Protocol

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)

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TITLE PAGE

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Protocol Number: 209809/Version 1.0

Compound Number or Name: GSK3745417

Brief Title: A Phase 1, open label study of intravenous GSK3745417 to evaluate safety, tolerability, pharmacokinetics, pharmacodynamics and determine RP2D & schedule in participants with relapsed or refractory Myeloid Malignancies including AML and HR-MDS

Study Phase: Phase 1

Sponsor Name and Legal Registered Address:

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Medical Monitor Name and Contact Information

Can be found in the Study Reference Manual.

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Date

The signed page is a separate document.

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

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1. PROTOCOL SUMMARY

1.1. Synopsis

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).

Rationale:

GSK3745417 is an intravenously delivered STING (STimulator of Interferon Genes) agonist currently under evaluation in solid tumors in the FTIH 208850 dose escalation study. Recent evidence has shown that in addition to immune-mediated activity, GSK3745417 exhibits a cytolytic effect, a second mechanism of action, in AML cells in nonclinical studies. STING is expressed at a higher level on AML cells compared with other tumor types [The Cancer Genome Atlas (TCGA) - National Cancer Institute]. The high level of STING expression combined with preclinical evidence of antitumor activity makes AML a suitable indication to establish proof of mechanism and evaluate the clinical activity of GSK3745417. The goal of the study is to identify an RP2D and schedule with a manageable safety profile. Study 209809 is proposed to evaluate safety, pharmacokinetics, pharmacodynamics, and preliminary clinical activity of GSK3745417 in relapsed or refractory AML and high-risk myelodysplastic syndrome (HR-MDS).

Objectives and Endpoints

Dose Escalation (Part 1)		
	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 (Part 1)		
	Objectives	**Endpoints**
	CCI [redacted]	

Dose Expansion (Part 2)		
	Objectives	**Endpoints**
Primary	• To evaluate clinical efficacy following the daily dosing "induction" period of GSK3745417 in participants with relapsed/refractory AML and HR-MDS. • To determine the safety, tolerability, and recommended Phase 2 dose (RP2D) for "maintenance"	• Objective response rate (ORR) after the daily dosing "induction" period of GSK3745417 • Frequency and severity of Adverse Events (AEs), Serious Adverse Events, (SAEs), Dose Limiting Toxicity (DLT), withdrawals due to AEs during "maintenance" dosing
Secondary	• To further evaluate the safety, tolerability of one or more RP2D for maintenance	The following may be included based on the availability of data and appropriateness: • AEs, SAE, AESIs leading to dose modifications or delays
	• 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	CC1 [redacted]	

Dose Expansion (Part 2)		
	Objectives	**Endpoints**
	CCI [redacted]	

Overall Design and Brief Summary:

This is a Phase 1, open label, dose escalation study to evaluate safety, pharmacokinetics, and pharmacodynamics of intravenous GSK3745417 in participants with relapsed or refractory AML or high risk MDS.

The study will be conducted in a staged approach consisting of 2 parts. 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 a maximum tolerated dose (MTD) has been established, additional cohorts may be opened to refine dosing frequency optimization. Each cohort will include at least 3 participants and dosing of participants entering the study will be staggered by at least 5 days from D1 of previous patient for the first cohort only. 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 starting dose-based MTD is reached. Individual patients may titrate above the starting dose-based MTD based on tolerability. Dose escalation cohorts will start with Cycle 1 at 12.5 µg GSK3745417. Within a cohort for an individual subject the dose may double for Cycle 2, and double again for Cycle 3 based on individual tolerability. The starting dose of subsequent cohorts will increase by 2-fold from Cycle 1 of the previous cohort. Patients may be dose reduced for subsequent cycles if there is lack of tolerability in the previous cycle (Section 6.4). The DLT period will be 28 days starting at Day 1 of Cycle 1 of each cohort. After 3 induction cycles, if a complete response (CR) or partial

response (PR) (IWG) is observed (See Appendix 9) 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 if the assessment by the investigator determined a benefit and GSK Medical Monitor agrees.

For Part 1, approximately 22 participants will receive dosing in the hospital on a 5 days on/2 days off schedule for 2 weeks, and then have an additional 2 weeks off dose for observation. The participant will be observed for at least 24 hours after the final dose in each cycle. All participants will be hospitalized the day before a new dosing cycle starts to receive tumor lysis syndrome (TLS) prophylaxis in line with institutional guidelines (all participants should receive IV fluids ± allopurinol as well as alkalinization of urine with renal consult if this is in line with institutional guidance). TLS prophylaxis will continue alongside daily dosing as clinically indicated. To further reduce the risk of TLS, guidance in Section 6.4.1.2 must be followed to determine when daily dosing should be held.

A 5 / 2 / 5 q28d dosing regimen is being evaluated in Part 1 since it is hypothesized that increased dosing frequency of GSK3745417 will enhance the direct cell killing effect by more constantly engaging target. After 3 cycles, if a CR or PR (IWG) is observed, each patient will continue with maintenance weekly dosing at the Cycle 3 dose level until disease progression or unacceptable toxicity. Participants with PR after 3 induction cycles might receive additional cycles if the assessment by the investigator determined a benefit and GSK Medical Monitor agrees.

