participants will be enrolled into Part 1 Dose Confirmation phase. • Once the Recommended Myeloid Monotherapy Dose is determined, additional participants (for a total of up to 35 participants treated at this dose) will be enrolled. Overall, up to 41 participants will be enrolled in Part 1. • 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

Overview of Study Design and Key Features	
	response will be assessed by bone marrow biopsy and defined per IWG criteria for MDS/CMML subjects and AML subjects. • Participants in dose confirmation who were treated at the same dose level as those in expansion phase will be included in the analysis as appropriate. • The evaluation is designed to exclude a 30% clinical benefit rate (CBR) representing best available therapy in favour of a 50% CBR.
	PART 2 • Part 2 was to 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 was to explore the clinical efficacy of the combination of GSK3326595 with 5-Azacitidine, in treatment-naïve patients with MDS or CMML (Part 2 Dose Expansion phase) • Part 2 will consist of two dose escalation cohorts with intermittent dosing to select a safe and tolerable GSK3326595 dose and regimen in combination with 5-Azacitidine (the Recommended Combination Dose and Regimen). Once the Recommended Combination Dose and Regimen was to be determined, additional participants were planned to be enrolled to assess the clinical activity of GSK3326595 plus 5-Azacitidine in newly-diagnosed MDS and CMML participants. • The N-CRM was to be utilized to guide dose escalation decisions based on the rate of DLTs observed in participants. Participants were planned to be enrolled in cohorts of approximately 3. • The Recommended Combination Dose was to be the dose that maximizes the posterior probability of target toxicity (16% ≤ DLT rate < 33%) while controlling the posterior probability of excessive/unacceptable toxicity (33% < DLT rate) no more than 25%, or a lower dose that provides adequate PK exposure and biologic/clinical activity with superior tolerability. • Overall, approximately 83 participants were to be enrolled in Part 2: approximately 24 participants in each dose escalation cohort and up to 35 participants in Dose Expansion cohort. • Part 2 Dose Expansion was planned to employ a Bayesian design. • Participants in dose escalation who were treated at the same dose level as those in expansion phase could have been included in the analysis as appropriate.
Dosing	PART 1 • The starting dose of GSK3326595 is 400 mg QD., as determined in study 204653. 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. • 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. • If dose modification of GSK3326595 is required, the pre-planned dose levels in Table 4 in the protocol will be utilized.

Overview of Study Design and Key Features	
	PART 2 • Dosing of GSK3326595 was planned to start at 200 mg QD in cohort 1 and 100 mg BID in cohort 2 and escalate up to the Recommended Myeloid Combination Dose • The dose of GSK3326595 administered in combination with 5-Azacitidine was planned not exceed the Recommended Myeloid Monotherapy Dose unless emerging data suggest that a therapeutic dose in combination requires a higher daily dose of GSK3326595. • The 5-Azacitidine regimen was planned to be administered subcutaneously or intravenously at the 75 mg/m^2 dose for 7 days in a 28-day cycle, as detailed in the Food and Drug Administration (FDA) package insert. The 5-Azacitidine regimen was not to be altered beyond the approved dose and schedule. • If dose modification of GSK3326595 is required, the pre-planned dose levels in Table 7 in the protocol was planned to be utilized.
Time & Events	• Refer to Table 1 to Table 3: Schedule of Activities (SoA) in protocol
Treatment Assignment	• Part 1: GSK3326595 and the dose level is the only treatment assignment. • Part 2: GSK3326595 and the dose level and schedule plus 5-Azaciditine are the only treatment assignment.
Interim Analysis	• The interim analyses will be conducted separately for Part 1 and Part 2 according to the design. • For both Parts the response evaluable participants are defined as those who have had at least two post-baseline assessments, have progressed or died, or have permanently discontinued from study intervention. • For both Parts the interim analyses will be for futility only, i.e. none of these Parts will stop early for efficacy. • For both Parts, statistical rules for interim analyses are intended as a guideline. Actual decisions will depend on the totality of the data.
	PART 1 • The first interim futility analysis will be conducted when a minimum of 8 participants become evaluable. • The subsequent interim futility analysis will be performed every 2-3 months with minimum of 5 additional evaluable participants. • The decision rules based on the predictive probability are indicated in Table 6 in protocol.
	PART 2 • The first interim futility analysis was to be conducted when a minimum of 8 participants become evaluable. • The subsequent interim futility analysis was to be performed every additional 9 evaluable participants. • The decision rules based on the predictive probability are indicated in Table 8 in protocol.
Final Analysis	• The study will be considered completed for purposes of a final analysis for Part 1 or Part 2 when 70% of the participants enrolled in Part 1 have died and 70% of the participants enrolled in Part 2 dose expansion have died.

2.4. Statistical Hypotheses / Statistical Design

2.4.1. Part 1

Dose confirmation

Hypothesis: No formal statistical hypotheses will be tested.

Design and sample size considerations: The Part 1 dose confirmation will be guided by the N-CRM model. 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%

The thresholds were derived via discussion with the clinical team. It is estimated that at least 6 and up to 12 participants will be enrolled to determine the Recommended Myeloid Monotherapy Dose. CRM model may not be employed until the first DLT occurs and the prior distribution assumptions may use the information from the GSK3326595 first time in human study 204653.

Dose expansion

Hypothesis: Dose expansion is designed to exclude a 30% CBR representing best available therapy in favour of a 50% CBR.

Design and sample size considerations: The Part 1 dose expansion will employ the Bayesian predictive probability method to frequently monitor CBR. 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 maximum sample size is 35 participants, and the design will have type I error of 0.07 and power of 83%. The methodology is based on the predictive probability of success if enrolment continues to 35 [Lee, 2008]. The calculations were performed using Predictive Probability Design Software for Phase II Cancer Clinical Trials Version 1.0.0.

2.4.2. Part 2

Dose escalation

Hypothesis: No formal statistical hypotheses will be tested.

Design and sample size considerations: The Part 2 dose escalation will employ N-CRM design, similar to that of Part 1 dose escalation. 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, results from Part 1 of this study and discussions with the clinical and statistical team. Prior information was elicited and derived using all quartiles method. 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: $\alpha = -1.7681\ (2.5018)$, $\ln(\beta) = -5.7972\ (0.0012)$, $\rho = -0.9975$
BID schedule: $\alpha = -1.4373\ (2.2972)$, $\ln(\beta) = -0.1725\ (0.4273)$, $\rho = -0.9964$

The simulation results are shown in Table 1. 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. The calculations were conducted using FACTS version 6.1 software.

Table 1 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
75 mg BID	0	9.2	15	38.2	20	65.0	25	75.0

Dose expansion

Hypothesis: It is designed to exclude a 17% CR rate for 5-Azacitidine in favour of a 32% CR rate.

Design and sample size considerations: The Part 2 dose expansion will employ the Bayesian predictive probability method to monitor the 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), centered on 0.32. 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 2. The calculations were performed using SAS version 9.4 and R software.

Table 2 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

3. PLANNED ANALYSES

3.1. Interim Analyses

Timing of Analyses

Part 1 Dose Confirmation
Cohorts will be recruited in blocks of approximately three participants. Approximately six participants will initially be enrolled at the starting dose. The maximum number of participants assigned to any single dose will be at the discretion of the Sponsor in consultation with the investigators.

Part 1 Dose Expansion
The first interim futility analysis (IFA) will be conducted when a minimum of evaluable 8 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 with minimum of 5 additional evaluable participants.

Part 2 Dose Escalation
It is estimated that approximately 48 participants will be enrolled to determine the Recommended Combination Dose. The interim analyses are planned after approximately 3 participants at a dose level become DLT evaluable.

Part 2 Dose Expansion
The first IFA will be conducted when a minimum of 8 participants become evaluable. The subsequent interim futility analysis will be performed every additional 9 evaluable participants, i.e. PPD and PPD

For both Parts expansion cohorts, the interim analyses will be for futility only, i.e. none of the parts will stop early for efficacy.

3.1.1. Part 1 Dose Confirmation

Decision Making
For the primary endpoint, in the absence of DLTs, the dose escalation rules are deterministic and no posterior distribution summaries will be provided. If DLTs are observed, an N-CRM model will be implemented to guide dose escalation/de-escalation decisions. 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. Next recommended dose level will be presented. The study team will review critical data defined in the Dose Escalation Plan prior to the dose escalation/de-escalation decision.

3.1.1.1. Displays to Be Created for Part 1 Dose Confirmation

Study Data Tabulation Model (SDTM) datasets will be available 6-8 weeks after first subject first visit. Before that, DM data dump in spreadsheets containing relevant study data will be supplied if needed.

For dose escalation/de-escalation decisions, data review will be primarily based on GSK's Spotfire system. The following three listings will be created by Statistics and Programming group. The analysis will be based on the All Treated Population.

(1) Listing of All Adverse Events
(2) Listing of All Laboratory Data for Participants with Grade 2 or Above Lab Tests
(3) Listing of Study Treatment Exposure

Details of the planned displays will be presented in Appendix 12: List of Data Displays.

3.1.2. Part 1 Dose Expansion Interim Futility Analysis

Decision Making
The primary endpoint is CBR, defined as the percentage of participants with complete remission (CR), complete marrow remission (mCR), partial remission (PR), stable disease (SD) lasting at least 8 weeks, and hematologic improvement (HI), as per IWG criteria for MDS/CMML/AML. SD duration is calculated from the first study treatment dose date. The decision rules, specifying the number of participants with a CBR needed for continuing enrolment or, stopping for futility, are indicated in Table 3.

Table 3 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.

Participants in dose confirmation who were treated at the same dose level as those in expansion phase will be included in the analysis as appropriate.

3.1.2.1. Displays to Be Created for Part 1 Dose Expansion Interim Futility Analysis

The All Treated Population (refer to Section 4) will be used for study population and safety analyses. The Response Evaluable Population will be used for efficacy analysis at interim.

A summary of the number of subjects in each of the analysis populations will be provided. Also, a summary of treatment status and reasons for discontinuation of study treatment will be produced.

The demographic characteristics (e.g., race, age, ethnicity, sex, height, and baseline body weight) will be summarized. Disease characteristics will be summarized.

Summaries of best overall response and subjects who achieved clinical benefit per IWG criteria for MDS/CMML/AML will be provided for the study team to examine the stopping rules for futility. In the efficacy table, CBR will be summarized along with 95% exact confidence interval (CI). Subjects with unknown or missing response will be treated as non-responders i.e. these subjects will be included in the denominator when calculating the percentage.

A swimmer plot of the duration of study treatment, including the occurrences of dose modification, number of lines of prior anti-cancer therapies, onset of CR/mCR/PR /HI/SD, disease progression, SAE and death, will be provided.

A listing of subject status and best overall response (BOR) per IWG criteria for MDS/CMML/AML subjects will be provided. This listing will be sorted by date of first dose and will show whether each subject is ongoing with study treatment, whether the subject has had at least two post-baseline disease assessments, whether the subject is evaluable for the futility analysis, and BOR.

An overview summary of adverse events (AEs), including counts and percentages of subjects with any AE, AEs related to GSK3326595, Grade 3/4 AEs, Grade 3/4 AEs related to GSK3326595, AEs leading to dose reductions of GSK3326595, AEs leading to dose interruptions of GSK3326595, AEs leading to permanent discontinuation of GSK3326595, SAEs, SAEs related to GSK3326595, fatal SAEs, and fatal SAEs related to GSK3326595 will be provided. AEs will be summarized by maximum grade and preferred term. SAEs and SAEs related to study treatment will be summarized by preferred term separately.

Details of the planned displays will be presented in Appendix 12: List of Data Displays.

3.1.3. Part 2 Dose Escalation

Decision Making
For the primary endpoint, the analysis is planned as per Section 3.1.1.

3.1.3.1. Displays to Be Created for Part 2 Dose Escalation

For each dose escalation meetings, the following two outputs will be created by Statistics and Programming group. The analysis will be based on the All Treated Population. SDTM datasets and DM data dump may be supplied if needed as per Section 3.1.1.1.

(1) Listing of All Adverse Events
(2) Summary of Dose-Limiting Toxicities

Details of the planned displays will be presented in Appendix 12: List of Data Displays.

3.1.4. Part 2 Dose Expansion Interim Futility Analysis

Decision Making
The primary endpoint is CR rate, defined as the percentage of participants achieving a CR as per IWG criteria. The decision rules, specifying the number of participants with a complete remissions needed for continuing enrolment or, stopping for futility, are displayed in Table 4. For example, if in the first 17 participants there is one or fewer complete remissions observed, the study can be stopped for futility.

Table 4 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.

Participants in dose confirmation who were treated at the same dose level as those in expansion phase will be included in the analysis as appropriate.

3.1.4.1. Displays to Be Created for Part 2 Dose Expansion Interim Futility Analysis

The outputs specified in Section 3.1.2.1 will be produced for each interim analysis, except the primary endpoint for the Part 2 is CR rate, not CBR. In addition, summary of treatment exposure of GSK3326595 and 5-Azacitidine; summary of dose reductions of GSK3326595 and 5-Azacitidine will be provided. In addition to safety analyses the following information will be added: AEs related to 5-Azacitidine and study treatment, Grade 3/4 AEs related to 5-Azacitidine and study treatment, AEs leading to dose

reductions of 5-Azacitidine and study treatment, AEs leading to dose interruption/delay of 5-Azacitidine and study treatment, AEs leading to dose delay of 5-Azacitidine, AEs leading to infusion of 5-Azacitidine interrupted but completed, AEs leading to infusion of 5-Azacitidine stopped early and not completed, AEs leading to permanent discontinuation of 5-Azacitidine, SAEs related to 5-Azacitidine and study treatment, fatal SAEs related to 5-Azacitidine, and study treatment.

