Statistical Analysis Plan

Study ID: 209809

Official Title of Study: A Phase 1, Open Label Study of Intravenous GSK3745417 to Evaluate Safety, Tolerability, Pharmacokinetics, Pharmacodynamics and Determine RP2D and Schedule in Participants With Relapsed or Refractory Myeloid Malignancies Including Acute Myeloid Leukemia (AML) and High-risk Myelodysplastic Syndrome (HR-MDS)

NCT ID: NCT05424380

Date of Document: 24-Feb-2025

Information Type: Statistical Analysis Plan (SAP)

TITLE PAGE

Protocol Title: A Phase 1, open label study of intravenous GSK3745417 to evaluate safety, tolerability, pharmacokinetics, pharmacodynamics and determine RP2D and schedule in participants with relapsed or refractory myeloid malignancies including acute myeloid leukemia (AML) and high-risk myelodysplastic syndrome (HR-MDS)

Study Number: 209809

Compound Number: GSK3745417

Abbreviated Title: PH1, GSK3745417, Open Label, safety, tolerability, PK and PD study in Participants with AML and HR-MDS

Sponsor Name: GlaxoSmithKline Research & Development Limited

Regulatory Agency Identifier Number(s)

Registry	ID
IND	159056
EudraCT	2021-005234-41

XBU Statistical Analysis Plan (SAP) Template v2.0 17 January 2022

TABLE OF CONTENTS

PAGE

LIST OF TABLES

PAGE

No table of figures entries found.

VERSION HISTORY

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
SAP	13-JUN-2022	1.0 (25-JAN-2022)	Not Applicable	Original version
Amendment 1	16-FEB-2024	1.0 (25-JAN-2022)	Removal of Part 2 analysis and adjustments to Part 1 analysis to algin with study termination	Study termination
Amendment 2	24-FEB-2025	1.0 (25-JAN-2022)	Correct data error in version history table	Study Closure

1. INTRODUCTION

The purpose of this SAP is to describe the planned analyses to be included in the Clinical Study Report (CSR) for Study 209809. Due to the termination of this study, only the planned Part 1 analyses described in the protocol will be produced for a synoptic CSR.

Additional details with regards to data handling conventions and the specification of data displays will be provided in the Output and Specification (OPS) document. Additional data will be available to view via RAPIDO DV (for more details see OPS).

1.1. Objectives, Estimands and Endpoints

Dose Escalation		
	Objectives	**Endpoints**
Primary	• To determine the safety, tolerability, and RP2D of a daily dosing schedule (induction) of GSK3745417	• Frequency and severity of Adverse Events (AEs), Serious Adverse Events, (SAEs), Dose Limiting Toxicity (DLT), withdrawals due to AEs
Secondary	• To characterize the pharmacokinetics (PK) of GSK3745417, and relevant metabolites, as applicable, after single and repeat-dose administration.	• GSK3745417 concentrations in plasma or PK parameters
Exploratory	CCI [redacted]	

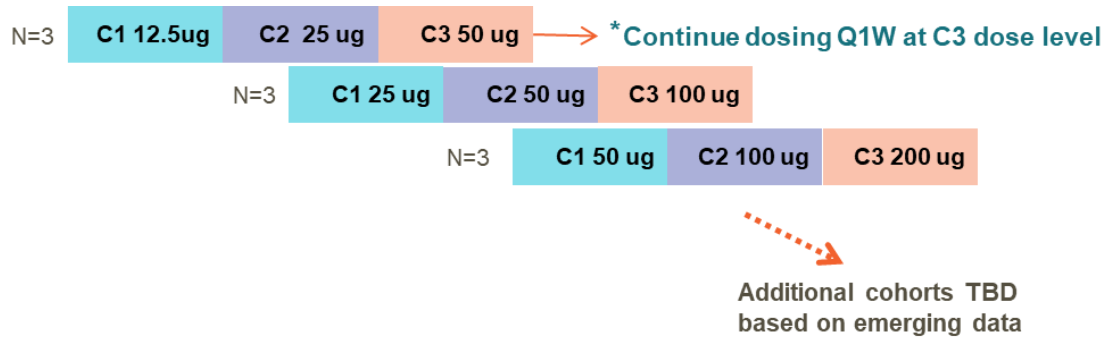
Dose Escalation		
	Objectives	**Endpoints**
	CCI [redacted]	

Estimands will not be considered for this first-time-in-human (FTIH) study.