For Part 2, efficacy will be evaluated after an induction phase in approximately 50 participants, 25 AML participants and 25 HR-MDS participants. The induction phase consists of a treatment regimen cycles at the dose/doses determined to be safe in Part 1 (RP2D). The number of cycles, number of doses investigated in the induction phase, and/or dosing schedule of 5 / 2 / 5 q28d treatment will be determined and may be modified based on a review of safety and PK data generated from Part 1. After the induction phase, patients will continue to either a weekly (Q1W), every three weeks (Q3W), or less frequent dosing schedule for maintenance treatment, if a CR or PR is observed (See Response Criteria for Participants with AML Appendix 9; See IWG Criteria for Response for Participants with MDS Appendix 8). Participants with stable disease or PR after 3 induction cycles might receive additional cycles if the assessment by the investigator determined a benefit and GSK Medical Monitor agrees. Up to three dose levels for maintenance treatment will be evaluated in the maintenance dose escalation. The DLT period for the maintenance dose escalation portion of Part 2 will be 28 days starting at Day 1 of each cycle. Dose escalation for the maintenance schedule will start at the highest dose cleared for safety in Part 1. Part 2 will evaluate the efficacy of the induction regimen separately for AML and HR-MDS as well as the tolerability and duration of response of the Q1W or Q3W maintenance schedules to determine the best dose and schedule for further studies.

Number of Participants:

Approximately 22 participants may be enrolled in Part 1, and approximately 50 participants may be enrolled in Part 2. The total number of participants to be enrolled is an estimate and will depend on the number needed to adequately characterize the DLT and PD profile and determine the MTD(s)/RP2D(s). All participants who take at least one dose of study intervention will be considered evaluable for analysis.

Intervention Groups and Duration:

The study includes a screening period, a treatment period (consisting of - 3-cycle induction phase and a maintenance phase), and a follow-up period. Participants will be screened for eligibility beginning up to 4 weeks before the start of treatment. GSK3745417 will be centrally administered IV according to the dosing schedule in the corresponding cohort the participant is enrolled.

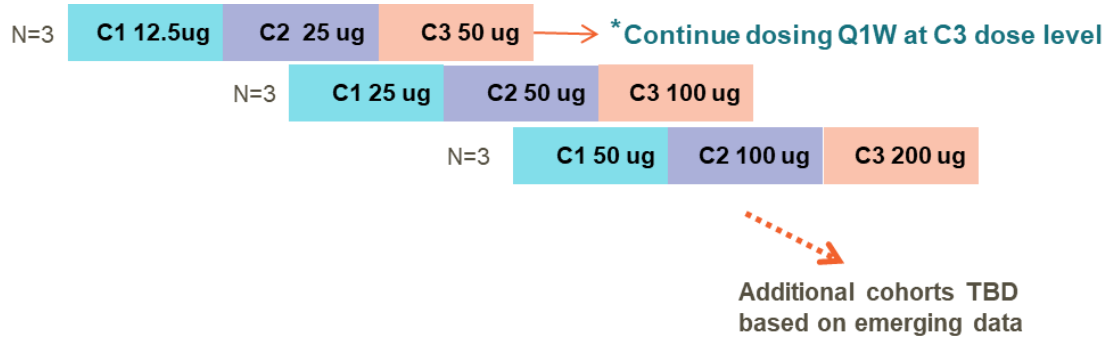
Participants will be assessed for response according to the IWG response criteria for AML or MDS at end of each induction cycle including (at 28 days [after Cycle 1], at 56 days [after Cycle 2], and at 84 days [after Cycle 3]). Within the maintenance phase, assessment will be at 3 weeks and then every 6 weeks thereafter. Participants will be treated until disease progression, unacceptable toxicity, withdrawal of consent, or termination of the study by GSK.

Data Monitoring/ Other Committee: No

1.2. Schema

Part 1: Dose Escalation Cohorts for Daily Dosing MTD

Figure 1 Part 1 Induction Intra-patient Dose-Escalation Study



* Patients in C3 dose level in all cohorts will be continuing dosing Q1W at C3 dose level