Details of the planned displays will be presented in Appendix 12: List of Data Displays.

3.2. Main analyses

Timing of Analyses

Part 2 Dose Selection
Dose selection analysis is planned after MTD has been selected with 6 DLT evaluable patients and further 6 DLT evaluable patients have been recruited for each dose schedule.

Part 2 Dose Expansion
The main analysis will be conducted when 35 participants become evaluable for the primary endpoint.

3.2.1. Part 2 Dose Selection

Decision Making
For the primary endpoint, Recommended Combination Dose will be the dose that maximizes the posterior probability of target toxicity interval 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. For the important secondary endpoint ORR, the following guideline is planned to be considered to help with the dose and regimen selection for expansion cohort:

Go: Pr (true ORR > 0.30|data) > 55%
And Stop otherwise.

The simulations were conducted to understand the operating characteristics of the rules under different true ORR. A vague prior was used to assess the operating characteristics of the design with the prior distribution for the ORR rate of Beta (0.017, 0.036), centered on 0.32. The minimum observed value that meets the guideline is 4 or more ORR out of 12 participants. The analysis is Bayesian conjugate beta binomial. The actual number of responders analysed may be different to anticipated 12 patients. With such decision-making framework, the operating characteristics are presented in Table 5. The calculations were performed using R software.

Table 5 Operating characteristics for ORR endpoint

True ORR	Go (%)	Stop (%)	Consider (%)
0.20	20%	80%	0%
0.30	50%	50%	0%
0.50	92%	8%	0%

The study team will review critical data defined in the Dose Escalation Plan prior to the dose escalation/de-escalation decision. For the primary endpoint, the analysis is planned as per Section 3.1.1.

3.2.1.1. Displays to Be Created for Part 2 Dose Escalation

In addition to displays to be created in the Section 3.1.3.1, the following information is planned to be presented: key baseline data: demography, eligibility, regimen, medical history, disease characteristics, prior treatment, spliceosome mutation status; exposure to study drugs: dosing start and end dates, scheduled and actual dose, dose or schedule modifications and reason (as applicable); treatment discontinuation including reasons for withdrawal: primary reason and date of discontinuation; all AEs and SAEs, all AEs grade 3-5, all AEs and SAEs: preferred term, start date, outcome, end date, frequency, max grade, grade at onset, causality, actions taken re AE treatment. Grade changes; all AEs and SAEs leading to drug interruption, reduction or discontinuation; All related AEs and SAEs leading to drug interruption, reduction or discontinuation; Reason for Withdrawal; Concomitant Medications: drug name, dose/units, frequency, route, reason for medication, start/end dates; Clinical Laboratory Data: Visit date, lab test, result, lab ranges, clinical significance; Vital Signs; Electrocardiogram; ECOG; Protocol deviations; clinical response (including response by presence or absence of the spliceosome mutations).

3.2.2. Part 2 Dose Expansion

Decision Making

For the primary endpoint, Positive and Negative guidelines are described in Section 2.4.2. 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. If neither guidelines are met, ORR and safety will be taken in the decision making.

3.2.2.1. Displays to Be Created for Part 2 Dose Escalation

In addition to displays to be created in the Section 3.1.4.1, the following information is planned to be presented: clinical response (including response by presence or absence of the spliceosome mutations).

3.3. Final Analyses

3.3.1. Part 1 and Part 2 Final Analysis

The Part 1 and Part 2 final analysis for CSR purposes will be performed after the completion of the following sequential steps:

1. When 70% of the participants enrolled in Part 1 and 70% participants enrolled in Part 2 Dose Expansion cohort have died or termination of the study by the sponsor. Survival follow up for remaining participants may not be needed.
2. All required database cleaning activities have been completed and final database freeze (DBF) has been declared by Data Management.

Data from the dose confirmation and expansion cohort will be combined as appropriate.

4. ANALYSIS POPULATIONS

Population	Definition / Criteria	Analyses Evaluated
Screened	• All participants who were screened for eligibility with signed consent	• Study Population
Enrolled	• All participants who sign the ICF	• Study Population
DLT Evaluable	• For DLT assessment (Part 1 dose confirmation and Part 2 dose escalation): defined as participants who received at least 75% of GSK3326595 (and all 7 doses of 5-Azacitidine for Part 2) of the planned doses within the 28-day DLT observation period or those who have had a DLT.	• DLT
Response Evaluable	• For interim futility analyses (Part 1 expansion and Part 2 expansion) and for Part 2 Dose Escalation analysis: defined as participants who have had two post baseline disease assessments, have progressed or died, or permanently discontinued from the study intervention	• Separate population flag for each interim futility analyses of Part 1, Part 2 and Part 2 Dose Escalation analysis
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.	• Study Population • Safety • Efficacy
Pharmacokinetic (PK)	• Participants from the All Treated Population for whom a PK sample is obtained and analysed • Separate PK populations will be defined for each drug, i.e. GSK3326595 and 5-Azacitidine	• PK

Refer to Appendix 12: List of Data Displays which details the population used for each display.

5. CONSIDERATIONS FOR DATA ANALYSES AND DATA HANDLING CONVENTIONS

5.1. Study Treatment & Sub-group Display Descriptors

Part 1 begins with dose confirmation of GSK3326595 followed by a single-arm dose expansion cohort to determine the CBR of GSK3326595.

Part 2 is composed of dose escalation cohorts followed by a single-arm dose expansion cohort to determine the CR rate of the combination of GSK3326595 plus 5-Azacitidine.

In the data displays 5-Azacitidine will be abbreviated as 5-aza. Data will be listed and summarized per the GSK reporting standards whenever applicable. In Part 1 and Part 2 data will be listed and summarized by dose levels where applicable.

Treatment Group Descriptions			
IVRS Randomization System		Data Displays for Reporting	
Code	Description	Treatment Label	Order in TLF
Part 1			
	GSK3326595 400mg	GSK3326595 400mg	1
	GSK3326595 300mg	GSK3326595 300mg	2
Part 2 Escalation Cohort			
	GSK3326595 QD + 5-aza	GSK3326595 QD + 5-aza	1
	GSK3326595 BID + 5-aza	GSK3326595 BID + 5-aza	2
Part 2 Expansion Cohort			
	GSK3326595 + 5-aza	GSK3326595 + 5-aza	1

Part 2 codes were not added due to Part 2 closure

5.2. Analysis Datasets

Analysis datasets are “analysis-ready” datasets, i.e., analysis datasets that have a structure and content that allows statistical analysis to be performed with minimal programming, as sorting of the observations or the selection of the appropriate records from the analysis dataset. No complex data manipulations such as transformations or transpositions are required to perform the supported analysis.

Analysis datasets will be created according to CDISC standards using GSK standard ADaM specifications (where available), and data will be listed and summarized according to GSK Integrated Data Standards Library (IDSL) reporting standards. Formatting for dates, times, and decimal places will follow GSK standards except where specified.

5.3. Reporting Conventions

- Unless otherwise specified, the denominator in percentage calculation at each scheduled visit will be based on the number of subjects with non-missing value at each particular visit.
- All data are reported according to the actual treatment received by the subject.
- Data will be listed by treatment group, center ID, and subject.
- Planned times relative to investigational product dosing will be used in all summary tables and figures.
- Actual, rather than planned, sampling times will be used in the derivation of PK parameters and in the individual concentration-time plots. Planned times will be used in the descriptive summaries and in mean and median plots. Listings of PK concentration-time data will be done by actual sampling times relative to dosing time.
- Unless stated otherwise, descriptive summaries will include n, mean, standard deviation, median, minimum and maximum for continuous variables and n and percent for categorical variables. Display minimum and maximum in the same precision as data was collected, mean and median using 1 additional decimal place, and standard deviation using 2 additional decimal places.
- This is a multicenter study. Data from all study sites will be integrated and no controlling for center-effect will be considered in the statistical analyses.
- Analyses are to be performed using the SAS System, Version 9.4 or higher. Programs will be imported into HARP and the final output will be produced by running drivers in HARP. Some graphics may be produced using S-Plus (R) 7.0.6 or higher. In addition R Software Version 4.0.2 or higher and FACTS version 6.1 or higher may be used for the analysis.
- Deviations from the analyses in the RAP will be identified in the final CSR.

5.4. Baseline Definitions

For all endpoints (except as noted in baseline definitions) the baseline value will be the latest pre-dose assessment within 14 days prior to first dose with a non-missing value, including those from unscheduled visits. If time is not collected, Day 1 assessments are assumed to be taken prior to first dose and used as baseline. For laboratory data except for Troponin, baseline will be the latest non-missing pre-dose value from central lab. If no central lab value is available, the latest non-missing pre-dose value from local lab will be used. Troponin data is analysed separately for central and local labs, where the latest non-missing pre-dose value from each lab, respectively, acts as the baseline. If there are multiple assessments on the same day, the mean will be used as the baseline value.

For ECG analyses, subject level baseline is defined as the mean of triplicate baseline assessments.

For ECOG analyses baseline is defined as the latest non missing value before the first dose.

For liver function test baseline is defined as the latest non missing value before the first dose.

For subjects who did not receive any study intervention (GSK3326595 or 5-Azacitidine) during the study, baseline will be defined as the latest, non-missing collected value.

Unless otherwise stated, if baseline data is missing no derivation will be performed and baseline will be set to missing.

Parameter	Study Assessments Considered as Baseline			Baseline Used in Data Display
	Screening (within 35 days prior to first dose)	Screening (within 14 days prior to first dose)	Day 1 (Pre-Dose)	
Efficacy				
Bone marrow biopsy		X		Screening visit
Safety				
Laboratory		X	X	Latest up to Day 1
Vital Signs		X	X	Latest up to Day 1
ECG*		X	X	Latest up to Day 1
LVEF	X			Screening visit

*Average of triplicate assessments to be used.

5.4.1. Change from baseline

Change from baseline is calculated as:

- For records occurring after baseline: (visit value) – baseline value.

Percent change from baseline is calculated as:

- For records occurring after baseline: ((change from baseline) / baseline value) * 100

If either the baseline or visit value is missing, the change from baseline and/or percent change from baseline is set to missing as well.

5.5. Multiple Assessments

All data will be reported according to the nominal visit date for which it was reported (that is, no visit windows will be applied during dataset creation). Unscheduled data will only be included in the display sections that report worst- case post-baseline (except for PK parameters). For summaries that collapse data across multiple planned time intervals, select the mean data at each collapsed interval.

If multiple assessments on different days are reported for the same scheduled assessment, then the worst case assessment for that scheduled assessment will be analyzed.

If multiple assessments are reported on the same date for the same scheduled planned time, then the mean of multiple measurements reported for the same date will be analyzed, with the exception of laboratory data reported from both central and local laboratories such as Troponin. Troponin T is collected by both central and local lab, and Troponin I by central lab only, so these two lab parameters will be analysed separately by central and local lab. If laboratory data is reported from both central and local laboratories with the same date, then the central laboratory data will be analyzed to provide consistency with measurements from other subjects.

For ECG data where 3 assessments are collected for each scheduled planned time, the average of the 3 measures will be used for analysis at each scheduled planned time.

Data from all assessments (scheduled and unscheduled), including multiple assessments, will be included in listings.

5.6. Multicenter Studies

In this multicenter global study, enrolment will be presented by regions where applicable.

Summaries of data by center will not be provided.

5.7. Examination of Covariates, Other Strata and Subgroups

5.7.1. Covariates and Other Strata

All analyses are descriptive or unadjusted. No analyses are planned to adjust for any covariate and prognostic factor.

5.7.2. Examination of Subgroups

A table of summary of investigator assessed clinical benefit response by central review spliceosome mutation status across dose levels will be produced which will contain CBR and ORR with no CI.

5.7.3. Multiple Comparisons and Multiplicity

No multiple comparisons or multiplicity adjustments are planned in this study.

5.8. Other Considerations for Data Analyses and Data Handling Conventions

Other considerations for data analyses and data handling conventions are outlined in the appendices:

Section	Component
Section 14.3	Appendix 3: Assessment Windows
Section 14.4	Appendix 4: Study Phases and Treatment Emergent Adverse Events
Section 14.5	Appendix 5: Data Display Standards & Handling Conventions
Section 14.6	Appendix 6: Derived and Transformed Data
Section 14.7	Appendix 7: Reporting Standards for Missing Data
Section 14.8	Appendix 8: Values of Potential Clinical Importance

6. STUDY POPULATION ANALYSES

6.1. Overview of Planned Study Population Analyses

The study population analyses will be based on the All Treated population, unless otherwise specified.

Study population analyses including analyses of subject's disposition, protocol deviations, demographic and baseline characteristics, concomitant medications, exposure and treatment compliance, disease characteristics at initial diagnosis and at screening, prior and follow-up anti-cancer therapy, and duration of follow up will be based on GSK Core and Oncology Data Standards. Details of the planned displays are presented in Appendix 12: List of Data Displays.

6.2. Subject's Disposition

A summary of subject status and reason for study withdrawal and a summary of treatment status and reasons for discontinuation of study treatment will be presented. Reason for study withdrawal and reason for study treatment discontinuation will be listed separately.

A summary and listing of screening status and screen failures will be provided using the screened population.

Number of participants by country and site will be summarized and listed.

Number of participants in each of the analysis populations described in Section 4 will be provided using the screened population. A summary and a listing of enrolled participants excluded from the All Treated population will also be provided.