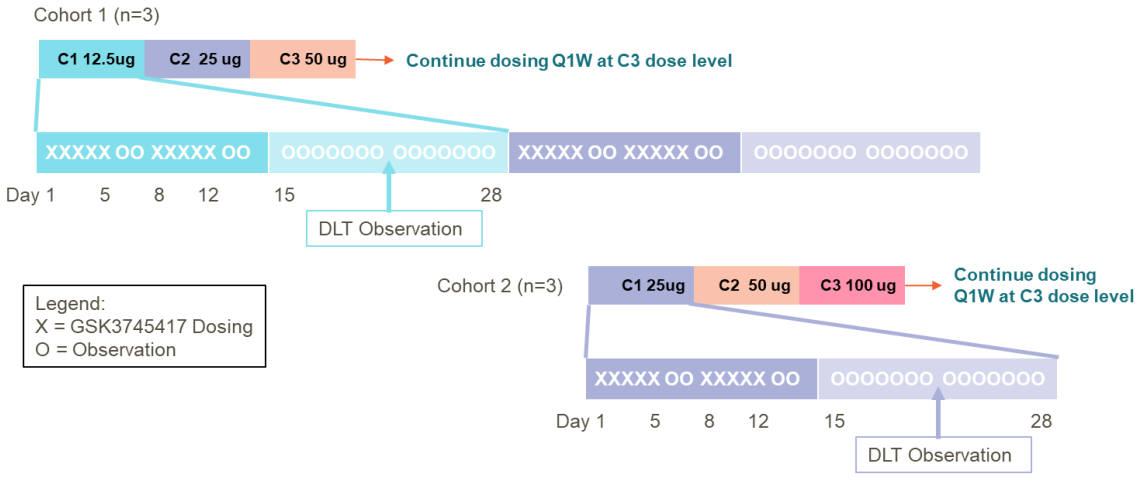
1.2. Study Design

Overview of Study Design and Key Features

Part 1 Induction Intra-patient Dose-Escalation Study



Part 1: Dosing and Observation Timeline for Each Cycle



Design Features	• This is a Phase 1 open-label study of intravenous GSK3745417 to evaluate safety, tolerability, pharmacokinetics, pharmacodynamics and determine RP2D and schedule in participants with relapsed or refractory acute myeloid leukemia (AML) and high-risk myelodysplastic syndrome (HR-MDS). • The study will be conducted in a staged approach consisting of 2 parts. Part 1 represents dose escalation to determine a cohort level MTD and incorporates intra-patient dose escalation within cohorts to minimize the potential for a participant to be exposed to a non-efficacious sub-therapeutic dose. Due to termination of this asset, Part 2 of this study will not be conducted. • The total duration of study participation begins with the signing of the informed consent form (ICF) and continues through the final protocol-defined follow-up assessment period. The maximum duration of study participation will depend on the participant's duration of study intervention.

Overview of Study Design and Key Features	
Study intervention	• Part 1 will evaluate a dosing schedule of a 5 days on/2 days off schedule for 2 weeks, and then have an additional 2 weeks off dose for observation for a total of 28 days in each cycle (5 / 2 / 5 q28d). Once an MTD has been established, additional cohorts may be opened to refine dosing frequency optimization. Each cohort will include at least 3 participants. Part 1 will include intra-patient dose escalation for 3 cycles, according to safety and tolerability parameters. The starting dose for Cycle 1 will be escalated in the next dose escalation cohort until a cohort level MTD is reached. • After 3 induction cycles, if a CR or PR (per appropriate response criteria) is observed, each patient will continue with maintenance weekly dosing at the Cycle 3 dose level until disease progression or unacceptable toxicity. Participants with progressive disease after 3 induction cycles will be withdrawn from study. Participants with stable disease or PR after 3 cycles might receive additional cycles.
Study intervention Assignment	• This is a FTIH, open-label, non-randomized study.

2. STATISTICAL HYPOTHESES

With respect to the primary objectives and endpoints of the dose escalation (Part 1), no specific statistical hypotheses are being tested. The primary focus will be on determining the RP2D for induction for further exploration based upon the safety, PK, and anticancer activity profiles of GSK3745417 alone.

2.1. Multiplicity Adjustment

Not applicable.

3. ANALYSIS SETS

Analysis Set	Definition / Criteria	Analyses Evaluated
Screened	• All participants who were screened for eligibility.	• Study Population
Enrolled	• All participants who entered the study (who received GSK3745417 or underwent a post-screening procedure). Note: Screening failures (who never passed screening even if rescreened) and participants screened but never enrolled into the study (met eligibility but not needed) are excluded as they did not enter the study.	• Study Population
Safety	• All participants who take at least 1 dose of study intervention. Participants will be analysed according to the intervention they actually received.	• Study Population • Safety • Efficacy
DLT-evaluable	• All participants who take at least 1 dose of study intervention and are followed for the DLT observation period or are withdrawn within the DLT observation period due to meeting the DLT criteria. • Participants unable to receive at least 70% of scheduled doses within the DLT period for other reasons other than toxicity will not be considered evaluable	• Safety
PK	• All participants from the Safety Analysis Set for whom a PK sample is obtained and analysed.	• PK

4. STATISTICAL ANALYSES

4.1. General Considerations

4.1.1. General Methodology

The Safety Analysis Set will be used for all study population, efficacy, and safety analyses, unless otherwise specified. AE and PK related tables, listings and figures will be summarized by dose level. Study population and efficacy tables and listings will be summarized by treatment sequence.