Figure 2 Part 1: Dosing and Observation Timeline for Each Cycle

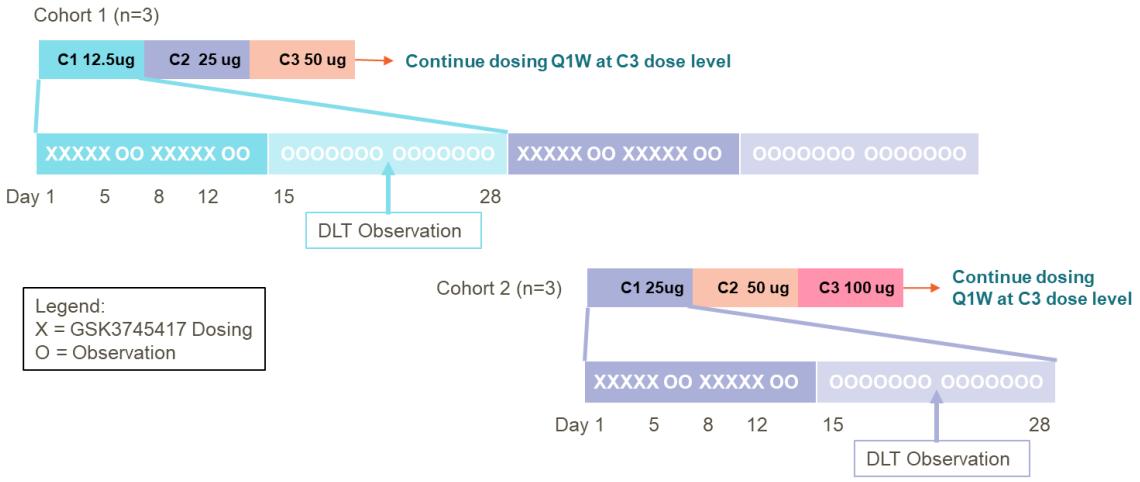
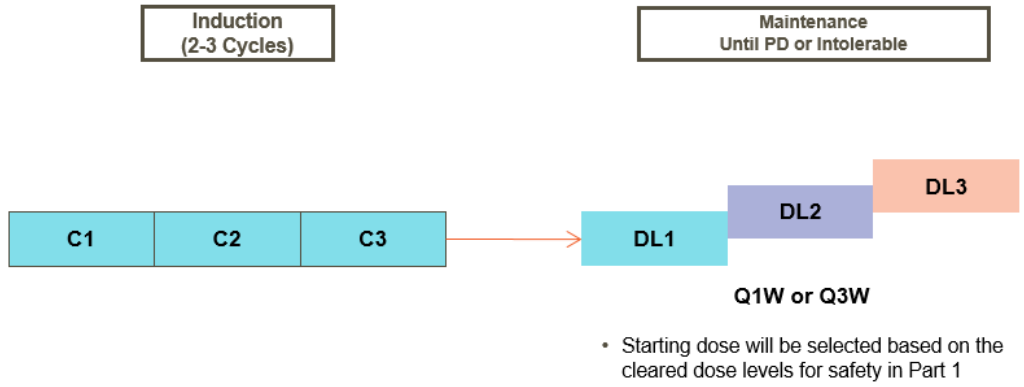


Figure 3 Part 2: Expansion Study: Induction and Maintenance Dose Escalation



1.3. Schedule of Activities (SoA)

- The schedule of activities for each Part of the study may be found on the following pages. For all parts, the following apply:
- The timing of planned study assessments may change during the study based on emerging data/in-stream data review to ensure appropriate monitoring.
- Any changes in the timing of time points for any planned study assessments as the result of emerging pharmacokinetic/pharmacodynamic data from this study must be documented and approved by the relevant study team member and then archived in the sponsor and site study files but will not constitute a protocol amendment.

- The Competent Authority (CA) and ethics committee (EC) will be informed of any safety issues that constitute a substantial amendment and require alteration of the safety monitoring scheme or amendment of the informed consent form (ICF). The changes will be approved by the CA and the EC before implementation.
- For Part 1, Table 1 applies to Cycles 1, 2, and 3 in the Dose Escalation Cohort After completing the assessments in Cycle 3, participants would proceed to complete the assessments in Table 3 for the maintenance phase.
- For Part 2, after completing the assessments in Table 2, participants would proceed to complete the assessments in either Table 3 or Table 4 for the maintenance phase.

1.3.1. Part 1 – Dose Escalation

Table 1 Schedule of Activities: Part 1 - Dose Escalation Cohort(s)

DE Cohort	Screening[a]	Cycle (Induction Period)			Follow-Up (post-final dose administered)		
Study Procedure		**Intervention Period (In-Patient)**		**Observation Period (Outpatient)**	**TDV[b]**	**Follow-Up**	**Notes**
Week	**≤4**	**1 - 2**		**3 - 4**	**+4**		
Day	**≤28**	**-1**	**1 - 13**	**14 - 28**	**+30d**		
Informed Consent	X						
Inclusion and Exclusion criteria	X						
Demographics, Medical History, Prior Medications, Disease Characteristics	X						Include use of antibiotics, probiotics and anti-infectives taken 60 days prior to study intervention.
Anticancer Therapy and Response to Prior Anticancer Therapy	X						
Participant Registration	X						
Safety Assessments							
In-House Monitoring		X	X				Participants should be monitored in a medically qualified unit/clinic/hospital starting on Day -1 through Day 13 (24 hours after the administration of GSK3745417 on Day 12) of each cycle.
Physical Exam	X		X		X		A complete physical exam is required at screening, including cardiac and neurological examinations; brief or targeted physical exams will be performed on Day 1 at predose (within 1h prior to dosing) and