6.3. Protocol Deviations

Important protocol deviations (including deviations related to study inclusion/exclusion criteria, conduct of the trial, patient management or patient assessment) will be summarized in All Treated population and all protocol important deviations will be listed. Protocol deviations will be classified as 'important' and 'non-important' based on Protocol Deviation Specifications.

Protocol deviations will be tracked by the study team throughout the conduct of the study in accordance with the Protocol Deviation Specifications developed by PAREXEL.

- Data will be reviewed prior to freezing the database to ensure all deviations are captured and categorized on the protocol deviations dataset.
- This dataset will be the basis for the summaries and listings of protocol deviations.

A separate summary and listing of all inclusion/exclusion criteria deviations will also be provided. This summary will be based on data as recorded on the inclusion/exclusion page of the eCRF.

There is no Per-Protocol Population for this study. Protocol deviations will not be used to determine membership in any particular study population for this study.

6.4. Demographic and Baseline Characteristics

All demographic characteristics (e.g. race, age, ethnicity, sex, height, and baseline body weight) will be summarized and listed. Age, height, and weight will be summarized using the mean, standard deviation, minimum, median and maximum. Age will be also categorized as ≤18, 19-64, ≥65. The count and percentage will be computed for race, sex, and ethnicity.

In a separate summary, age will be categorized as 18-64, 65-84 and ≥85 using EudraCT standard. Race and racial combinations will be summarized in a separate table. Subject-level race detail will be listed.

6.5. Concomitant Medications

All concomitant medications will be summarized and listed. Concomitant medications will be coded using GSK Drug coding dictionary and summarized. The summary of concomitant medications will show the number and percentage of participants taking concomitant medication by Ingredient. Multi-ingredient products will be summarized by their separate ingredients rather than as a combination of ingredients. Anatomical Therapeutic Chemical (ATC) classification Level 1 (Body System) information will be included in the dataset created but will not appear on the listing or summary.

In the summary of concomitant medications, each participant is counted once within each unique ingredient. For example, if a participant takes Amoxycillin on two separate occasions, the participant is counted only once under the ingredient ‘Amoxycillin’. In the summary of concomitant medications, the ingredients will be summarized by the base only.

Blood products and blood supportive care products will be summarized and listed.Past and current medical conditions will be summarized separately in two tables.

6.6. Exposure and Treatment Compliance

The calculation of overall compliance is based on the entire interval of dosing for GSK3326595. The formula is compliance (%) = [total cumulative actual dose / (duration of study treatment * prescribed dose)] *100 where duration of study treatment is last dose-first dose +1.

Overall compliance for GSK3326595 and 5-Azacitidine (for Part 2) and based on the exposure data will be summarized and listed separately. Percentage overall compliance will be summarized using the mean, standard deviation, minimum, median and maximum. In addition, percentage overall compliance will be categorized and summarized by <80%, 80%-105% and >105%.

In addition, summaries of study treatment exposure and dose modifications (e.g., number of dose reductions, number of dose interruptions) for GSK3326595 and 5-Azacitidine

(for Part 2) will further characterize compliance. These analyses are described in Section 8.1'Extent of Exposure'.

6.7. Disease Characteristics

Disease characteristics at initial diagnosis including primary neoplasm type and time since diagnosis to first dose will be summarized and listed. Also, disease characteristics at screening including time since diagnosis to 1st study dose, time since progression to first dose, CNS disease, loss of function mutation, gene/protein type and disease classification (WHO classification of AML, IPSS-R category, and CPPS/CPPS mol-specific category where applicable) will be summarized and listed.

6.8. Prior and Follow-Up Anti-Cancer Therapy

The number and percentage of participants that received any prior anti-cancer therapy, radiotherapy, or stem cell transplant will be summarized Prior anti-cancer therapy will be coded using GSK Drug coding dictionary, then summarized by ingredient. The number of prior anti-cancer therapy regimens will be summarized.

Participant-level details of the prior anti-cancer therapy, prior radiotherapy and stem cell transplant will be provided in a listing.

The number and percentage of participants that received follow-up anti-cancer therapy, radiotherapy, surgical procedure for cancer under study, and stem cell transplant will be summarized. A summary of follow-up surgical procedure for cancer under study will be provided. Participant level details of the follow-up anti-cancer therapy will be provided in a listing. Also follow-up radiotherapy and follow-up surgeries will be listed.

6.9. Duration of Follow-Up

Duration of follow-up is defined as the time from study start to last contact or death and will be summarized in a table. Duration= Date of Last Study Contact – Date of First Exposure to Treatment +1.

7. EFFICACY ANALYSES

7.1. Primary Efficacy Analyses

7.1.1. Endpoint / Variables

7.1.1.1. Clinical Benefit Rate in Part 1

The primary endpoint of Part 1 is Clinical Benefit Rate (CBR). It is defined as the percentage of participants with CR, mCR, PR, HI, or SD lasting at least 8 weeks for MDS/CMML/AML subjects.

For MDS/CMML/AML subjects, BOR is defined as the best response (complete remission [CR] > complete marrow remission [mCR] > partial remission [PR] > hematologic improvement [HI] > stable disease [SD] > disease progression [PD] > not-evaluable [NE]) from treatment start date until disease progression or initiation of new anti-cancer therapy, whichever is earlier, as assessed by IWG criteria.

7.1.1.2. Complete Remission Rate in Part 2

Part 2 was closed due to study termination and no analysis will be performed. The primary endpoint of Part 2 Expansion Cohort (secondary for Escalation Cohort) is CR Rate defined as the percentage of participants with CR as BOR per IWG criteria.

BOR is defined in Section 7.1.1.1.

7.1.2. Summary Measure

7.1.2.1. Clinical Benefit Rate in Part 1

For MDS/CMML/AML subjects, the number of participants with the BOR in the following response categories will be summarized: CR, mCR, PR, SD ≥ 8 weeks, SD < 8 weeks, HI, clinical benefit response (CR+mCR+PR+SD ≥ 8 weeks+HI), PD and NE. CBR and the corresponding exact 2-sided 95% confidence interval (CI, Clopper-Pearson confidence limits for the binomial proportion) for CBR will also be provided. Participants with unknown or missing responses will be included in the denominator when calculating percentages of CBR.

A listing of response at each assessment by subject, including visit, date of assessment, response day, response, and best overall response, will be provided.

7.1.2.2. Complete Remission Rate in Part 2

Part 2 was closed due to study termination and no analysis will be performed. The number and percentage of participants with the BOR in the following response categories will be summarized: CR, mCR, PR, overall response (CR+mCR+PR), SD ≥ 8 weeks, SD < 8 weeks, HI, PD and NE. The corresponding exact 2-sided 95% CI (Clopper-Pearson confidence limits for the binomial proportion) for CR rate will also be provided. Participants with unknown or missing responses will be treated as non-responders, i.e.,

these participants will be included in the denominator when calculating percentages of CR rate.

A listing of response at each assessment by subject, including visit, date of assessment, response day, response, and best overall response, will be provided.

7.1.3. Population of Interest

7.1.3.1. Part 1

The primary efficacy analysis will be based on the All Treated opulation. Participants enrolled in Part 1 Dose Confirmation will be included in the Dose Expansion cohort analysis given the subject was treated at the same dose as the Dose Expansion cohort.

7.1.3.2. Part 2

Part 2 was closed due to study termination and no analysis will be performed. The primary efficacy analysis will be based on the All Treated population. Participants enrolled in Part 2 Dose Escalation will be included in the Dose Expansion cohort analysis given the subject was treated at the same dose as the Dose Expansion cohort.

7.1.4. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 12: List of Data Displays and will be based on GSK data standards and statistical principles.

Unless otherwise specified, endpoints / variables defined in Section 7.1.1 will be summarized using descriptive statistics, graphically presented (where appropriate) and listed.

7.2. Secondary Efficacy Analyses

7.2.1. Endpoint / Variables

7.2.1.1. Overall Response Rate

ORR is defined as the percentage of participants achieving a CR, mCR, or PR, per IWG criteria for MDS/CMML/AML subjects. ORR will be included in Part 1.

7.2.1.2. Progression Free Survival

Progression free survival (PFS) is defined as time from first dose to disease progression or recurrence, as defined by IWG criteria, or death due to any cause, whichever occurs earlier. Determination of dates of PFS events and dates for censoring are described in Table 6. PFS will be included in Part 1.

Table 6 Assignments of Progression and Censoring Dates for PFS and TTP Analysis

Situation	PFS		TTP	
	Date of Event (Progression/ Recurrence/Death) or Censored	Event (Progression/ Recurrence /Death) Or Censored	Date of Event (Progression/ Recurrence) or Censored	Event (Progression/ Recurrence) Or Censored
No adequate baseline assessments and the subject has not died (if the subject has died follow the rules for death indicted at the bottom of the table)	First dose	Censored	First dose	Censored
No post-baseline assessments and the subject has not died (if the subject has died follow the rules for death indicted at the bottom of the table)	First dose	Censored	First dose	Censored
Progression/Relapse documented between scheduled visits	Date of assessment of progression /relapse	Event	Date of assessment of progression /relapse	Event
With post-baseline assessment but no progression/Relapse after response (or death)	Date of last 'adequate' assessment of response[1]	Censored	Date of last 'adequate' assessment of response[1]	Censored
No adequate post-baseline assessment before start of new anticancer therapy	First dose	Censored	First dose	Censored
With adequate post-baseline assessment and new anticancer treatment started (prior to documented disease progression/recurrence).[2]	Date of last 'adequate' assessment of response[1] (on or prior to starting anti-cancer therapy)	Censored	Date of last 'adequate' assessment of response[1] (on or prior to starting anti-cancer therapy)	Censored
Death before first scheduled assessment (or Death at baseline or without any adequate assessments) or new anticancer therapy	Date of death	Event	Date of death	Censored

Situation	PFS		TTP	
	Date of Event (Progression/ Recurrence/Death) or Censored	Event (Progression/ Recurrence /Death) Or Censored	Date of Event (Progression/ Recurrence) or Censored	Event (Progression/ Recurrence) Or Censored
Death between adequate assessment visits	Date of death	Event	Date of death	Censored
Death or progression/recurrence after more than one missed scheduled assessment	• If death or PD is on or prior to day 174 (W25D1 + 5-day window), then a participant will be identified as an extended loss to follow up if the participant did not have an adequate assessment during the time period of 89 days (4 weeks + 8 weeks + 5-day window) prior to death or PD; • Else if death or PD is after day 174 (W25D1 + 5-day window) and on or prior to day 342 (W49D1 + 5-day window), then a participant will be identified as an extended loss to follow up if the participant did not have an adequate assessment during the time period of 173 days (12 wk + 12 wk + 5-day window) prior to death or PD. PFS will be censored at the date	Censored	Same as PFS	Censored

Situation	PFS		TTP	
	Date of Event (Progression/ Recurrence/Death) or Censored	Event (Progression/ Recurrence /Death) Or Censored	Date of Event (Progression/ Recurrence) or Censored	Event (Progression/ Recurrence) Or Censored
	of last adequate disease assessment of response prior to PD/death.			

[1]An adequate assessment is defined as an assessment where the determined response is CR, mCR, PR, HI, or SD for MDS/CMML/AML subjects.
[2] If PD and new anti-cancer therapy occur on the same day assume the progression/recurrence was documented first e.g., outcome is progression and the date is the date of the assessment of progression.

7.2.1.3. Overall Survival

OS is defined as time from first dose to death due to any cause. Subjects who are alive will be censored at the date of last contact. OS will be included in Part 1.

7.2.2. Summary Measure

7.2.2.1. Overall Response Rate

For Part 1, the ORR will include both MDS/CMML and AML subjects as one single proportion. The corresponding exact 2-sided 95% CI (Clopper-Pearson confidence limits for the binomial proportion) for ORR will also be provided. Participants with unknown or missing responses will be included in the denominator when calculating percentages of ORR.

7.2.2.2. Progression Free Survival

For Part 1, the distribution of PFS (in months) by the interval of 3 months will be estimated using the Kaplan-Meier method. The median, 25th and 75th percentiles of time to progression or death will be estimated and corresponding 2-sided 95% CI will be estimated using the Brookmeyer-Crowley method (1982) using log log transformation.

Kaplan-Meier curve (if data warrant) and a listing of PFS data will be provided.

7.2.2.3. Overall Survival

For Part 1, a table, a figure, and a listing will be produced for OS (in months) using methods specified in Section 7.2.2.2 for PFS endpoint.