The DLT-evaluable Analysis Set will be used for assessment of dose-limiting toxicities.

Confidence intervals will use 95% confidence levels unless otherwise specified.

Unless otherwise specified, continuous data will be summarized using descriptive statistics: n, mean, standard deviation (std), median, minimum, and maximum. Categorical data will be summarized as the number and percentage of participants in each category.

4.1.2. Baseline Definition

For all endpoints (except as noted in baseline definitions), the baseline value will be the latest pre-dose of GSK3745417 assessment with a non-missing value, including those from unscheduled visits, if available. If time is not collected, Day 1 assessments are assumed to be taken prior to first dose and used as baseline.

For laboratory data, baseline will be the latest non-missing pre-dose value.

For ECG analyses, if the latest, non-missing pre-dose values is from triplicate, the subject level baseline is defined as the mean of triplicate baseline assessments.

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

4.2. Primary Endpoint(s) Analyses

4.2.1. Definition of endpoint(s)

An AE is considered a DLT if it is considered by the investigator to be clinically relevant and attributed (definitely, probably, or possibly) to the study intervention and meets at least 1 of the criteria listed in Table 7 of the protocol. If an AE is considered related to the underlying disease, it is not a DLT. The DLT period is 28 days starting at Day 1 of each cycle. The analysis of DLTs will be based on the DLT-Evaluable Analysis Set, unless otherwise specified.

The definitions of an AE or Serious Adverse Event (SAE) can be found in Appendix 3 of the protocol. AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative). The analysis of AEs and SAEs will be based on the Safety Analysis Set, unless otherwise specified.

4.2.2. Main analytical approach

Adverse events analyses including the analysis of AEs, SAEs, and other significant AEs will be based on GSK Core Data Standards. Summary tables will focus on treatment-emergent AEs (TEAE) only. Details on treatment-emergent AEs are provided in Section 6.2.2. AEs will be coded using the standard MedDRA and grouped by system organ class

(SOC). AEs will be graded by the investigator according to the NCI-CTCAE (version 5.0).

A summary of treatment-emergent adverse events by system organ class and preferred term and maximum grade will be produced. A summary of common non-serious TEAEs that occurred in strictly 10% of the participants or above will be provided (no rounding for the percentage will be used in terms of 10% threshold, e.g., events with 9.9% incidence rate should not be included in this table). A summary of common (>=10%) TEAEs by overall frequency. The summary of common non-serious AEs will be grouped by SOC and PT. A summary of common adverse events by overall frequency will be produced.

The summary will use the following algorithms for counting the participant:

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

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

The date of the first occurrence of an AE will be used to indicate which dose level an AE should be reported in.

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. Study treatment-related AEs will be summarized by SOC, PT, and maximum grade. An overall frequency summary of non-serious drug related treatment emergent adverse events will also be produced.

Serious TEAEs will be summarized by SOC, PT, and maximum grade, as well as a separate summary of serious TEAEs by SOC and PT (Number of subjects and Occurrences). A separate summary of serious fatal and non-fatal drug-related treatment emergent by overall frequency will be created for disclosure requirements to regulatory agencies, displayed by PT.

Additionally, a summary of the number of patients experiencing DLTs in each cohort will be provided for the dose escalation period. DLTs will be summarized according to GSK Oncology Data Standards.

All AEs (including SAEs and subject IDs for each individual AE) will be listed. A listing of reasons for considering as a serious adverse event will be generated.

4.3. Secondary Endpoint(s) Analyses

4.3.1. Key secondary endpoint(s)

4.3.1.1. Definition of endpoint(s)

The following PK parameters will be determined if data permit:

- Cmax, Cmin, and Tmax
- Area under the plasma concentration-time curve (AUC(0-t), AUC(0-τ), [repeat dosing]])
- Apparent terminal phase elimination rate constant (λz) (single dose)
- Apparent terminal phase half-life (t1/2) (single dose)
- Systemic clearance of parent drug (CL)
- Volume of distribution (V)
- Other parameters and analyses as appropriate and data permits, such as dose proportionality and time-invariance.

4.3.1.2. PK Evaluation

Pharmacokinetic parameters for GSK3745417 administered IV in this study will be calculated by standard non-compartmental analysis according to current working practices and using the currently supported version of Phoenix WinNonlin.