DE Cohort	Screening[a]	Cycle (Induction Period)			Follow-Up (post-final dose administered)		
Study Procedure		**Intervention Period (In-Patient)**		**Observation Period (Outpatient)**	**TDV[b]**	**Follow-Up**	**Notes**
Week	**≤4**	**1 - 2**		**3 - 4**	**+4**		
Day	**≤28**	**-1**	**1 - 13**	**14 - 28**	**+30d**		
							Day 13 of each cycle, and as clinically indicated. Refer to Section 8.2.1 for physical examination details.
ECOG PS	X		X		X		Should be assessed at each cycle
Vital Signs	X	X	X		X		Should be collected at each cycle at least 6 times on Day -1 within 24 hours prior to dosing, Day 1, 5, 8, and 12 at predose (within 1h prior to dosing), end of injection (EOI)+30m, +1h, +2h, +4h, +6h, +8h, +12h, +24h and, at least four times every day until discharge or more frequently if clinically indicated.
Weight	X	X			X		Should be collected at each cycle.
Echocardiogram	X	Week 1 and then Q8W. Additional echocardiography may occur as clinically indicated					If available, a 3D ECHO is preferred, otherwise a 2D ECHO may be performed. Where the quality of the ECHO examination is sub-optimal, MUGA scans may be used. The modality used at baseline should be repeated throughout the study to ensure comparison to baseline. At TDV, ECHO/MUGA does not need to be performed if an on-study ECHO has been conducted within the 4 weeks prior to visit. ECHO should be performed in the final week of the observation period.
IV Contrast-enhanced Brain MRI (preferred) or IV Contrast-	X	Repeat if clinically indicated					Scans performed as standard of care prior to study consent will be acceptable as long as assessment is Brain imaging to be performed only if clinically indicated.

DE Cohort	Screening[a]	Cycle (Induction Period)			Follow-Up (post-final dose administered)		
Study Procedure		**Intervention Period (In-Patient)**		**Observation Period (Outpatient)**	**TDV[b]**	**Follow-Up**	**Notes**
Week	**≤4**	**1 - 2**		**3 - 4**	**+4**		
Day	**≤28**	**-1**	**1 - 13**	**14 - 28**	**+30d**		
enhanced Brain CT Scan							
12-lead ECG	X		X		X		Triplicate ECGs should be performed at screening. Single ECGs should be obtained at each cycle on Day 1 and Day 4 at predose (within 1h prior to dosing) and EOI+2h. In cases of TLS, triplicate ECGs will be obtained at screening. Single ECGs should be obtained prior to GSK3745417 dosing, within 5 min EOI, and within 2 hours prior to completion of clinic visit. Post Week 6, next ECG should be on Week 9 and then Q3W thereafter. Patients with new onset symptoms consistent with immune-mediated pericarditis or myocarditis should have additional ECGs as clinically indicated.
Holter Monitoring		X	X				Baseline and Day -1 and Day 1 of Cycle 1 after dosing, starting at least -24h predose, followed by normal activity (ambulatory) until -30 min predose, when participant will be lying supine until time 0. Postdose, the participant will by lying supine for at least 3 minutes to align with the PK plasma sampling at EOI +5m, +15m, +30m, +45m, +1h, +2h, +4h, +6h, +8h, +12h and +24h. Holter monitoring will end at 24h after the first study intervention. The Holter will remain with the participant until 24h post-dose and then will be removed. The requirement for Holter

DE Cohort	Screening[a]	Cycle (Induction Period)			Follow-Up (post-final dose administered)		
Study Procedure		**Intervention Period (In-Patient)**		**Observation Period (Outpatient)**	**TDV[b]**	**Follow-Up**	**Notes**
Week	**≤4**	**1 - 2**		**3 - 4**	**+4**		
Day	**≤28**	**-1**	**1 - 13**	**14 - 28**	**+30d**		
							monitoring may be waived for individual participants upon approval from GSK.
Neurological Assessment including ICE scoring	X	Conduct if clinically indicated					Refer to Section 6.4.1 for neurological assessment details.
AE/SAE Review		Assess at each visit from first dose until the TDV for AEs and until 90 days after the last dose for AESI and SAEs					
Concomitant Medication Review		Continuous: Assess at each visit from first dose of study intervention					
Follow-Up Phone Call				X			Participants should be contacted by phone 24-72 hours and 1 week (+24 hours) following discharge from clinic to assess for any AEs or cytokine related events.
Safety Laboratory Assessments							
Human Immunodeficiency Virus (HIV), Hepatitis B Surface Antigen (HBsAg), Hepatitis C Virus (HCV) Antibody	X						

DE Cohort	Screening[a]	Cycle (Induction Period)			Follow-Up (post-final dose administered)		
Study Procedure		**Intervention Period (In-Patient)**		**Observation Period (Outpatient)**	**TDV[b]**	**Follow-Up**	**Notes**
Week	**≤4**	**1 - 2**		**3 - 4**	**+4**		
Day	**≤28**	**-1**	**1 - 13**	**14 - 28**	**+30d**		
Pregnancy Test	X		≤72 hours (serum)	X	X	Q12W	Negative serum pregnancy test required at screening and within 72 hours prior to date of first dose of study treatment for females of childbearing potential. Urine pregnancy test will be conducted every 4 weeks for duration of study, on last day of treatment (if possible), at TDV, and at the Follow-Up visit.
CBC with differential	X	X	X	X	X		Sample collection times: Single sample from Day -1 to Day 13, prior to each administration of GSK3745417. At least every 6 hours for the first 48 hours following initiation of daily dosing period, then at least twice daily up to an including Day 5 dosing of each daily dosing period, and more frequently as clinically indicated. On the days when GSK3745417 is not administered, samples will be collected at approximately the same times as on the days of GSK3745417 administration. A sample will also be taken between Day 20 and Day 22 during the outpatient period of the cycle.
Clinical Chemistry (including laboratory parameters for TLS diagnosis and management)	X	X	X	X	X		Sample collection times: Cycle 1, and any cycle with a dose increase: single sample on Day –1; Days 1 and 2 at predose, EOI+6h, +12h, +18h and +24h; Days 3 - 5 – at predose and EOI+6hrs; Days 6 and 7 – single daily