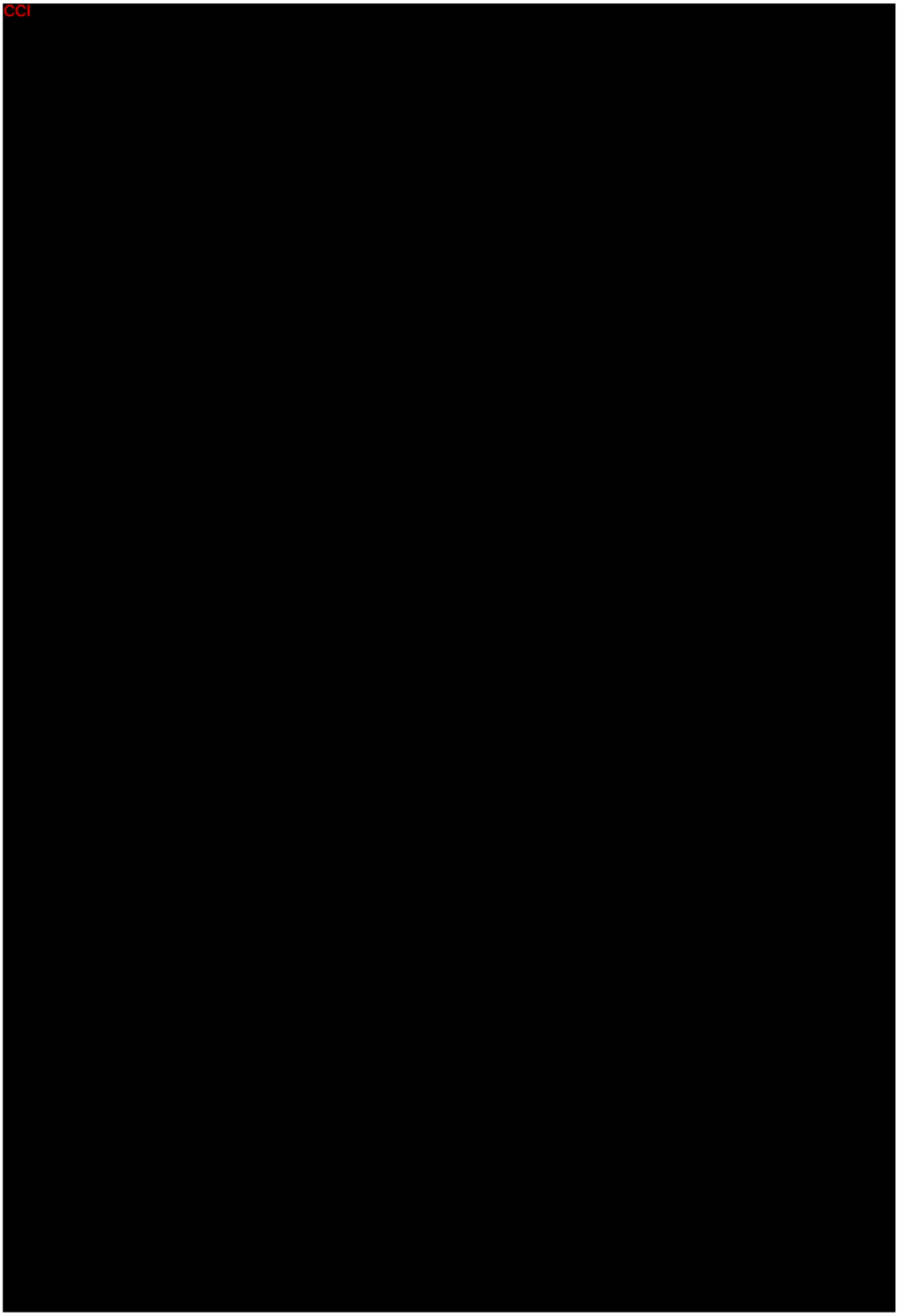
7.2.3. Population of Interest

The populations will be the same as in the primary efficacy analyses, detailed in Section 6.1.

7.2.4. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 12: List of Data Displays and will be based on GSK data standards and statistical principles.

Unless otherwise specified, endpoints / variables defined in Section 7.2.1 will be summarized using descriptive statistics, graphically presented (where appropriate) and listed.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8. SAFETY ANALYSES

All safety analyses will be performed on the All Treated population and will be separately conducted for Part 1 and Part 2.

Unless otherwise specified, safety summaries will be conducted by dose level within Part 1 Dose Confirmation and Part 2 Dose Escalation cohorts respectively. In Part 1, participants in Dose Confirmation treated at Recommended Myeloid Monotherapy Dose will be included in the Dose Expansion cohort analysis. Similarly, in Part 2, participants in Dose Escalation treated at Recommended Combination Dose will be included in the Dose Expansion cohort analysis.

8.1. Extent of Exposure

The duration of exposure to study treatment in months (from first day to last day of treatment) will be summarized. Descriptive statistics including mean, median, standard deviation, minimum, and maximum will be calculated for time on study treatment. In addition, time on study treatment will be categorized in different time periods: <3 months, 3 months to 6 months, >6 months to 12 months and >12 months.

For GSK3326595, the subject's average daily dose, defined as the cumulative dose divided by the duration of exposure for each subject, will be summarized. Within Part 2, extent of exposure will be summarized separately for GSK3326595 and 5-Azacitidine. For 5-Azacitidine, the number of cycles will be summarized. In addition, the duration of study treatment (from the first dose of GSK3326595 or 5-Azacitidine to the last dose of GSK3326595 or 5-Azacitidine) will be summarized.

Subject level details for extent of exposure to study treatment will be listed. The listing will be sorted by part, disease cohort, center, and subject ID. It will include start and stop dates, scheduled dose, actual dose, cumulative dose, average daily dose and number of days on the study treatment.

Dose reductions will be summarized by number of reductions and reasons for reductions. Dose interruptions/delays will be summarized by number of interruptions/delays, reasons for the interruptions/delays, and interruption/delay duration (days). The mean, standard deviation, median, minimum value, and maximum value will be computed for the duration of interruptions. For 5-Azacitidine, the incidences of infusion stopped early and not completed, and infusion interrupted but completed will also be summarized. Summary of dose escalation will also be provided if applicable.

All the dose reductions, dose escalations, and dose delays/interruptions will be listed separately. For 5-Azacitidine, the cases of infusion stopped early and not completed, and infusion interrupted but completed will also be listed.

A swimmer plot of the duration of study treatment, including the occurrences of dose modification, number of lines of prior anti-cancer therapies, onset of CR/mCR/PR/HI/, progression, SAE and death, will be provided.

The details of the planned displays are provided in Appendix 12: List of Data Displays.

8.2. Adverse Events Analyses

Adverse events analyses including the analysis of adverse events (AEs), Serious (SAEs) and other significant AEs will be based on GSK Core Data Standards. Details on treatment emergent AEs are provided in Appendix 4, Section 14.4.2.

In Part 1 Dose Confirmation and Part 2 Dose Escalation, Dose limiting toxicity (DLT) will also be summarized and listed according to GSK Oncology Data Standards using the DLT Evaluable population.

AEs will be graded by the investigator according to the National Cancer Institute-Common Toxicity Criteria for Adverse Events (NCI-CTCAE) v4.03. AEs will be coded to the Preferred Term (PT) level using the Medical Dictionary for Regulatory Affairs (MedDRA).

An overview summary of AEs, including counts and percentages of subjects with any AE, AEs related to GSK3326595, Grade 3/4 AEs, Grade 3/4 AEs related to GSK3326595, AEs leading to dose reductions of GSK3326595, AEs leading to dose interruptions of GSK3326595, AE leading to study treatment withdrawn, Treatment-related AE leading to study treatment withdrawn, SAEs, SAEs related to GSK3326595, fatal SAEs, and fatal SAEs related to GSK3326595 will be produced. Within Part 2, AEs related to any study treatment, AEs related to 5-Azacitidine, Grade 3/4 AEs related to any study treatment, Grade 3/4 AEs related to 5-Azacitidine, AEs leading to dose reductions of 5-Azacitidine, AEs leading to dose delays of 5-Azacitidine, AEs leading to infusion of 5-Azacitidine interrupted but completed, AEs leading to infusion of 5-Azacitidine stopped early and not completed, AEs leading to permanent discontinuation of 5-Azacitidine, SAEs related to any study treatment, SAEs related to 5-Azacitidine, fatal SAEs related to any study treatment, and fatal SAEs related to 5-Azacitidine will be included as well.

Comment: in tables we also report all AEs by PT, by PT and SOC and by PT, SOC and maximum grade (Table 3.2 to Table 3.4)

Similarly grade 2-5AEs that occurred in strictly 5% or more subjects will be summarized.

A summary of non-serious AEs that occurred in strictly 5% or more of the subjects will be provided. This summary will contain the number and percentage of subjects with the event and the number of occurrences of the events. The summary table will be displayed by System Organ Class (SOC) and PT.

The relationship between MedDRA SOC, PT, and Verbatim Text will be displayed.

A summary of number and percentage of subjects with any AEs by maximum grade will be produced. AEs will be sorted by PT in descending order of total incidence. The summary will use the following algorithms for counting the subject:

- **Preferred term row**: Subjects experiencing the same AE preferred term several times with different grades will only be counted once with the maximum grade.

- **Any event row**: Each subject with at least one AE will be counted only once at the maximum grade no matter how many events they have.

In addition, the frequency and percentage of AEs (all grades) will be summarized and displayed in two ways: 1) in descending order of total incidence by PT only and 2) in descending order of total incidence by SOC and PT. In the SOC row, the number of subjects with multiple events under the same system organ class will be counted once.

Summary of study treatment-related AEs by SOC and PT will be provided. A study treatment-related AE is defined as an AE for which the investigator classifies the relationship to study treatment as "Yes". A worst case scenario approach will be taken to handle missing relatedness data, i.e. the summary table will include events with the relationship to study treatment as 'Yes' or missing. Within Part 2, separate summaries will be provided for study treatment-related AEs, one for GSK3326595-related and one for 5-Azacitidine-related, as well as a summary of AEs related to any study treatment.

All AEs will be listed. Additionally, a listing of subject IDs for each individual AE will be produced.

The details of the planned displays are provided in Appendix 12: List of Data Displays.

8.3. Deaths and Serious Adverse Events

In the event that a subject has withdrawn consent to data collection, no data after the withdrawal of consent date to data collection from this subject including death is supposed to appear in the database, which should be part of the data cleaning process. All deaths will be summarized based on the number and percentage of subjects. This summary will classify subjects by primary cause of death. A supportive listing will be generated to provide subject-specific details on subjects who died.

A summary of the number and percentage of subjects and the number of occurrences of serious, drug-related serious, fatal serious, and drug-related fatal serious adverse events will be created.

All SAEs will be tabulated based on the number and percentage of subjects who experienced the event. The frequency and percentage of SAEs will be summarized in descending order of total incidence by PT only. Separate summaries will also be provided for study treatment-related SAEs. A study treatment-related SAE is defined as an SAE for which the investigator classifies the relationship to study treatment as "Yes". A worst case scenario approach will be taken to handle missing data, i.e. the summary table will include events with the relationship to study treatment as 'Yes' or missing. Within Part 2, separate summaries will be provided for study treatment-related SAEs, one for GSK3326595-related and one for 5-Azacitidine-related as well as a summary of SAEs related to any study treatment.

SAEs are included in the listing of all adverse events. Separate supportive listings with subject-level details will be generated for fatal SAEs.Reasons for AE considered as a SAE will be listed.

8.4. Adverse Events Leading to Dose Modification of Study Treatment

The following categories of AEs will be summarized separately in descending order of total incidence by PT only and separate supportive listings will be generated with subject level details for those subjects:

- AEs Leading to Permanent Discontinuation of GSK3326595
- AEs Leading to Dose Interruptions of GSK3326595
- AEs Leading to Dose Reductions of GSK3326595

Within Part 2, the following categories of AEs will be summarized and listed in addition to AEs leading to dose modification of GSK3326595.

- AEs Leading to Permanent Discontinuation of 5-Azacitidine
- AEs Leading to Dose Delay of 5-Azacitidine
- AEs Leading to Dose Reductions of 5-Azacitidine
- AEs Leading to Infusion of 5-Azacitidine Interrupted but Completed
- AEs Leading to Infusion of 5-Azacitidine Stopped Early and Not Completed

8.5. Clinical Laboratory Analyses

Laboratory evaluations including the analyses of chemistry laboratory tests, hematology laboratory tests, urinalysis, and liver function tests will be based on GSK Core Data Standards. The details of the planned displays are in Appendix 12: List of Data Displays.

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.

Clinical Laboratory Tests are listed in Table 77.

Table 7 List of Clinical Laboratory Tests

Laboratory Assessments	Parameters
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit RBC Indices: MCV, MCH, %Reticulocytes WBC count with Differential: Neutrophils, Lymphocytes, Monocytes, Eosinophils, Basophils, Myeloblasts (if present)
Clinical Chemistry	BUN Creatinine Glucose (nonfasting)

Laboratory Assessments	Parameters
	Amylase Potassium Sodium Calcium Lipase AST/SGOT ALT/SGPT Alkaline phosphatase Serum bicarbonate Total and direct bilirubin Total protein Albumin
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	TSH, T3, T4 – Screening, Week 5 Day 1, and Week 9 Day 1 and every 8 weeks thereafter and EOT.
Coagulation	PTT, PT/INR
Cardiac Safety	Local Troponin (I or T, based on local standards; note that the same test (either I or T) should be performed at each timepoint) Central Troponin T (separate tube for central laboratory analysis)
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	• NGAL, KIM-1, and albumin/creatinine ratio (urine) • Cystatin C (serum)

Laboratory Assessments	Parameters
ml/min/1.73 m2)	
Pregnancy Testing	• Human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)
Screening Tests	• Follicle-stimulating hormone and estradiol (as needed in women of nonchildbearing potential only) • Serology (HIV antibody, HBsAg, and HCV antibody). A positive HCV antibody must be confirmed via second study (e.g., HCV RNA or comparable test)

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; HBsAg = Hepatitis B surface antigen; HCV = hepatitis C virus; MCH = mean corpuscular haemoglobin; MCV = mean corpuscular volume; RBC = red blood cells; SGOT = serum glutamic-oxaloacetic transaminase; SGPT = serum glutamic-pyruvic transaminase; T3 = free Tri-iodothyronine; T4 = free thyroxine; TSH = Thyroid stimulating hormone; WBC = white blood cells

Laboratory grades will be reported using the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) v4.03.

Summary of lab values change from baseline by scheduled visits using mean, median, standard deviation, minimum, and maximum will be provided. This will be done separately by chemistry and hematology tests.