Analysis procedures will follow GSK VQD-REF-015788 unless otherwise noted below. All calculations of non-compartmental parameters will be based on actual sampling times. PK analysis of GSK3745417 will be the responsibility of the Clinical Pharmacology Modeling and Simulation (CPMS) Department, GSK. PK analysis of GSK3745417 drug concentration-time data will be conducted by noncompartmental methods under the direction of CPMS, GSK.

Statistical analyses of the PK parameters data will be the responsibility of Clinical Statistics, GSK. All PK analyses will be performed on the PK Analysis Set.

Drug concentration-time data will be listed for each participant and summarized by descriptive statistics at each time point by dose. PK parameter data will be listed for each participant and summarized by descriptive statistics by dose and visit.

All derived PK parameters will be summarised using descriptive statistics, graphically presented (where appropriate) and listed. For each of these parameters, except Tmax, the following summary statistics will be calculated for each dose level and treatment day: median, minimum, maximum, arithmetic mean, 95% CI for the arithmetic mean, std, coefficient of variation (%CV = 100*(sqrt (exp(SD^2) - 1))) (where SD = SD of natural log transformed data), geometric mean, 95% confidence interval for the geometric mean and std of natural logarithmically transformed data. For Tmax, median, maximum, minimum, arithmetic mean, 95% CI, and std will be calculated. The first point, last point

and number of points used in the determination of λz will be included on the listing of the derived parameters.

All PK parameters will be reported to at least 3 significant digits, but to no more significant digits than the precision of the original data.

The data from this study may be combined with the data from other studies for a population PK analysis and/or exposure-response analysis, which will be reported separately.

The following PK statistical analyses will only be performed if sufficient data are available (i.e., if participants have well defined serum profiles). Analyses may not be performed on Cmax or AUC if the team considers there are a large amount of data either below the limit of quantification or non-calculable; alternatively, if the dose with limited data is at the lower end of the dose range, the data of this dose will be excluded, and the appropriate analysis conducted on the rest of the data. However, if there are non-calculable PK parameter data at intermittent doses no statistical analyses will be performed. A minimum of 3 doses will be required to assess dose proportionality.

Dose proportionality of GSK3745417 will be assessed by visual inspection of:

- Scatter plots (+geometric mean and 95% confidence intervals, as appropriate) of GSK3745417 dose-normalized PK parameter vs dose will be produced for [or AUC(0-t) and Cmax.

- Scatter plots of GSK3745417 log10 PK parameter vs log10 dose will be produced for AUC(0-t) and Cmax.

The PK parameters will be dose-normalized by the actual dose that each patient received (i.e., Cmax/actual dose).

Other PK figures may be produced if deemed appropriate.

4.3.2. Supportive secondary endpoint(s)

The list of terms for adverse events of special interest (AESI) is in Appendix 4 of the protocol and includes events that may be immune-related or related to cytokine release syndrome (CRS) or tumor lysis syndrome (TLS). AESIs and the type of event will be recorded in the CRF.

The list of AESIs is provided below and may be updated at the time of database lock based on the MedDRA version in use at the time of reporting and/or any additional safety information available from GSK that may determine a need to consider additional events of interest.

Cytokine-related AEs

Cardiopulmonary or hemodynamic toxicity starting within 24 hours of study treatment that requires >40% FiO2, vasopressor administration, antiarrhythmic agent, or other significant medical intervention. Asystole, as measured by ECG, or bradycardia that is symptomatic and requires medical intervention. Some of the MedDRA preferred terms relevant to cytokine-related AEs include cytokine release syndrome, cytokine storm, cytokine increased and systemic inflammatory response syndrome.

Immune-related AEs

Pneumonitis (reported as AESI if ≥ Grade 2)		
Acute interstitial pneumonitis	Interstitial lung disease	Pneumonitis
Colitis (reported as AESI if ≥ Grade 2 or any grade resulting in dose modification or use of systemic steroids to treat the AE)		
Intestinal Obstruction	Colitis	Colitis microscopic
Enterocolitis	Enterocolitis hemorrhagic	Gastrointestinal perforation
Necrotizing colitis	Diarrhea	
Endocrine (reported as AESI if ≥ Grade 3 or ≥ Grade 2 and resulting in dose modification or use of systemic steroids to treat the AE)		
Adrenal Insufficiency	Hyperthyroidism	Hypophysitis
Hypopituitarism	Hypothyroidism	Thyroid disorder
Thyroiditis	Hyperglycemia, if ≥Grade 3 and associated with ketosis or metabolic acidosis (DKA)	
Endocrine (reported as AESI)		
Type 1 diabetes mellitus (if new onset)		
Hematologic (reported as AESI if ≥ Grade 3 or any grade resulting in dose modification or use of systemic steroids to treat the AE)		
Autoimmune hemolytic anemia	Aplastic anemia	Thrombotic Thrombocytopenic Purpura (TTP)
Idiopathic (or immune) Thrombocytopenia Purpura (ITP)	Disseminated Intravascular Coagulation (DIC)	Hemolytic Uremic Syndrome (HUS)
Any Grade 4 anemia regardless of underlying mechanism		
Hepatic (reported as AESI if ≥ Grade 2, or any grade resulting in dose modification or use of systemic steroids to treat the AE)		
Hepatitis	Autoimmune hepatitis	Transaminase elevations (ALT and/or AST)
Infusion Reactions (reported as AESI for any grade)		
Allergic reaction	Anaphylaxis	CRS
Serum sickness	Infusion reactions	Infusion-like reactions