DE Cohort	Screening[a]	Cycle (Induction Period)			Follow-Up (post-final dose administered)		
Study Procedure		**Intervention Period (In-Patient)**		**Observation Period (Outpatient)**	**TDV[b]**	**Follow-Up**	**Notes**
Week	**≤4**	**1 - 2**		**3 - 4**	**+4**		
Day	**≤28**	**-1**	**1 - 13**	**14 - 28**	**+30d**		
							sample, Days 8 - 12 – at EOI+6hrs: Day 13 – single sample prior to discharge. Clinical chemistry including uric acid and phosphate will be measured at least every 6 hours for the first 48 hours following initiation of daily dosing period, then at least twice daily up to an including Day 5 dosing of each daily dosing period, and more frequently as clinically indicated. Clinical chemistry samples should be collected more frequently if clinically indicated (such as cases of TLS). A sample will also be taken between Day 20 and Day 22 during the outpatient period of the cycle. See Section 10.2 for complete list of required laboratory assessments.
C-Reactive Protein	X		X	X	X		Sample collection times: Day 1 at predose, EOI+8h and +24h for first dose, then pre dose at Day 5 and Day 12 of each cycle.
Thyroid function[c]	X		X		X		Sample collection times: Day 1 at predose of Cycles 1 and 3.
Troponin I and T	X		X		X		See Section 6.4.1.5 for management of cardiac events. Samples will be collected on Day 13.
BNP (or NTproNBNP)	X	Repeat as clinically indicated					Repeat test as outlined in management of cardiac events (Section 6.4.1.5)
eGFR	X						See Section 7.1.2 for management of renal events (if needed).

DE Cohort	Screening[a]	Cycle (Induction Period)			Follow-Up (post-final dose administered)		
Study Procedure		**Intervention Period (In-Patient)**		**Observation Period (Outpatient)**	**TDV[b]**	**Follow-Up**	**Notes**
Week	**≤4**	**1 - 2**		**3 - 4**	**+4**		
Day	**≤28**	**-1**	**1 - 13**	**14 - 28**	**+30d**		
Urinalysis[c]	X		X		X		Sample collection times: Days 1, 8 and 13 of each cycle. If urinalysis is abnormal, a microscopy should be performed.
Coagulation[c]	X		X				Sample collection times: at screening and prior to administration of first dose of GSK3745417 and at Day 8 of each cycle. Additional coagulation samples should be collected in the event of CRS (see Section 6.4.1.4)
Study Intervention							
Administer GSK3745417			X				GSK3745417 will be administered the same dose within each cycle on Days 1 – 5 and Days 8 - 12 QD. Participants will receive up to 3 cycles of treatment before moving to Q1W or Q3W dosing (Section 6.1). See Section 4.1 for maximum duration of study intervention. See Section 4.1 for safety and tolerability parameters to be reviewed prior to each daily dose
Non-Azole Antifungal		X	X	X			Non-azole antifungals should be administered if indicated, per local standard, on Day -1 through Day 28 of each cycle.
Tumor Lysis Syndrome Prophylaxis		X					All participants should receive tumor lysis syndrome (TLS) prophylaxis prior to date of first dose of each cycle on Day -1 according to institutional guidelines (e.g., participants should receive IV fluids ± allopurinol and consider alkalization of urine and

DE Cohort	Screening[a]	Cycle (Induction Period)			Follow-Up (post-final dose administered)		
Study Procedure		**Intervention Period (In-Patient)**		**Observation Period (Outpatient)**	**TDV[b]**	**Follow-Up**	**Notes**
Week	**≤4**	**1 - 2**		**3 - 4**	**+4**		
Day	**≤28**	**-1**	**1 - 13**	**14 - 28**	**+30d**		
							renal consult). TLS prophylaxis and fluids should be continued over each dosing cycle as clinically indicated. Refer to Section 6.4.1.2 for prophylaxis and management of TLS.
Efficacy Assessments							
BM Sample for Disease Assessment	X		D40 (i.e.D12 of Cycle 2)	D84 (i.e. D28 of Cycle 3)	X		BM aspirate and core biopsy samples are required at Screening, Day 12 of Cycle 2 (within EOI+24hr), and D28 of Cycle 3 (+2 days is allowed, but must be before Day 1 of next cycle). The collection time point is mandatory after the last cycle of intense dosing (i.e. D28 of Cycle 3) before moving into maintenance +2 days is allowed for BM sample collection at each time point provided it occurs before next treatment cycle starts. Both BM aspirate and core biopsy samples should be used for Disease Assessment and pharmacodynamics.
Pharmacokinetics (PK), Pharmacodynamics, and Genomics							
BM Samples	X		D40 (i.e.D12 of Cycle 2)	D84 (i.e. D28 of Cycle 3)			BM aspirate and core biopsy samples are required at Screening, Day 12 of Cycle 2 (within EOI+24hr), and Day 28 of Cycle 3 (+2 days is allowed, but must be before Day 1 of next cycle). Consult GSK Medical Monitor if bone marrow samples could not be obtained for any reason during these time points.