Summaries of worst case grade increase from baseline grade will be provided for all the lab tests that are gradable by CTCAE v4.03. These summaries will display the number and percentage of subjects with a maximum post-baseline grade increasing from their baseline grade. Any increase in grade from baseline will be summarized along with any increase to a maximum grade of 3 and any increase to a maximum grade of 4.

Missing baseline grade will be assumed as grade 0. For laboratory tests that are graded for both low and high values, summaries will be done separately and labeled by direction, e.g. sodium will be summarized as hyponatremia and hypernatremia.

For lab tests that are not gradable by CTCAE v4.03, summaries of worst case changes from baseline with respect to normal range will be generated. Decreases to low, changes to normal or no changes from baseline, and increases to high will be summarized for the worst case post-baseline. If a subject has a decrease to low and an increase to high during the same time interval, then the subject is counted in both the “Decrease to Low” categories and the “Increase to High” categories.

A supporting listing of laboratory data for subjects with any value outside normal range will be provided. This will be done separately by chemistry and hematology tests. A separate listing of laboratory data with character values will also be provided.

Detailed derivation of baseline assessment is specified in Section 5.4.

Unless otherwise specified, the denominator in percentage calculation at each scheduled visit will be based on the number of subjects with non-missing value at each particular visit.

A summary of worst case urinalysis results post-baseline relative to baseline will be generated. Also, a listing of urinalysis data for participants with any value of potential clinical importance will be provided. For the listing potential clinical importance is defined as if there is 'any increase' in protein or occult blood results during the study, or if microscopy is performed.

8.5.1. Analyses of Liver Function Tests (LFT)

Summaries of hepatobiliary laboratory events including possible Hy's law cases will be provided in addition to what has been described above.

Possible Hy's law cases are defined as any elevated ALT≥3×ULN, total bilirubin≥2×ULN and ALP<2×ULN/missing. Total bilirubin≥2×ULN can be within 28 days following the ALT elevation and if direct bilirubin is available on the same day, it must be ≥ 35% of total bilirubin. ALP<2xULN/missing means the criteria is satisfied unless the ALP is ≥2xULN at any time of bilirubin elevation within the 28 days window.

Medical conditions and substance use for participants with liver stopping events will be listed separately.

LFT patient profiles plots for subjects experiencing an ALT, AST or total bilirubin of toxicity grade 2 or above will be produced.

A scatter plot of maximum total bilirubin versus maximum ALT will be generated. Also, a scatter plot of maximum vs baseline for ALT will be produced.

8.6. Other Safety Analyses

The analyses of non-laboratory safety test results including ECGs and vital signs will be based on GSK Core Data Standards, unless otherwise specified. LVEF and Performance status will be summarized and listed based on GSK Oncology Data Standard. The details of the planned displays are presented in Appendix 12: List of Data Displays.

8.6.1. Performance Status

ECOG performance status will be summarized at baseline and post-baseline scheduled visits. Summaries will use frequency and percentage of subjects at each planned assessment time.

A supporting listing will also be provided.

8.6.2. ECG

Triplicate 12-lead ECGs will be obtained using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT and QTcF intervals. Baseline QTcF value is determined by the mean of the triplicate Day1 pre-dose QTcF results. If these

results are not available, the mean QTcF of the screening triplicate ECG results should be used.

A summary of the number and percentage of subjects who had normal and abnormal (clinically significant and not clinically significant) ECG findings will be displayed by scheduled visits as well as for the worst case post-baseline. Also a summary of change from baseline in ECG values by visit will be produced.

The QTc values based on Fridericia formula will be rounded to the integer and the values will be categorized into the following ranges: Grade 0 (<450), Grade 1 (450-480), Grade 2 (481-500), and Grade 3 (≥501). Summaries of grade increase will be provided. These summaries will display the number and percentage of subjects with any grade increase, increase to grade 2 and increase to grade 3 in the worst case post-baseline.

The changes in QTcF values will be categorized into the clinical concern ranges which are specific to changes in QTcF: 31-60 and >60 msec. A summary of change in QTcF value will display the number and percentage of subjects with a change within each range in the worst case post-baseline. Subjects with missing baseline values will be excluded from this summary.

Listing of all ECG values for participants with any value of potential clinical importance provided. Also, a listing of QTcF values of potential clinical importance will be provided.

A figure plotting the baseline QTcF and the worst-case post-baseline values will be produced. The figure will have reference lines at 450 and 500 msec for both the ordinate and the abscissa axes. There will be diagonal reference lines at equality (i.e. a 45-degree line), at equality plus 30 msec, and at equality plus 60 msec.

8.6.3. Vital Signs

Values of vital signs as well as the change from baseline will be summarized by scheduled visit using mean, median, standard deviation, minimum and maximum.

In addition, vital sign values will be categorized as follows:

- Systolic BP (mmHg):
  Grade 0 (<120), Grade 1 (120-139), Grade 2 (140-159) and Grade 3 (≥160)
- Diastolic BP (mmHg):
  Grade 0 (<80), Grade 1 (80-89), Grade 2 (90-99), and Grade 3 (≥100)
- Heart rate (beats/min):
  <60, 60-100, and >100
- Temperature (°C):
  ≤35, 36-37, ≥38

Summaries of increase in vital signs from the baseline with respect to the categories defined above will be performed.

A listing of vital signs with values of potential clinical importance will be provided.

8.6.4. Cardiovascular Risk Factors

Summary of Family History of Cardiovascular Risk Factors Summary of Substance Use will be summarised in All Treated population by dose level.

8.6.5. LVEF

Worst-case post-baseline LVEF change from baseline will be summarized. The change from baseline will be categorized as follows:

- No change or any increase
- Any decrease:
    - >0 - <10% Decrease
    - 10 - 19% Decrease
    - ≥20% Decrease
- ≥10% decrease and ≥ LLN
- ≥10% decrease and < LLN
- ≥20% decrease and ≥ LLN
- ≥20% decrease and < LLN

LVEF results will also be listed with subject level details including absolute change from baseline.

8.6.6. Pregnancies

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE or SAE as described in the protocol. If subjects and subjects' partner become pregnant while on the study, the information will be included in the narratives and no separate table or listing will be produced.

9. PHARMACOKINETIC ANALYSES

9.1. Primary Pharmacokinetic Analyses

9.1.1. Drug Concentration Measures

Refer to Appendix 5: Data Display Standards & Handling Conventions (Section 14.5.3 Reporting Standards for Pharmacokinetic)

9.1.2. Derived Pharmacokinetic Parameters

Pharmacokinetic (PK) parameters will be calculated by standard non-compartmental analysis according to current working practices and using the currently supported version of Phoenix WinNonlin. All calculations of non-compartmental parameters will be based on actual sampling times. Pharmacokinetic parameters listed will be determined from the plasma concentration-time data, as data permits.

Parameter	Parameter Description
C_{max}	Maximum observed plasma concentration
T_{max}	Time to C_{max}
AUC_{0-t}	Area under plasma concentration-time curve from 0 to each time point
$AUC_{0-\infty}$	Area under plasma concentration-time curve from 0 to end
$AUC_{0-\tau}$	Area under plasma concentration-time curve from 0 to half-life
$t_{1/2}$	Half life time
CL/F	Oral clearance
TI	Time invariance equal to $\frac{AUC(0-\tau),Day\ 15}{AUC(0-\infty),Day\ 1}$
AR	Accumulation ratio equal to $\frac{AUC(0-\tau),Day\ 15}{AUC(0-\tau),Day\ 1}$

9.1.3. Population of Interest

The primary pharmacokinetic analyses will be based on the PK population, unless otherwise specified.

9.1.4. Statistical Analyses / Methods

Individual plasma concentration data will be summarized using descriptive statistics of n, mean, standard deviation, median, minimum, maximum, by planned assessment time points and by treatment. Individual plasma concentration data and mean value will be plotted in both original and logarithm scales by time points and by treatment. PK parameters listed in Section 9.1.2 will be summarized using descriptive statistics of mean, standard deviation, median, minimum, maximum, geometric mean and standard deviation, as well as CV%.

Details of the planned displays are provided in Appendix 12: List of Data Displays and will be based on GSK Data Standards and statistical principles.

Unless otherwise specified, endpoints / variables defined in Section 9.1.2 will be summarized using descriptive statistics, graphically presented (where appropriate) and listed.

9.2. Secondary Pharmacokinetic Analyses

Secondary PK endpoints are not planned to be analysed.

10. PHARMACODYNAMIC (AND / OR BIOMARKER) ANALYSES

Biomarker data is being collected, but there will be no biomarker analyses formalized in the RAP.

11. POPULATION PHARMACOKINETIC (POPPK) ANALYSES

No POPPK analyses will be conducted.

12. PHARMACOKINETIC / PHARMACODYNAMIC ANALYSES

No pharmacokinetic/pharmacodynamic analyses will be conducted.

13. REFERENCES

Brookmeyer R, Crowley J. A confidence interval for the median survival time. Biometrics, 1982; 38:29-41.

Lee JJ, Liu DD. A predictive probability design for phase II cancer clinical trials. Clinical Trials 2008: 5. 93–106.

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14. APPENDICES

14.1. Appendix 1: Protocol Deviation Management and Definitions for Per Protocol Population

14.1.1. Exclusions from Per Protocol Population

No Per Protocol population is defined and used for this study.

14.2. Appendix 2: Schedule of Activities

14.2.1. Protocol Defined Schedule of Events

Refer to Protocol Section 1.3.

14.3. Appendix 3: Assessment Windows

No assessment window will be applied.

14.4. Appendix 4: Study Phases and Treatment Emergent Adverse Events

14.4.1. Study Phases

14.4.1.1. Study Phases for Concomitant Medication

Study Phase	Definition
Prior	• Study Treatment Start Date is missing (i.e., subject did not start study treatment), or • Medication End Date < Study Treatment Start Date
Concomitant	• Medication End Date is on or after Study Treatment Start Date, or • Medication End Date is completely missing and Start Date < Study Treatment End Date
Follow-up	• Medication End Date is on or after Study Treatment Start Date, or • Start date > Study Treatment End Date

NOTES:

- Please refer to Appendix 7: Reporting Standards for Missing Data for handling of partially missing dates for concomitant medication.

14.4.1.2. Medical History

Study Phase	Definition
Past	Medical condition is not marked as ongoing on eCRF
Current	• Medication End Date is on or after Study Treatment Start Date, or Medical condition is not past

14.4.2. Treatment Emergent Flag for Adverse Events

Flag	Definition
Treatment Emergent	All AEs satisfied either of conditions are considered treatment emergent: If AE onset date is on or after treatment start date or missing and on or before treatment stop date plus thirty days. ○ Study Treatment Start Date ≤ AE Start Date ≤ Study Treatment Stop Date + 30 ○ ○ AE Start Date is completely missing ○ Study Treatment Start Date ≤ AE Worsening Date ≤ Study Treatment Stop Date + 30 Partially missing AE Start Date will be imputed following rules in Section 14.7.2.1 for determining Treatment Emergent AEs.

NOTES:

- Time of study treatment dosing and start time of AEs should be considered, if collected.

14.5. Appendix 5: Data Display Standards & Handling Conventions

14.5.1. Reporting Process

Software	
• The currently supported versions of SAS software and TSCG will be used.	
Reporting Area	
HARP Server	: US1SALX00259
HARP Compound	: gsk3326595\mid208809
Analysis Datasets	
• Analysis datasets will be created according to CDISC standards (SDTM IG Version 3.1.3 & ADaM IG Version 1.1].	
Generation of RTF Files	
• RTF files will be generated upon request.	

14.5.2. Reporting Standards

General

• The current GSK Integrated Data Standards Library (IDSL) will be applied for reporting, unless otherwise stated (IDSL Standards Location: https://spope.gsk.com/sites/IDSLLibrary/SitePages/Home.aspx):
  • 4.03 to 4.23: General Principles
  • 5.01 to 5.08: Principles Related to Data Listings
  • 6.01 to 6.11: Principles Related to Summary Tables
  • 7.01 to 7.13: Principles Related to Graphics

Formats
• GSK IDSL Statistical Principles (5.03 & 6.06.3) for decimal places (DP's) will be adopted for reporting of data based on the raw data collected, unless otherwise stated. • Numeric data will be reported at the precision collected on the eCRF. • The reported precision from non eCRF sources will follow the IDSL statistical principles but may be adjusted to a clinically interpretable number of DP's.
Planned and Actual Time

• Reporting for tables, figures and formal statistical analyses:
  ○ Planned time relative to dosing will be used in figures, summaries, statistical analyses and calculation of any derived parameters, unless otherwise stated.
  ○ The impact of any major deviation from the planned assessment times and/or scheduled visit days on the analyses and interpretation of the results will be assessed as appropriate.
• Reporting for Data Listings:
  ○ Planned and actual time relative to study drug dosing will be shown in listings (Refer to IDSL Statistical Principle 5.05.1).
  ○ Unscheduled or unplanned readings will be presented within the subject's listings.

Unscheduled Visits
• Unscheduled visits will not be included in summary tables, except in cases where worst-case post-baseline is calculated. • Unscheduled visits will not be included in figures, unless otherwise specified. • All unscheduled visits will be included in listings.

Descriptive Summary Statistics	
Continuous Data	Refer to IDSL Statistical Principle 6.06.1
Categorical Data	N, n, frequency, %
Graphical Displays	
• Refer to IDSL Statistical Principals 7.01 to 7.13.	