Neurologic (reported as AESI for any grade)		
Autoimmune neuropathy	Guillain-Barré syndrome	Demyelinating polyneuropathy
Myasthenic syndrome		
Ocular (report as AESI if ≥ Grade 2 or any grade resulting in dose modification or use of systemic steroids to treat the AE)		
Uveitis	Iritis	
Renal (reported as AESI if ≥ Grade 2)		
Nephritis	Nephritis autoimmune	Renal Failure
Renal failure acute	Creatinine elevations (report as AESI if ≥Grade 3 or any grade resulting in dose modification or use of systemic steroids to treat the AE)	
Skin (reported as AESI for any grade)		
Dermatitis exfoliative	Erythema multiforme	Stevens-Johnson syndrome
Toxic epidermal necrolysis		
Skin (reported as AESI if ≥ Grade 3)		
Pruritus	Rash	Rash generalized
Rash maculo-papular		
Any rash considered clinically significant in the physician's judgment		
Other (reported as AESI for any grade)		
Myocarditis	Pancreatitis	Pericarditis
Any other Grade 3 event which is considered immune-related by the physician		

Summaries of the number and percentage of subjects with treatment-emergent AESIs will be provided for each type of event separately by PT and maximum grade. A summary of the number of participant and occurrences of treatment-emergent cytokine release syndrome adverse events and infusion related reactions will be produced. These summaries will be based on data as recorded in the eCRF.

4.4. Exploratory Endpoint(s) Analyses

CCI

CCI

4.5. Other Safety Analyses

The safety analyses will be based on the Safety Analysis Set, unless otherwise specified.

4.5.1. Extent of Exposure

Exposure to GSK3745417 will be summarized according to cumulative actual dose, number of cycles, time on study treatment (weeks) with separate sections for induction dosing and maintenance dosing in one table. Descriptive statistics including mean, median, standard deviation, minimum, and maximum will be calculated.

The cumulative dose, converted to and displayed in mg, is the sum of the actual dose administered in micrograms during each infusion for a subject throughout the study. For induction dosing, cumulative dose will be summarized by cycle. For induction cycles, the number of cycles will be calculated by the number of GSK3745417 doses received during the induction phase divided by 10. For subsequent maintenance cycles, the number cycles will be calculated by (last maintenance infusion date – first maintenance infusion date + 7)/28.

Subject level details for extent of exposure to study treatment will be listed. The listing will include cycle, total dose taken per cycle, cycle day, start and stop dates, scheduled dose, actual dose, and cumulative dose. Exposure data will be listed in both units (mg and μg).

4.5.2. COVID-19

4.5.2.1. COVID-19 Assessment and COVID-19 AEs

A standardized MedDRA Query (SMQ) will be used to identify all COVID-19 AEs.

4.5.2.2. Impact of COVID-19 Pandemic on Safety Results

Since all subjects are dosed after the pandemic started, the outputs showing the incidence rates for events occurring before or after the start of the COVID-19 pandemic are not applicable.

4.5.3. Additional Safety Assessments

Any additional safety data will be produced using listings via RAPIDO data viewer. This includes a listing of liver monitoring/stopping event reporting, liver stopping event profile, ECOG performance status, and LVEF.

4.5.4. Deaths

All deaths will be summarized based on the number and percentage of participants. This summary will classify participants by time of death relative to the last dose of medication (>30 days or ≤30 days) and primary cause of death in the order listed in the eCRF. A supportive listing will be generated to provide participant-specific details on participants who died.

4.5.5. 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 reported as an AE or SAE.

4.6. Other Analyses

Data from all participating centres will be integrated and no controlling for center-effect will be considered in the statistical analyses.

4.7. Interim Analyses

Due to study termination, no interim analyses will be conducted.

4.8. Changes to Protocol Defined Analyses

Study termination occurred just as Part 1 (dose escalation) had finished recruitment. Therefore, no participants will be recruited to Part 2 of study design mentioned within the protocol (Dated: 25-Jan-2022) and hence no data will be collected or analysed. Additionally, no interim analyses will occur as there is no need to initiate Part 2.