DE Cohort	Screening[a]	Cycle (Induction Period)			Follow-Up (post-final dose administered)		
Study Procedure		**Intervention Period (In-Patient)**		**Observation Period (Outpatient)**	**TDV[b]**	**Follow-Up**	**Notes**
Week	**≤4**	**1 - 2**		**3 - 4**	**+4**		
Day	**≤28**	**-1**	**1 - 13**	**14 - 28**	**+30d**		
							Alternative on-treatment biopsy timings may be explored, as discussed with GSK Medical Monitor. Additional unscheduled BM aspirate and/or biopsies may be performed any time during the treatment period upon participant consent for this optional procedure.
Progressive Disease BM Sample					X		Although not required, BM aspirate and core biopsy at the time of disease progression is highly encouraged.
Whole blood (flow cytometry)			X	X	X		Sample collection should occur on Days 1, 5, 9, 12, 13 and 28 of each cycle. On Days 1 and 9: predose, EOI+4h, EOI+8h, EOI+12h, and EOI+24h time points will be collected; On Day 5: predose and EOI+8h will be collected; On Day12: predose, EOI+8h, and EOI+24h time points will be collected; For Days 13 & 28: only one time point (any time) will be collected. Collection of samples at disease progression is optional.
Serum (cytokines)			X	X	X		Sample collection should occur on Days 1, 5, 9, and 12 of each cycle. On Days 1 and 9: predose, EOI+4h, EOI+8h, EOI+12h, and EOI+24h time points will be collected;

DE Cohort	Screening[a]	Cycle (Induction Period)			Follow-Up (post-final dose administered)		
Study Procedure		**Intervention Period (In-Patient)**		**Observation Period (Outpatient)**	**TDV[b]**	**Follow-Up**	**Notes**
Week	**≤4**	**1 - 2**		**3 - 4**	**+4**		
Day	**≤28**	**-1**	**1 - 13**	**14 - 28**	**+30d**		
							On Day 5 and 12: predose and EOI+8h will be collected. Collection of serum samples at disease progression is optional.
GSK3745417 plasma PK			X				Cycle 1: PK sample collection times: Day 1 at predose (within 1h prior to dosing), EOI +5m, +15m, +30m, +45m, +1h, +2h, +4h, +6h, +8h, +12h and +24h; Day 4 at predose; Day 5 at predose and EOI+5m, +4h, +8h, +24h; Days 8 at predose (within 1h prior to dosing) and EOI+4h, EOI+8h, EOI+12h and EOI+24h; and Day 12 at predose (within 1h prior to dosing) and EOI+8h and EOI+24h. Cycle 2: PK sample collection times: Day 1 at predose (within 1h prior to dosing) and EOI +5m, +1h, +4h, +8h, +12h and +24h; Day 4 at predose; Day 5 at predose and EOI +5m, +4h, +8h, +24h and Days 8 and Day 12 at predose (within 1h prior to dosing) and EOI +8h Cycle 3: PK sample collection times: Days 1 and 5 at predose (within 1h prior to dosing) and EOI +5m, +1h, +4h, +8h, 12h and +24h; Day 4 at predose; and Days 8 and Day 12 at predose and EOI +5m, +4h, +8h, and +24h.

DE Cohort	Screening[a]	Cycle (Induction Period)			Follow-Up (post-final dose administered)		
Study Procedure		Intervention Period (In-Patient)		Observation Period (Outpatient)	TDV[b]	Follow-Up	Notes
Week	≤4	1 - 2		3 - 4	+4		
Day	≤28	-1	1 - 13	14 - 28	+30d		
CCI	[redacted]						

Abbreviations: AE= adverse event; AESI=adverse events of special interest; CBC=Complete blood count; d=day; ECG=electrocardiogram; ECHO=echocardiography; ECOG PS=Eastern Cooperative Oncology Group Performance Score; eGFR= Estimated glomerular filtration rate; EOI=end of injection; h=hour; ICF=informed consent form; m=min; Q1W=Every 1 week; Q3W=Every 3 weeks; Q6W=Every 6 weeks; Q9W=Every 9 weeks; Q12W=Every 12 weeks; SAE=serious adverse event; W=week; TLS = Tumor Lysis Syndrome; TDV=treatment discontinuation visit