14.5.3. Reporting Standards for Pharmacokinetic

Pharmacokinetic Concentration Data	
PC Windows Non-Linear (WNL) File	PC WNL file (CSV format) for the non compartmental analysis by Clinical Pharmacology Modelling and Simulation function will be created according to [Insert document name]. Note: Concentration values will be imputed as per GUI_51487
Descriptive Summary Statistics, Graphical Displays and Listings	Refer to IDSL PK Display Standards. Refer to IDSL Statistical Principle 6.06.1. Note: Concentration values will be imputed as per GUI_51487 for descriptive summary statistics/analysis and summarized graphical displays only.
NONMEM/Pop PK File	Not applicable.
NONMEM/PK/PD File	Not applicable.
Pharmacokinetic Parameter Derivation	
PK Parameter to be Derived by Programmer	The following PK parameters will be derived by the Programmer: Cmax, Tmax, AUC0-t, AUC0- ∞, AUC0- τ, t1/2, CL/F, TI, AR]
Pharmacokinetic Parameter Data	
Is NQ impacted PK Parameters Rule Being Followed	Yes, refer to Standards for Handling NQ Impacted PK Parameters.
Descriptive Summary Statistics, Graphical Displays and Listings	Refer to IDSL PK Display Standards.

14.6. Appendix 6: Derived and Transformed Data

14.6.1. General

Multiple Measurements at One Analysis Time Point
• Mean of the measurements will be calculated and used in any derivation of summary statistics but if listed, all data will be presented. • If multiple assessments on different days are reported for the same scheduled assessment, then the worst case assessment for that scheduled assessment will be analyzed. • Participants having both High and Low values for Normal Ranges at any post-baseline visit for safety parameters will be counted in both the High and Low categories of "Any visit post-baseline" row of related summary tables. This will also be applicable to relevant Potential Clinical Importance summary tables.
Study Day
• Calculated as the number of days from First Dose Date: o Ref Date = Missing → Study Day = Missing o Ref Date < First Dose Date → Study Day = Ref Date – First Dose Date o Ref Date ≥ First Dose Date → Study Day = Ref Date – (First Dose Date) + 1
Change from Baseline
• Change from Baseline = Post-Baseline Visit Value – Baseline • % Change from Baseline= 100 x (Post-Baseline Visit Value – Baseline) / Baseline • Maximum Increase/Decrease from Baseline = maximum (Increase/Decrease from Baseline) • If either the Baseline or Post-Baseline Visit Value is missing, Change from Baseline and % Change from Baseline is set to missing
Date of New Anti-Cancer Therapy
• Derived as the earliest date of new anti-cancer therapy, stem cell transplant, radiotherapy or cancer-related surgical procedure. • Missing or partial dates will be imputed for derivation of new anti-cancer therapy following rules specified in Section 14.7.2.1.

14.6.2. Study Population

Treatment Compliance
• Treatment compliance of GSK3326595 will be calculated based on the formula: **Treatment Compliance (%) = Total Cumulative Actual Dose / (Duration of Study Treatment * Prescribed Dose) * 100** where duration of study treatment is last dose - first dose +1 • Treatment compliance could be greater than 100% if there are events of overdose.
Extent of Exposure
• Missing treatment stop date will be imputed following rules specified in Section 14.7.2.1. • Daily Oral Drugs o Number of days of exposure (duration on study treatment) to study drug will be calculated based on the formula: **Duration of Exposure in Days = Treatment Stop Date – Treatment Start Date + 1** o Participants who were enrolled but did not report a treatment start date will be categorized as having zero days of exposure.

Treatment Compliance
○ The cumulative dose will be based on the formula: **Cumulative Dose = Sum of (Number of Days x Total Daily Dose)** ○ If there are any treatment breaks during the study, exposure data will be adjusted accordingly.
Time since Initial Diagnosis
• Calculated as the number of days from the Date of Initial Diagnosis: ○ If First Dose Date is missing → Elapse Time = Missing ○ If Date of Initial Diagnosis is completely/partially missing → Elapse Time = Missing ○ Otherwise → Elapse Time = First Dose Date – Date of Initial Diagnosis + 1 • To report in months, divide the number of days by 30.4375; to report in weeks divide the number of days by 7; to report in years divide the number of days by 365.25. No imputation is needed for partial dates.

14.6.3. Safety

Adverse Events
Adverse Events of Special Interest
• There are no AESI defined for this study therefore the analysis will not be performed.
Duration of AE
• Calculated as the number of days from AE Start Date to AE Stop Date: ○ AE Start Date = Missing → Elapse Time = Missing ○ AE Stop Date = Missing → Elapse Time = Missing ○ Otherwise → Elapsed Time = AE Stop Date – AE Start Date + 1 • To report in months, divide the number of days by 30.4375; to report in weeks divide the number of days by 7; to report in years divide the number of days by 365.25.

14.7. Appendix 7: Reporting Standards for Missing Data

14.7.1. Premature Withdrawals

Element	Reporting Detail
General	• Subject study completion was defined as if the subject has been followed until death or study completion. • Withdrawn subjects may be replaced in the study as specified in the protocol. • All available data from participants who were withdrawn from the study will be listed and all available planned data will be included in summary tables and figures, unless otherwise specified.

14.7.2. Handling of Missing Data

Element	Reporting Detail
General	• Missing data occurs when any requested data is not provided, leading to blank fields on the collection instrument: ○ These data will be indicated by the use of a "blank" in subject listing displays. Unless all data for a specific visit are missing in which case the data is excluded from the table. ○ Answers such as "Not applicable" and "Not evaluable" are not considered to be missing data and should be displayed as such.
Outliers	• Any participants excluded from the summaries and/or statistical analyses will be documented along with the reason for exclusion in the clinical study report.

14.7.2.1. Handling of Missing and Partial Dates

Element	Reporting Detail
General	• Partial dates will be displayed as captured in subject listing displays. However, where necessary, display macros may impute dates as temporary variables for sorting data in listings only. In addition, partial dates may be imputed for 'slotting' data to study phases (see Section 14.4.1) or for specific analysis purposes as outlined below.
Adverse Events	• Imputations in the adverse events dataset are used for slotting events to the appropriate study time periods and for sorting in data listings. • The eCRF allows for the possibility of partial dates (e.g., only month and year) to be recorded for AE start and end dates; that is, the day of the month may be missing. In such a case, the following conventions will be applied for calculating the time to onset and the duration of the event: ○ Missing Start Day: ▪ If study treatment start date is missing (i.e. participant did not start study treatment), then set AE start date = 1st of month. ▪ Else if study treatment start date is not missing: If month and year of AE start date = month and year of study treatment start date then ☐ If AE stop date contains a full date and is earlier than study treatment start date, then set AE start date= 1st of month. ☐ Else set AE start date = study treatment start date. Else set AE start date = 1st of month. ○ Missing Start Day and Month: ▪ If study treatment start date is missing (i.e. participant did not start study treatment), then set AE start date = January 1.

Element	Reporting Detail
	▪ Else if study treatment start date is not missing: If year of AE start date = year of study treatment start date then ☐ If AE stop date contains a full date and is earlier than study treatment start date, then set AE start date = January 1. ☐ Else set AE start date = study treatment start date. Else set AE start date = January 1. • Completely missing start dates will remain missing, with no imputation applied. Consequently, time to onset and duration of such events will be missing. • Completely or partially missing end dates will remain missing, with no imputation applied. Consequently, duration of such events will be missing. • Start dates later than death date will be imputed as the study treatment start date • End dates later than death date will be imputed as the death date
Concomitant Medications/ Blood Supportive Products	• Completely missing start dates will not be imputed • Partial start dates for any concomitant medications recorded in the CRF will be imputed using the following convention: o If day and month are missing: – If treatment start date is missing (i.e., subject did not start study treatment), a '01' will be used for the day and 'Jan' will be used for the month; – If treatment start date is not missing ▪ If year of start date = year of study treatment start date · If stop date contains a full date which is earlier than the treatment start date, a '01' will be used for the day and 'Jan' will be used for the month; · else study treatment start date will be used ▪ else a '01' will be used for the day and 'Jan' will be used for the month o If day is missing: – If treatment start date is missing (i.e., subject did not start study treatment), a '01' will be used for the day; – If treatment start date is not missing ▪ If year and month of start date = year and month of study treatment start date · If stop date contains a full date which is earlier than the treatment start date, a '01' will be used for the day; · else study treatment start date will be used ▪ else a '01' will be used for the day and 'Jan' will be used for the month • Completing missing end dates will not be imputed • Partial end dates for any concomitant medications recorded in the CRF will be imputed using the following convention: o If day and month are missing – Earliest of (Dec 31st, date of last contact) will be used o If day is missing – Earliest of (last day of the month, date of last contact) will be used
New Anti-Cancer Therapy/	Start dates for follow-up anti-cancer therapy, stem cell transplant, radiotherapy, and surgical procedures will be imputed in order to define event and censoring rules for

Element	Reporting Detail

Stem Cell Transplant/ Radiotherapy/ Surgical Procedures for Efficacy Evaluation (e.g., response rate, time to event)	progression-free survival, response rate, or duration of response (i.e. start date for new anti-cancer therapy). Dates will only be imputed when a month and year are available but the day is missing. The following rules will be used to impute the date when partial start dates are present on anti-cancer therapy, stem cell transplant, radiotherapy, and/or surgical procedures dataset[s]:
	• Completely missing start dates will remain missing, with no imputation applied;
	• Partial start dates will be imputed using the following convention:
	  • If both month and day are missing, no imputation will be applied;
	  • If only day is missing:
	  ○ If the month of partial date is the same as the month of last dosing date, minimum of (last dosing date + 1, last day of the month) will be used for the day;
	  ○ If the month of partial date is the same as the month of last disease assessment and the last disease assessment is PD, minimum of (last date of disease assessment + 1, last day of the month) will be used for the day;
	  ○ If both conditions above are met, the later date will be used for the day;
	  ○ Otherwise, a '01' will be used for the day;
	• Completely or partial missing end dates will remain missing, with no imputation applied;

Prior Anti-Cancer Therapy/ Radiotherapy/ Surgical Procedures	Start and end dates are generally not imputed. If start or end dates need to be imputed for an analysis (e.g., to calculate duration of prior therapy or elapsed time as covariates for efficacy analyses), following rules will be applied. Imputed dates are not used for summary of anti-cancer therapy or radiotherapy.
	
	• If start/end date is completely missing or both day and month are missing, no imputation will be applied
	• If day is missing for start date, first of the month will be used
	• If day is missing for stop date,
	  ○ If first dosing date is the first of the month, minimum of (last day of the month from the partial date, first dosing date) will be used
	  ○ Else minimum of (last day of the month from the partial date, first dosing date - 1) will be used

Treatment end date	• If there is more than one study treatment, imputation of missing treatment end date will be applied to all applicable treatments following rules below and treatment end date is the latest treatment end date across all study treatments.
	• In general, completely missing end dates are not imputed, with the following exceptions for imputation of missing treatment end date at interim analyses.
	• For imputation of missing exposure end date at an interim analysis when subjects are still on treatment, the following conventions will be applied:
	  ○ If the missing end date is in the last exposure record, the earliest of: the date of the data cut-off, the date of permanently discontinued from the study treatment, the date of withdrawal from the study, or the death date will be used
	  ○ If the missing end date is not in the last exposure record, treatment start date for the record will be used
	• The imputed treatment end date will be used to calculate cumulative dose and duration of treatment as specified in Section 6.6

14.8. Appendix 8: Values of Potential Clinical Importance

To identify laboratory values of potential clinical importance, National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE v4.03) will be used to assign grades for laboratory parameters including clinical chemistry, hematology, liver function tests, QTc (Fridericia's) values, and vital signs (heart rate, blood pressure, temperature).

Reference ranges for all laboratory parameters collected throughout the study are provided by the laboratory. A laboratory value that is outside the reference range is considered either high abnormal (value above the upper limit of the reference range) or low abnormal (value below the lower limit of the reference range). Note: a high abnormal or low abnormal laboratory value is not necessarily of clinical concern. The laboratory reference ranges will be provided on the listings of laboratory data. Clinical laboratory test results outside of the reference range will be flagged in the listings.

14.8.1. ECG

The following criteria will be used to flag electrocardiogram (ECG) values that are values of potential clinical importance:

To identify QTc (Fridericia's) values of potential clinical importance, NCI-CTCAE v4.03 will be used to assign grades (see adverse event 'Electrocardiogram QT corrected interval prolonged'). The CRF collects either QTcF. Note that there is a slight inconsistency between CTCAE v4.03 and ICH E14 (Absolute QTc interval prolongation). It was decided to align with CTCAE for the oncology standard categories.

ECG Parameter	Potential Clinical Importance (PCI) Range	Unit
Absolute QTcF interval	≥450 to <481 (Grade 1) ≥481 to <501 (Grade 2) ≥501 (Grade 3)	msec
Increase from baseline QTcF	Increase of ≥31 to ≤60 Increase of >60	msec

The following criteria will be used to flag other ECG values that are values of potential clinical importance:

ECG Parameter	Potential Clinical Importance (PCI) Range	Unit
Absolute PR interval	<110 (L) >220 (H)	Msec
Absolute QRS interval	<75 (L) >110 (H)	Msec

14.8.2. Vital Signs

To identify heart rate values of potential clinical importance, NCI-CTCAE v4.03 will be used to assign categories that align with the grades for 'Sinus bradycardia', 'Sinus tachycardia', 'Supraventricular tachycardia', and 'Ventricular tachycardia'.

The following criteria will be used to flag vital sign values that are values of potential clinical importance:

Vital Sign Parameter	Potential Clinical Importance (PCI) Range	Unit
Absolute Heart Rate	<60 (L) >100 (H)	bpm

To identify blood pressure values of potential clinical importance, NCI-CTCAE v4.03 will be used to assign categories that align with the grades for 'Hypertension'.