5. SAMPLE SIZE DETERMINATION

Approximately 72 participants were planned to be enrolled to receive study intervention. The planned sample size for the study was chosen to allow adequate characterization of safety, clinical activity, PK, and PD profile based on the study objectives. For Part 1 dose escalation, the total sample size will depend on the number needed to adequately characterize the DLT profile and determine the MTD. For Part 2 dose expansion, approximately 50 participants were planned to be recruited. Refer to Section 9.2 of the protocol for details regarding sample size determination, statistical design, and operating characteristics.

6. SUPPORTING DOCUMENTATION

6.1. Appendix 1 Study Population Analyses

Unless otherwise specified, the study population analyses will be based on the Safety Analysis Set.

In this multicentre global study, enrolment will be presented by country and site.

6.1.1. Participant Disposition

A summary of the number and percentage of participants who completed the study as well as those who prematurely withdrew from the study or died will be provided. Reasons for study withdrawal will be listed. For those who have neither completed, died, nor withdrawn, they will be categorized as on study intervention or in follow up.

A participant is considered to have completed the study if they have completed all phases of the study including the last visit or the last scheduled procedure shown in the Schedule of Activities (Section 1.3 of the protocol). In addition, if the sponsor decides to close the study, participants who are receiving study intervention or are in the follow-up period will be considered to have completed the study.

A summary of study intervention status will be provided. This display will show the number and percentage of participants who have completed the scheduled study intervention, are ongoing with study intervention, died, or have discontinued study intervention prematurely, as well as primary reasons for discontinuation of study intervention. Reasons for study treatment discontinuation will be listed.

A listing of reasons for screen failure will be provided using the screened population. A listing of subjects excluded from any population, and a listing of subjects with inclusion/exclusion criteria deviations will be reported.

6.1.2. Demographic and Baseline Characteristics

The demographic characteristics including age, gender, ethnicity, height/weight at screening and race will be summarized with descriptive statistics using the Safety population. In addition, the following age categories will be summarized: 18-64, 65-84 and >=85 based on the Enrolled Analysis Set.

Disease characteristics at screening including primary tumor type, time since initial diagnosis, disease classification (WHO classification of AML or MDS and IPSS-R category), blast count percentage, and cytogenetics and molecular alterations will be summarized and listed. The following genetic markers have been identified by the study team for inclusion in displays: IDH1, IDH2, NPM1, FTL3, NRAS, c-KIT, TP53, CEBPA.

6.1.3. Protocol Deviations

Important protocol deviations will be listed.

Protocol deviations will be tracked by the study team throughout the conduct of the study. These protocol deviations will be reviewed to identify those considered as important as follows:

- Data will be reviewed prior to freezing the database to ensure all important deviations (where possible without knowing the study intervention details) are captured and categorised in the protocol deviations dataset.
- This dataset will be the basis for the summaries of important protocol deviations.

6.1.4. Prior and Concomitant Medications

Concomitant medications will be coded using the WHO Drug dictionaries. A listing of concomitant medications using ingredient will be produced.

Concomitant medications include any medication that was taken at some point during the on-intervention period as defined in Section 6.2.1.1.

6.1.5. Prior Anti-cancer Therapy

The number and percentage of participants that received any prior anti-cancer therapy or stem cell transplant will be summarized. Prior anti-cancer therapy will be summarized by ingredient.

6.1.6. Additional Analyses Due to the COVID-19 Pandemic

The incidence of AEs and SAEs (fatal and non-fatal) of COVID-19, COVID-19 AEs leading to study drug discontinuation or study withdrawal, and COVID-19 AEs by severity, will be obtained from standard AE and SAE summaries.

Since all subjects are dosed after the pandemic started and the outputs showing the incidence rates for events occurring before or after the start of the COVID-19 pandemic are not applicable.

6.2. Appendix 2 Data Derivations Rule

6.2.1. Criteria for Potential Clinical Importance

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.

National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE v4.0.3) will be used to assign grades to the relevant laboratory parameters, including clinical chemistry, hematology, coagulation, liver function tests, QTc (Fridericia's) values, and vital signs (heart rate, blood pressure, temperature, respiratory rate).