Timepoint Definitions for assessments:
X = Anytime during visit (sampling date/time should be recorded)
Predose = within 60 minutes before the start of the GSK3745417 injection
EOI+5m = at 5 minutes ±2 minutes from the end of the GSK3745417 injection
EOI+15m = at 15 minutes ±5 minutes from the end of the GSK3745417 injection
EOI+30m = at 30 minutes ±5 minutes from the end of the GSK3745417 injection
EOI+45m = at 45 minutes ±5 minutes from the end of the GSK3745417 injection
EOI+1h = at 1 hour ±15 minutes from the end of the GSK3745417 injection
EOI+2h = at 2 hours ±30 minutes from the end of the GSK3745417 injection
EOI+4h = at 4 hours ±30 minutes from the end of the GSK3745417 injection
EOI+6h = at 6 hours ±30 minutes from the end of the GSK3745417 injection
EOI+8h = at 8 hours ±1 hours from the end of the GSK3745417 injection
EOI+12h = at 12 hours ±1 hour from the end of the GSK3745417 injection
EOI+18h = at 18 hours ±2 hours from the end of the GSK3745417 injection
EOI+24h = at 24 hours ±2 hours from the end of the GSK3745417 injection and before the next infusion

a. All assessments performed at Screening must be performed within 28 days prior to first dose unless otherwise specified.
b. The assessments required at the study treatment discontinuation visit must be completed within 30 days from the date study treatment was discontinued and must occur prior to the start of subsequent anti-cancer therapy; the window for this visit is +10 days.
c. Procedures scheduled on study treatment administration days can be performed within 3 days prior to dosing day, unless otherwise specified.

1.3.2. Part 2 – Induction Cycle

Table 2 Schedule of Activities: Part 2 – Induction Cycles

	Screening[a]	Cycle (Induction Period)			Follow-Up (post-final dose administered)		
Study Procedure		**Intervention Period (In-Patient-Day1 of cycle 1)**		**Observation Period (Outpatient)**	**TDV[b]**	**Follow-Up**	**Notes**
Week	**≤4**	**1 - 2**		**3 - 4**	**+4**		
Day	**≤28**	**-1**	**1 - 13**	**14 - 28**	**+30d**		
Informed Consent	X						
Inclusion and Exclusion criteria	X						
Demographics, Medical History, Prior Medications, Disease Characteristics	X						Include use of antibiotics, probiotics and anti-infectives taken 60 days prior to study intervention.
Anticancer Therapy and Response to Prior Anticancer Therapy	X						
Participant Registration	X						
Safety Assessments							
In-House Monitoring		X	X				Participants should be monitored in a medically qualified unit/clinic/hospital starting on Day -1 through Day 13 (24 hours after the administration of GSK3745417 on Day 12) of each cycle.
Physical Exam	X		X		X		A complete physical exam is required at screening, including cardiac and neurological examinations; brief or targeted physical exams will be performed on Day 1 at predose (within 1h prior to dosing) and

	Screening[a]	Cycle (Induction Period)			Follow-Up (post-final dose administered)		
Study Procedure		**Intervention Period (In-Patient-Day1 of cycle 1)**		**Observation Period (Outpatient)**	**TDV[b]**	**Follow-Up**	**Notes**
Week	**≤4**	**1 - 2**		**3 - 4**	**+4**		
Day	**≤28**	**-1**	**1 - 13**	**14 - 28**	**+30d**		
							Day 13 of each cycle, and as clinically indicated. Refer to Section 8.2.1 for physical examination details.
ECOG PS	X		X		X		Should be assessed at each cycle
Vital Signs	X	X	X		X		Should be collected at each cycle at least 6 times on Day -1 within 24 hours prior to dosing, Day 1, 5, 8, and 12 at predose (within 1h prior to dosing), end of injection (EOI)+30m, +1h, +2h, +4h, +6h, +8h, +12h, +24h and, at least four times every day until discharge or more frequently if clinically indicated.
Weight	X	X			X		Should be collected at each cycle.
Echocardiogram	X	Week 1 and then Q8W except for the Part 2 Every three weeks daily dosing cohort where echocardiography will occur at Week 1 and then Q9W per protocol. Additional echocardiography may occur as clinically indicated					If available, a 3D ECHO is preferred, otherwise a 2D ECHO may be performed. Where the quality of the ECHO examination is sub-optimal, MUGA scans may be used. The modality used at baseline should be repeated throughout the study to ensure comparison to baseline. At TDV, ECHO/MUGA does not need to be performed if an on-study ECHO has been conducted within the 4 weeks prior to visit. ECHO should be performed in the final week of the observation period.
IV Contrast-enhanced Brain MRI (preferred) or IV Contrast-enhanced CT Scan	X	Repeat if clinically indicated					Brain imaging to be performed only if clinically indicated.

	Screening[a]	Cycle (Induction Period)			Follow-Up (post-final dose administered)		
Study Procedure		**Intervention Period (In-Patient-Day1 of cycle 1)**		**Observation Period (Outpatient)**	**TDV[b]**	**Follow-Up**	**Notes**
Week	**≤4**	**1 - 2**		**3 - 4**	**+4**		
Day	**≤28**	**-1**	**1 - 13**	**14 - 28**	**+30d**		
12-lead ECG	X		X		X		Triplicate ECGs should be performed at screening. Single ECGs should be obtained at each cycle on Day 1 and Day 4 at predose (within 1h prior to dosing) and EOI+2h. In cases of TLS, triplicate ECGs will be obtained at screening. Single ECGs should be obtained prior to GSK3745417 dosing, within 5 min EOI, and within 2 hours prior to completion of clinic visit. Post Week 6, next ECG should be on Week 9 and then Q3W thereafter. Patients with new onset symptoms consistent with immune-mediated pericarditis or myocarditis should have additional ECGs as clinically indicated.
Holter Monitoring		X	X				Baseline and Day -1 and Day 1 of Cycle 1 after dosing, starting at least -24h predose, followed by normal activity (ambulatory) until -30 min predose, when participant will be lying supine until time 0. Postdose, the participant will by lying supine for at least 3 minutes to align with the PK plasma sampling at EOI +5m, +15m, +30m, +45m, +1h, +2h, +4h, +6h, +8h, +12h and +24h. Holter monitoring will end at 24h after the first study intervention. The Holter will remain with the participant until 24h post-dose and then will be removed. The requirement for Holter monitoring may be waived for individual participants upon approval from GSK.