Vital Sign Parameter	Potential Clinical Importance (PCI) Range	Unit
Absolute Systolic Blood Pressure	≥120 to <140 (Grade 1) ≥140 to <160 (Grade 2) ≥160 (Grade 3)	mmHg
Absolute Diastolic Blood Pressure	≥80 to <90 (Grade 1) ≥90 to <100 (Grade 2) ≥100 (Grade 3)	mmHg

To identify temperature values of potential clinical importance, NCI-CTCAE v4.03 will be used to assign categories that align with the grades for 'Hypothermia' and 'Fever'.

Vital Sign Parameter	Potential Clinical Importance (PCI) Range	Unit
Absolute Temperature	≤35 (L) ≥38 (H)	Degrees C

14.8.3. Urinalysis

Values of potential clinical importance will be defined as per GSK IDSL standards.

14.9. Appendix 9: Population Pharmacokinetic (PopPK) Analyses

No POPPK analyses will be conducted.

14.10. Appendix 10: Pharmacokinetic / Pharmacodynamic Analyses

Biomarker data is being collected, but there will be no biomarker analyses formalized in the RAP.

14.11. Appendix 11: Abbreviations & Trade Marks

14.11.1. Abbreviations

Abbreviation	Description
ADaM	Analysis Data Model
AE	Adverse Event
AESI	Adverse Event of Special Interest
AIC	Akaike's Information Criteria
A&R	Analysis and Reporting
BAC	Best Available Care
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
CPMS	Clinical Pharmacology Modelling & Simulation
CS	Clinical Statistics
CSR	Clinical Study Report
CTR	Clinical Trial Register
DBF	Database Freeze
DBR	Database Release
DOB	Date of Birth
DP	Decimal Places
eCRF	Electronic Case Record Form
EMA	European Medicines Agency
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Clinical Results Disclosure Requirements
GSK	GlaxoSmithKline
IA	Interim Analysis
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
IDSL	Integrated Data Standards Library
IP	Investigational Product
ITT	Intent-To-Treat
PCI	Potential Clinical Importance
PD	Pharmacodynamic
PK	Pharmacokinetic
PP	Per Protocol
PopPK	Population PK
QC	Quality Control
QTcF	Fridericia's QT Interval Corrected for Heart Rate
RAP	Reporting & Analysis Plan
SAC	Statistical Analysis Complete
SDTM	Study Data Tabulation Model
SOP	Standard Operation Procedure
SRT	Safety Review Team
TA	Therapeutic Area
TFL	Tables, Figures & Listings

14.11.2. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
None

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14.12. Appendix 12: List of Data Displays

14.12.1. Data Display Numbering

The following numbering will be applied for RAP generated displays:

Section	Tables	Figures
Study Population	1.1 to 1.n	1.1 to 1.n
Efficacy	2.1 to 2.n	2.1 to 2.n
Safety	3.1 to 3.n	3.1 to 3.n
Pharmacokinetic	4.1 to 4.n	4.1 to 4.n
Population Pharmacokinetic (PopPK)	5.1 to 5.n	5.1 to 5.n
Pharmacodynamic and / or Biomarker	6.1 to 6.n	6.1 to 6.n
Pharmacokinetic / Pharmacodynamic	7.1 to 7.n	7.1 to 7.n
Section	**Listings**	
ICH Listings	1 to x	
Other Listings	(x+1) to z	

14.12.2. Mock Example Shell Referencing

Non IDSL specifications will be referenced as indicated.

Section	Figure	Table	Listing
Study Population	POP_Fn	POP_Tn	POP_Ln
Efficacy	EFF_Fn	EFF_Tn	EFF_Ln
Safety	SAFE_Fn	SAFE_Tn	SAFE_Ln
Pharmacokinetic	PK_Fn	PK_Tn	PK_Ln
Population Pharmacokinetic (PopPK)	POPPK_Fn	POPPK_Tn	POPPK_Ln
Pharmacodynamic and / or Biomarker	PD_Fn	PD_Tn	PD_Ln
Pharmacokinetic / Pharmacodynamic	PKPD_Fn	PKPD_Tn	PK/PD_Ln

NOTES:

- Non-Standard displays are indicated in the 'IDSL / Example Shell' or 'Programming Notes' column as '[Non-Standard] + Reference.'

14.12.3. Deliverables

Delivery	Description
P1DC	Part 1 Dose Confirmation
P1IFA	Part 1 Dose Expansion Interim Futility Analysis
P2ESC	Part 2 Escalation Cohort Final Meeting (Dose Selection)
P2IFA	Part 2 Dose Expansion Interim Futility Analysis
SAC	Final Statistical Analysis Complete

14.12.4. Study Population Tables

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Subject Disposition					
1.1.	All Treated	ES8	Summary of Subject Status and Subject Disposition for the Study Conclusion Record	ICH E3, FDAAA, EudraCT	SAC
1.2.	All Treated	SD1	Summary of Treatment Status and Reasons for Discontinuation of Study Treatment	ICH E3	P1IFA, SAC
1.3.	Screened	ES6	Summary of Screening Status and Reasons for Screen Failure	Journal Requirements	SAC
1.4.	Enrolled	NS1	Summary of Number of Participant by Country and Site ID	EudraCT/Clinical Operations	SAC
Protocol Deviation					
1.5.	All Treated	DV1	Summary of Important Protocol Deviations	ICH E3	SAC
Population Analysed					
1.6.	Screened	SP1A	Summary of Study Populations	IDSL To include Enrolled, DLT Evaluable, Response Evaluable, All Treated, PK	P1IFA, SAC
1.7.	All Treated	SP2A	Summary of Exclusions from the Safety Population	IDSL If none, to remove	SAC
Demographic and Baseline Characteristics					
1.8.	All Treated	DM1	Summary of Demographic Characteristics	ICH E3, FDAAA, EudraCT	P1IFA, SAC
1.9.	Enrolled	DM11	Summary of Age Ranges	EudraCT	SAC
Disease Characteristics					
1.10.	All Treated	DC1	Summary of Disease Characteristics at Initial Diagnosis	ICH E3	P1IFA, SAC
1.11.	All Treated	DC2	Summary of Disease Characteristics at Screening	ICH E3	SAC
1.12.					SAC

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Prior and Concomitant Medications					
1.13.	All Treated	MH1	Summary of Past Medical Conditions	ICH E3	SAC
1.14.	All Treated	MH1	Summary of Current Medical Conditions	ICH E3	SAC
1.15.	All Treated	CM8	Summary of Concomitant Medications	ICH E3	SAC
Blood and Blood Supportive Care Products					
1.16.	All Treated	BP1A	Summary of Blood Products	Only produced if sufficient data (i.e. >5 events), otherwise only list	SAC
1.17.	All Treated	BP1B	Summary of Blood Supportive Care Products after the Start of Study Medication	Only produced if sufficient data (i.e. >5 events), otherwise only list	SAC
Anti-Cancer Therapy					
1.18.	All Treated	AC1	Summary of Prior Anti-Cancer Therapy	IDSL Include stem cell transplant	SAC
1.19.	All Treated	CM1	Summary of Prior Dictionary Coded Anti-Cancer Therapy	IDSL	SAC
1.20.	All Treated	AC3	Summary of Number of Prior Anti-Cancer Therapy Regimens	IDSL Include stem cell transplant	SAC
1.21.	All Treated	AC1	Summary of Follow-Up Anti-Cancer Therapy	IDSL Include stem cell transplant	SAC
Surgical/Medical Procedures					
1.22.	All Treated	MH1	Summary of Prior Cancer Related Surgical Procedures	IDSL	SAC
1.23.	All Treated	MH1	Summary of On-Study Cancer Related Surgical Procedures	IDSL	SAC
1.24.	All Treated	MH1	Summary of Follow-Up Cancer Related Surgical Procedures	IDSL	SAC
Follow-up					
1.25.	All Treated	FAC2	Summary of Duration of Follow-up		SAC

14.12.5. Efficacy Tables

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Responses					
2.1.	All Treated	RE1c	Summary of Investigator Assessed Clinical Benefit Response (International Working Group Criteria)	By dose level. For Part 1, include both AML and MDS/CMML subjects in the same table. Report CBR and ORR in one table (Part 1). 95% CI is based on Clopper-Pearson exact CI.	P1IFA, SAC
2.2.	All Treated	RE1c	Summary of Investigator Assessed Clinical Benefit Response (International Working Group Criteria) by Central Review Spliceosome Mutation Status	Across dose levels. Report CBR and ORR in one table (Part 1). No CI.	SAC
Time-to-Event Endpoints					
2.3.	All Treated	TTE1	Summary of Progression Free Survival Based on Investigator Assessments (International Working Group Criteria)	By dose level.	SAC
2.4.	All Treated	TTE1	Summary of Overall Survival	By dose level.	SAC

14.12.6. Efficacy Figures

Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Time-to-Event Endpoints					
2.5.	All Treated	TTE10	Graph of Kaplan Meier Survival Curves of Progression Free Survival with 95% Confidence Bands (Investigator Assessment using International Working Group Criteria)	If data warrant. By dose level.	SAC
2.6.	All Treated	TTE10	Graph of Kaplan Meier Survival Curves of Overall Survival with 95% Confidence Bands (Investigator Assessment using International Working Group Criteria)	If data warrant. By dose level.	SAC