6.2.1.1. ECG

ECG Parameter	Units		Clinical Concern Range	
			Lower	Upper
	Absolute			
Absolute QTcF Interval	msec	Grade 1	≥ 450	< 481
		Grade 2	≥ 481	< 501
		Grade 3	≥ 501	
	Change from Baseline			
Increase from Baseline QTcF	msec		> 30	≤ 60
	msec		> 60	

6.2.1.2. Vital Signs

Vital Sign Parameter (Absolute)	Units		Clinical Concern Range	
			Lower	Upper
Systolic Blood Pressure	mmHg	Grade 1	≥120	<140
	mmHg	Grade 2	≥140	<160
	mmHg	Grade 3	≥160	
Diastolic Blood Pressure	mmHg	Grade 1	≥ 80	< 90
	mmHg	Grade 2	≥ 90	< 100
	mmHg	Grade 3	≥ 100	
Heart Rate	bpm	L/H	< 60	> 100
Temperature	Degrees C	L/H	≤ 35	≥ 38
Respiratory Rate	Breaths/min	L/H	<12	≥ 25

6.2.2. Study Period

Assessments and events will be classified according to the time of occurrence relative to the study intervention period.

Pre-Intervention is defined as time prior to the first dose of study intervention.

On-Intervention is defined as time from first dose to last date plus 30 days. If time of assessment or study intervention is not collected, the following assessment on the first dose date will be assumed to be taken prior to the first dose and therefore considered pre-intervention: ECOG, ECG, Lab, and vital signs, and first dose date is considered on-intervention for AE and concomitant medication.

Post-Intervention is defined as any time post on-intervention window, i.e. > last dose date + 30 days.

Anti-cancer therapy will be classified as either prior to screening or following study treatment as per GSK Display Standards.

6.2.2.1. Treatment Emergent Flag for Adverse Events

Flag	Definition
Treatment Emergent	For AEs: • Study Treatment Start Date ≤ AE Start Date ≤ Treatment Discontinuation Visit or Study Treatment Stop Date + 30 Days if TDV is missing • AE Start Date is missing For SAEs/AESIs: • Study Treatment Start Date ≤ AE Start Date or pre-existing (prior to exposure) AE Worsening Date ≤ Study Treatment Stop Date + 90 days or Start of Anti-Cancer Therapy, whichever occurs first • AE Start Date is missing • Missing AE Start Date will be imputed following rules in Appendix 2 for determining Treatment Emergent AEs.

NOTES:

- If the study treatment stop date is missing, then the AE will be considered to be On-Treatment.

6.2.3. Study Day and Reference Dates

The safety reference date is the study intervention start date and will be used to calculate study day for safety measures.

The efficacy reference date is the study intervention start date and will be used to calculate study day for efficacy measures and baseline characteristics, as well as efficacy durations.

The study day is calculated as below:

- Assessment Date = Missing → Study Day = Missing
- Assessment Date < Reference Date → Study Day = Assessment Date – Ref Date
- Assessment Data ≥ Reference Date → Study Day = Assessment Date – Ref Date + 1

6.2.4. Assessment Window

For data summaries by visit, the nominal visit description will be used.

For PK data, the data from unscheduled visits will be slotted as follows:

Elapsed time from dose to start of PK sample collection(ARELTM) in hours is calculated as = (start datetime of PK sample collection – reference dose datetime) /3600.

Elapsed time from dose to start of PK sample collection(ARELTM) in minutes is calculated as = (start datetime of PK sample collection – reference dose datetime) /60.

Slotting algorithm if elapsed time(ARELTM) is in minutes:

- 0 < ARELTM <= 1, ARELTM = 1 min
- 1< ARELTM < =5, ARELTM = 5 min
- 5 < ARELTM <=15, ARELTM = 15 min
- 25 <= ARELTM <=35, ARELTM = 30 min
- 40<=ARELTM<=50, ARELTM = 40 min

Slotting algorithm if elapsed time (ARELTM) is in hours:

- 0.75 <= ARELTM <=1.25, ARELTM = 1 hr
- 1.50 <= ARELTM <=2.50, ARELTM = 2 hrs
- 3 <= ARELTM < =5, ARELTM = 4 hrs
- 7 <= ARELTM < =9, ARELTM = 8 hrs
- 22 <= ARELTM < =26, ARELTM = 24 hrs

6.2.5. 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 (including the mean). For PK data, if there are multiple records observed at the same date and time for a subject, those data will be excluded from the WNL file and will not be used for the derivation of PK parameters.

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.

6.2.6. Handling of Partial Dates

<table>
<tr><th>Element</th><th>Reporting Detail</th></tr>
<tr><td>General</td><td>

Partial dates will be displayed as captured in participant 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 or for specific analysis purposes as outlined below.
Imputed partial dates will not be used to derive study day, time to onset or duration (e.g., time to onset or duration of adverse events), or elapsed time variables (e.g., time since diagnosis). In addition, imputed dates are not used for deriving the last contact date in overall survival analysis dataset.

</td></tr>
<tr><td>Adverse Events</td><td>

Partial dates for AE recorded in the CRF will be imputed using the following conventions:

<table>
<tr><td>Missing start day</td><td>If study intervention start date is missing (i.e., participant did not start study intervention), then set start date = 1st of month.