14.12.7. Safety Tables

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Adverse Events (AEs)					
3.1.	All Treated	AE13	Adverse Event Overview	Including subjects with any AE, AEs related to GSK3326595, Grade 3/4 AEs, Grade 3/4 AEs related to GSK3326595, AEs leading to dose reductions of GSK3326595, AEs leading to dose interruptions of GSK3326595, AEs leading to permanent discontinuation of GSK3326595, SAEs, SAEs related to GSK3326595, fatal SAEs, and fatal SAEs related to GSK3326595	P1IFA, SAC
3.2.	All Treated	AE1	Summary of All Adverse Events by System Organ Class and Preferred Term	ICH E3	SAC
3.3.	All Treated	AE5B	Summary of All Adverse Events by System Organ Class and Preferred Term and Maximum Grade	ICH E3	SAC
3.4.	All Treated	AE1	Summary of All Adverse Events by Preferred Term	ICH E3	SAC
3.5.	All Treated	AE3	Summary of Common (>=5%) Adverse Events by Overall Frequency	ICH E3	SAC
3.6.	All Treated	AE3	Summary of Common (>=5%) Grade 2-5 Adverse Events by Overall Frequency	ICH E3	SAC
3.7.	All Treated	AE1	Summary of All GSK3326595-Related Adverse Events by System Organ Class and Preferred Term	ICH E3	SAC
3.8.	All Treated	AE5B	Summary GSK3326595-Related Adverse Events by System Organ Class and Preferred Term and Maximum Grade	ICH E3	SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
3.9.	All Treated	AE3	Summary of Common (>=5%) Drug-Related Adverse Events by Overall Frequency	ICH E3	SAC
3.10.	All Treated	AE3	Summary of Common (>=5%) Drug-Related Grade 2-5 Adverse Events by Overall Frequency	ICH E3	SAC
3.11.	All Treated	AE15	Summary of Common (>=5%) Non-serious Adverse Events by System Organ Class and Preferred Term (Number of Participant and Occurrences)	FDAAA, EudraCT	SAC
3.12.	All Treated	AE3	Summary of Non-Serious GSK3326595-Related Adverse Events by Overall Frequency	Plain Language Summaries (PLS)	SAC
3.13.	All Treated	AE1	Summary of Adverse Events Leading to Dose Reductions of GSK3326595 by Preferred Term	ICH E3	SAC
3.14.	All Treated	AE1	Summary of Adverse Events Leading to Dose Interruptions / Delay of GSK3326595 by Preferred Term	ICH E3	SAC
Serious and Other Significant Adverse Events					
3.15.	All Treated	AE5B	Summary of Serious Adverse Events by System Organ Class and Preferred Term and Maximum Grade	ICH E3	SAC
3.16.	All Treated	AE16	Summary of Serious Adverse Events by System Organ Class and Preferred Term (Number of Participants and Occurrences)	FDAAA, EudraCT	SAC
3.17.	All Treated	AE1	Summary of Adverse Events Leading to Permanent Discontinuation of Study Treatment or Withdrawal from Study by System Organ Class and Preferred Term	IDSL	SAC
3.18.	All Treated	AE20	Summary of Serious Fatal and Non-Fatal GSK3326595-related Adverse Events by Overall Frequency	Plain Language Summary (PLS)	SAC
3.19.	All Treated	AE3	Summary of Serious Adverse Events Related to Study Treatment by Preferred Term		P1IFA, SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
3.20.	All Treated	ESI2A	Summary of Onset and Duration of First Occurrence of Selected Adverse Events	Anemia, neutropenia, thrombocytopenia (platelet count decrease and thrombocytopenia), fatigue, asthenia, febrile neutropenia	SAC
3.21.	All Treated	ESI1	Summary of Event Characteristics of Selected Adverse Events	Anemia, Thrombocytopenia, Fatigue	P2ESC, P2IFA, SAC
3.22.	All Treated	AE1	Summary of Adverse Events (Ocular Events) by System Organ Class and Preferred Term		SAC
3.23.	All Treated	AE1	Summary of Serious Adverse Events (Ocular Events) by System Organ Class and Preferred Term		SAC
Deaths					
3.24.	All Treated	DD1	Summary of Deaths	ICH E3 Report time to death from last dose (in days) as in the mock	SAC
Laboratory: Chemistry					
3.25.	All Treated	LB1	Summary of Chemistry Changes from Baseline	ICH E3 To include grade increase from Baseline Grade Creatinine	SAC
3.26.	All Treated	LB16	Summary Worst Case Chemistry Results by Maximum Grade Increase Post-Baseline Relative to Baseline	ICH E3 Report only worst-case post-baseline. Don't report by-visit summary rows. For CTCAE graded tests.	SAC
3.27.	All Treated	LB15	Summary of Worst Case Chemistry Results Relative to Normal Range Post-Baseline Relative to Baseline	ICH E3 Report only worst-case post-baseline. Don't report by-visit summary rows. For non-graded tests.	SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Laboratory: Haematology					
3.28.	All Treated	LB1	Summary of Haematology Changes from Baseline	ICH E3	SAC
3.29.	All Treated	LB15	Summary of Worst Case Haematology Results by Maximum Grade Increase Post-Baseline Relative to Baseline	ICH E3 Report only worst-case post-baseline. Don't report by-visit summary rows. For CTCAE graded tests.	SAC
3.30.	All Treated	LB16	Summary of Worst Case Hematology Results Relative to Normal Range Post-Baseline Relative to Baseline	ICH E3 Report only worst-case post-baseline. Don't report by-visit summary rows. For non-graded tests.	SAC
Laboratory: Urinalysis					
3.31.	All Treated	LB1	Summary of Urine Concentration Changes from Baseline	ICH E3	SAC
3.32.	All Treated	UR1	Summary of Worst Case Urinalysis Results (Discrete or Character Values) Post-Baseline Relative to Baseline	ICH E3 Define change categories according to actual values expected from lab dataset Report only worst-case post-baseline. Don't report by-visit summary rows.	SAC
Laboratory: Hepatobiliary (Liver)					
3.33.	All Treated	LIVER1	Summary of Liver Monitoring/Stopping Event Reporting	IDSL	SAC
3.34.	All Treated	LIVER10	Summary of Hepatobiliary Laboratory Abnormalities	IDSL	SAC
3.35.	All Treated	LIVER11	Summary of Liver Restart/Re-Challenges	IDSL	SAC
ECG					
3.36.	All Treated	EG1	Summary of ECG Findings	IDSL	SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
3.37.	All Treated	ECG10	Summary of Maximum QTcF Values Post-Baseline Relative to Baseline by Category	ICHE14 Report only worst-case post-baseline. Don't report by-visit summary rows.	SAC
3.38.	All Treated	EG2	Summary of Change from Baseline in ECG Values by Visit	IDSL	SAC
3.39.	All Treated	ECG11	Summary of Maximum Increase in QTc Values Post-Baseline Relative to Baseline by Category	ICHE14 Report only worst-case post-baseline. Don't report by-visit summary rows.	SAC
Vital Signs					
3.40.	All Treated	VS1	Summary of Change from Baseline in Vital Signs	ICH E3	SAC
3.41.	All Treated	VS6	Summary of Worst Case Vital Signs Results by Maximum Grade Increase Post-Baseline Relative to Baseline	ICH E3 Include blood pressure Report only worst-case post-baseline. Don't report by-visit summary rows.	SAC
3.42.	All Treated	VS3	Summary of Worst Case Vital Signs Results Relative to Normal Range Post-Baseline Relative to Baseline	ICH E3 Include heart rate and temperature Report only worst-case post-baseline. Don't report by-visit summary rows.	SAC
LVEF					
3.43.	All Treated	OLVEF1A	Summary of Left Ventricular Ejection Fraction Change from Baseline	IDSL	SAC
Dose Modifications					
3.44.	All Treated	EX1	Summary of Exposure to Study Treatment	ICH E3 Include duration of treatment (months)	SAC
3.45.	All Treated	ODMOD1	Summary of Dose Reductions of GSK3326595	ICH E3	SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
3.46.	All Treated	ODMOD2	Summary of Dose Interruptions of GSK3326595	ICH E3	SAC
Dose Limiting Toxicity (DLT)					
3.47.	All Treated	DL1	Summary of Dose-Limiting Toxicities during the Determinative Period	ICH E3	SAC
Performance Status					
3.48.	All Treated	PS1A	Summary of ECOG Performance Status	ICH E3	SAC
Cardiovascular Risk Factors					
3.49.	All Treated	FH1	Summary of Family History of Cardiovascular Risk Factors	IDSL	SAC
Troponin					
3.50.	All Treated	LB15	Summary of Worst-Case Troponin Results Relative to Normal Range Post-Baseline Relative to Baseline-Local Lab Assessment	IDSL	SAC
3.51.	All Treated	LB15	Summary of Worst-Case Troponin Results Relative to Normal Range Post-Baseline Relative to Baseline-Central Lab Assessment	IDSL	SAC
Laboratory: Coagulation					
3.52.	All Treated	LB1	Summary of Coagulation Changes from Baseline	IDSL	SAC
3.53.	All Treated	LB16	Summary of Worst-Case Coagulation Results by Maximum Grade Increase Post-Baseline Relative to Baseline	IDSL	SAC
3.54.	All Treated	LB15	Summary of Worst-Case Coagulation Results Relative to Normal Range Post-Baseline Relative to Baseline	IDSL	SAC

14.12.8. Safety Figures

Safety: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Exposure					
3.1.	All Treated	OEX12	Swimmer Plot of Duration of Study Treatment	IDSL	P1IFA, SAC
Laboratory					
3.2.	All Treated	LIVER14	Scatter Plot of Maximum vs. Baseline for ALT	IDSL	SAC
3.3.	All Treated	LIVER9	Scatter Plot of Maximum ALT vs. Maximum Total Bilirubin	IDSL	SAC
ECG					
3.4.	All Treated	EG12	QTcF Shifts from Baseline to Worst-case Post Baseline	IDSL	SAC

14.12.9. Pharmacokinetic Tables

Pharmacokinetic: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
PK					
4.1.	PK	PK01	Summary of GSK3326595 Pharmacokinetic Concentration-Time Data by Treatment and Study Day	Use descriptive statistics (n, mean, SD, median, min and max) by planned relative assessment time; concentrations in ng/mL. All planned time points. Part 1: A foot note to describe ID 600 and reference to PK Non-ICH: Listing 1: Listing of Pharmacokinetic Concentration-Time Data by Treatment.	SAC
4.2.	PK	PK06	Summary of Derived GSK3326595 Pharmacokinetic Parameters by Treatment and Study Day	PK parameters: Cmax, Tmax, Ctrough, AUC0-t, AUC0-tau, AUCinf, t½, λz , TI and AR determined from the concentration-time data in ng/ml; descriptive summaries: mean, SD, median, min, max, geometric mean & SD, CV%, and 95%CI of log-transformed parameters, if applicable. Part 1: A foot note to describe ID 600 and reference to PK Non-ICH: Listing 2 Listing of Derived Pharmacokinetic Parameters by Treatment.	SAC

14.12.10. Pharmacokinetic Figures

Pharmacokinetic: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
PK					
4.1.	PK	PK16A	Individual GSK3326595 Concentration-Time Plots (Linear and Semi-Log) by Treatment and Study Day	IDSL ng/mL Day 1 and Day 15 only. Part 1: ID 600 is excluded.	SAC
4.2.	PK	PK17	Mean Concentration-Time Plots (Linear and Semi-Log) by Treatment and Study Day	IDSL ng/mL Day 1 and Day 15 only. Part 1: ID 600 is excluded.	SAC
4.3.	PK	PK18	Median Concentration-Time Plots (Linear and Semi-Log) by Treatment and Study Day	IDSL ng/mL Day 1 and Day 15 only. Part 1: ID 600 is excluded.	SAC

14.12.11. ICH Listings

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Participant Disposition					
1.	All Treated	ES2	Listing of Reasons for Study Withdrawal	ICH E3	SAC
2.	All Treated	SD2	Listing of Reasons for Study Treatment Discontinuation	ICH E3	P1DC, SAC
Protocol Deviations					
3.	All Treated	DV2	Listing of Important Protocol Deviations	ICH E3 Report all important PDs	SAC
4.	All Treated	IE3	Listing of Participants with Inclusion/Exclusion Criteria Deviations	ICH E3	SAC
Populations Analysed					
5.	Enrolled	SP3	Listing of Participants Excluded from All Treated Population	ICH E3 Report participants enrolled but not treated	SAC
Demographic and Baseline Characteristics					
6.	All Treated	DM2	Listing of Demographic Characteristics	ICH E3	P1DC, SAC
7.	All Treated	DM9	Listing of Race	ICH E3	SAC
Exposure and Treatment Compliance					
8.	All Treated	EX3	Listing of Exposure to GSK3326595	ICH E3	SAC
Adverse Events					
9.	All Treated	AE8	Listing of All Adverse Events	ICH E3	P1DC, SAC
10.	All Treated	AE7	Listing of Subject Numbers for Individual Adverse Events	ICH E3	SAC
Serious and Other Significant Adverse Events					
11.	All Treated	AE8	Listing of Non-Fatal Serious Adverse Events	ICH E3	SAC

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
12.	All Treated	AE14	Listing of Reasons for Considering as a Serious Adverse Event	ICH E3	SAC
13.	All Treated	AE8	Listing of Adverse Events Leading to Permanent Discontinuation of GSK3326595 or Withdrawal from Study	ICH E3 To include Permanent Discontinuation or Withdrawal in the action taken	P1DC, SAC
14.	All Treated	AE8	Listing of Adverse Events Leading to Dose Interruptions/Delay of GSK3326595	ICH E3	SAC
15.	All Treated	AE8	Listing of Adverse Events Leading to Dose Reductions of GSK3326595	ICH E3	SAC
All Laboratory					
16.	All Treated	LB5	Listing of All Laboratory Data for Participants with Any Value of Outside Normal Range	ICH E3 To include chemistry, hematology,	SAC
17.	All Treated	UR2	Listing of Urinalysis Data for Participants with Any Value of Potential Clinical Importance	ICH E3	SAC

14.12.12. Non-ICH Listing

Non-ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Participant Disposition					
18.	Screened	ES7	Listing of Reasons for Screen Failure	required for submission studies only	SAC
19.	All Treated	TA1	Listing of Planned and Actual Treatments	IDSL Report only subjects whose actual starting dose is different from the assigned dose group.	SAC
Disease Characteristics					
20.	All Treated	DC3	Listing of Disease Characteristics at Initial Diagnosis		SAC
21.	All Treated	DC4	Listing of Disease Characteristics at Screening		SAC
Anti-Cancer Therapy					
22.	All Treated	AC6	Listing of Prior Anti-Cancer Therapy	List all prior anti-cancer therapy and prior stem cell transplant (but not radiotherapy or surgery)	SAC
23.	All Treated	AC6	Listing of Follow-Up Anti-Cancer Therapy		SAC
Surgical Procedures					
24.	All Treated	PR2	Listing of Prior Cancer Related Surgical Procedures		SAC
25.	All Treated	PR2	Listing of On-Study Cancer Related Surgical Procedures		SAC
26.	All Treated	PR2	Listing of Follow-Up Surgical Procedures		SAC
Prior and Concomitant Medications / Blood and Blood Supportive Care Products					
27.	All Treated	BP4	Listing of Blood Products		SAC

Non-ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
28.	All Treated	BP5	Listing of Blood Supportive Care Products		SAC
Dose Modifications					
29.	All Treated	ODMOD10A	Listing of Dose Reductions of GSK3326595		SAC
30.	All Treated	ODMOD11A	Listing of Dose Interruptions of GSK3326595		SAC
Dose-Limiting Toxicities					
31.	All Treated	DL3	Listing of Dose-Limiting Toxicities (DLT) During the Determinative Period	If applicable	SAC
Response					
32.	All Treated	RE5	Listing of Best Overall Response (Investigator Assessment using International Working Group Criteria)	Include Response assessment and Best Overall Response	SAC
Time to Event					
33.	All Treated	TTE9	Listing of Progression Free Survival Based on Investigator Assessment (International Working Group Criteria)		SAC
34.	All Treated	TTE9	Listing of Overall Survival		SAC
Hepatobiliary (Liver)					
35.	All Treated	LIVER5	Listing of Liver Monitoring/Stopping Event Reporting		SAC
36.	All Treated	LIVER15	Liver Stopping Event Profile		SAC
37.	All Treated	MH2	Listing of Medical Conditions for Participants with Liver Stopping Events		SAC
All Laboratory					
38.	All Treated	LB5	Listing of All Laboratory Data		SAC
40.	All Treated	OLB7	Listing of Central Troponin Data		SAC

Non-ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
41.	All Treated	OLB7	Listing of Local Troponin Data		SAC
ECG					
42.	All Treated	EG3	Listing of All ECG Values		SAC
43.	All Treated	EG5	Listing of All ECG Findings		SAC
Other Safety					
44.	All Treated	PREG1	Listing of Subjects or Partners of Subjects Who Became Pregnant During the Study		SAC
45.	All Treated	DD3	Subject Profile for Death	ICH E3	SAC
46.	All Treated	PS5A	Listing of ECOG Performance Status		SAC
PK					
47.	PK	PK07	Listing of Pharmacokinetic Concentration-Time Data by Treatment	IDSL Part 1: to add a dose column.	SAC
48.	PK	PK13	Listing of Derived Pharmacokinetic Parameters by Treatment	IDSL Part 1: to add a dose column.	SAC
Concomitant medications					
49.	All Treated	CM10	Listing of Concomitant Medications		SAC
Subject Disposition					
50.	Enrolled		Listing of Number of Participant by Country and Site ID		SAC