Else if study intervention start date is not missing:

• If only a single dose level was given in the same month, then AE start date = 1st of the month or treatment start date (whichever is later).

• If more than one dose level was given in the same month as the AE start date, then,

– If AE end date contains a full date and AE end date is earlier than study intervention start date of the highest dose given that month, then set AE start date= 1st of month.

– If AE end date contains a full date and AE end date is later than the study intervention start date of the highest dose given that month, then AE start date = study intervention start date of highest dose given that month.

– If AE end date is missing, then set AE start date as the study intervention start date of the highest dose given that month.

Else set start date = 1st of month.</td></tr>
<tr><td>Missing start day and month</td><td>If study intervention start date is missing (i.e., participant did not start study intervention), then set AE start date = January 1.

Else if study intervention start date is not missing:

• If year of AE start date = year of study intervention start date, then</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><th>Element</th><th colspan="2">Reporting Detail</th></tr>
<tr><td></td><td></td><td>– If AE stop date contains a full date and AE stop date is earlier than study intervention start date, then set AE start date = January 1.
– If AE stop date contains a full date and AE stop date is later than study intervention start date, then set start date = study intervention start date of most recent dose level given prior to the AE stop date.
Else set AE start date = January 1.</td></tr>
<tr><td></td><td>Missing end day</td><td>A '28/29/30/31' will be used for the day (dependent on the month and year).</td></tr>
<tr><td></td><td>Missing end day and month</td><td>No Imputation</td></tr>
<tr><td></td><td>Completely missing start/end date</td><td>No imputation. Consequently, time to onset and duration of such events will be missing.</td></tr>
<tr><td>Concomitant Medications/ Medical History</td><td colspan="2">• Partial dates for any concomitant medications recorded in the CRF will be imputed using the following convention:</td></tr>
<tr><td></td><td>Missing start day</td><td>If study intervention start date is missing (i.e., participant did not start study intervention), then set start date = 1st of month.
Else if study intervention start date is not missing:
• If month and year of start date = month and year of study intervention start date, then
– If stop date contains a full date and stop date is earlier than study intervention start date, then set start date= 1st of month.
– Else set start date = study intervention start date.
Else set start date = 1st of month.</td></tr>
<tr><td></td><td>Missing start day and month</td><td>If study intervention start date is missing (i.e., participant did not start study intervention), then set start date = January 1.
Else if study intervention start date is not missing:
• If year of start date = year of study intervention start date, then
– If stop date contains a full date and stop date is earlier than study intervention start date, then set start date = January 1.
– Else set start date = study. intervention start</td></tr>
</table>

<table>
<tr><th>Element</th><th>Reporting Detail</th></tr>
<tr><td></td><td>
<table>
<tr><td></td><td>date.

Else set start date = January 1.</td></tr>
<tr><td>Missing end day</td><td>A '28/29/30/31' will be used for the day (dependent on the month and year).</td></tr>
<tr><td>Missing end day and month</td><td>A '31' will be used for the day and 'Dec' will be used for the month.</td></tr>
<tr><td>Completely missing start/end date</td><td>No imputation</td></tr>
</table>
</td></tr>
<tr><td>Prior Anti-cancer Therapy/Radiothe rapy/Surgical Procedures/Stem Cell Transplant</td><td>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,
o If first dosing date is the first of the month, minimum of dates (impute last day of the partial date month to partial date, first dosing date) will be used
• Else minimum of dates (impute last day of the partial date month to partial date, first dosing date - 1) will be used</td></tr>
<tr><td>New Anti-cancer Therapy/ Radiotherapy/ Surgical Procedures/Cross over for Efficacy Evaluation (e.g., response rate, time to event)</td><td>Start dates for follow-up anti-cancer therapy, radiotherapy (where applicable), stem cell transplant, and surgical procedures (where applicable) will be imputed in order to define event and censoring rules for 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, radiotherapy, stem cell transplant, 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:
o If both month and day are missing, no imputation will be applied;
o If only day is missing:
▪ If the month of partial date is the same as the month of last dosing date, minimum of dates (last dosing date + 1, impute last day of the partial date month to partial date) 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 for MDS (Recurrences for AML), minimum of dates (last date of disease assessment + 1, impute last day of the partial date month to partial date) will be used for the date;
▪ If both conditions above are met, the later date will be used for the day;
▪ Otherwise, a ‘01’ will be used for the day;</td></tr>
</table>

Element	Reporting Detail
	• Completely or partial missing end dates will remain missing, with no imputation applied.

6.2.7. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
None

Trademarks not owned by the GlaxoSmithKline Group of Companies
NONMEM
SAS
WinNonlin

7. REFERENCES

NA