	Screening[a]	Cycle (Induction Period)			Follow-Up (post-final dose administered)		
Study Procedure		**Intervention Period (In-Patient-Day1 of cycle 1)**		**Observation Period (Outpatient)**	**TDV[b]**	**Follow-Up**	**Notes**
Week	**≤4**	**1 - 2**		**3 - 4**	**+4**		
Day	**≤28**	**-1**	**1 - 13**	**14 - 28**	**+30d**		
Neurological Assessment including ICE scoring	X	Conduct if clinically indicated					Refer to Section 6.4.1 for neurological assessment details.
AE/SAE Review		Assess at each visit from first dose until the TDV for AEs and until 90 days after the last dose for AESI and SAEs					
Concomitant Medication Review		Continuous: Assess at each visit from first dose of study intervention					
Follow-Up Phone Call				X			Participants should be contacted by phone 24-72 hours and 1 week (+24 hours) following discharge from clinic to assess for any AEs or cytokine related events.
Safety Laboratory Assessments							
Human Immunodeficiency Virus (HIV), Hepatitis B Surface Antigen (HBsAg), Hepatitis C Virus (HCV) Antibody	X						
Pregnancy Test	X		≤72 hours (serum)	X	X	Q12W	Negative serum pregnancy test required at screening and within 72 hours prior to date of first dose of study treatment for females of childbearing potential. Urine pregnancy test will be conducted every 4 weeks for duration of study, on last day of treatment (if possible), at TDV, and at the Follow-Up visit.

	Screening[a]	Cycle (Induction Period)			Follow-Up (post-final dose administered)		
Study Procedure		**Intervention Period (In-Patient-Day1 of cycle 1)**		**Observation Period (Outpatient)**	**TDV[b]**	**Follow-Up**	**Notes**
Week	**≤4**	**1 - 2**		**3 - 4**	**+4**		
Day	**≤28**	**-1**	**1 - 13**	**14 - 28**	**+30d**		
CBC with differential	X	X	X	X	X		Sample collection times: Single sample from Day -1 to Day 13, prior to each administration of GSK3745417. At least every 6 hours for the first 48 hours following initiation of daily dosing period, then at least twice daily up to an including Day 5 dosing of each daily dosing period, and more frequently as clinically indicated. On the days when GSK3745417 is not administered, samples will be collected at approximately the same times as on the days of GSK3745417 administration. A sample will also be taken between Day 20 and Day 22 during the outpatient period of the cycle.
Clinical Chemistry (including laboratory parameters for TLS diagnosis and management)	X	X	X	X	X		Sample collection times: Cycle 1, and any cycle with a dose increase: single sample on Day –1; Days 1 and 2 at predose, EOI+6h, +12h, +18h and +24h; Days 3 - 5 – at predose and EOI+6h; Days 6 and 7 – single daily sample, Days 8 - 12 – at EOI+6hrs: Day 13 – single sample prior to discharge. Clinical chemistry including uric acid and phosphate will be measured at least every 6 hours for the first 48 hours following initiation of daily dosing period, then at least twice daily up to an including Day 5 dosing of each daily dosing period, and more frequently as clinically indicated.

	Screening[a]	Cycle (Induction Period)			Follow-Up (post-final dose administered)		
Study Procedure		**Intervention Period (In-Patient-Day1 of cycle 1)**		**Observation Period (Outpatient)**	**TDV[b]**	**Follow-Up**	**Notes**
Week	**≤4**	**1 - 2**		**3 - 4**	**+4**		
Day	**≤28**	**-1**	**1 - 13**	**14 - 28**	**+30d**		
							Clinical chemistry samples should be collected more frequently if clinically indicated (such as cases of TLS). A sample will also be taken between Day 20 and Day 22 during the outpatient period of the cycle. See Section 10.2 for complete list of required laboratory assessments.
C-Reactive Protein	X		X	X	X		Sample collection times: Day 1 at predose, EOI+8h and +24h for first dose, then pre dose at Day 5 and Day 12 of each cycle.
Thyroid function[c]	X		X		X		Sample collection times: Day 1 at predose of Cycles 1 and 3.
Troponin I and T	X		X		X		See Section 6.4.1.5 for management of cardiac events. Samples will be collected on Day 13.
BNP (or NTproNBNP)	X	Repeat as clinically indicated					Repeat test as outlined in management of cardiac events (Section 6.4.1.5)
eGFR	X						See Section 7.1.2 for management of renal events (if needed).
Urinalysis[c]	X		X		X		Sample collection times: Days 1, 8 and 13 of each cycle. If urinalysis is abnormal, a microscopy should be performed.
Coagulation[c]	X		X				Sample collection times: at screening and prior to administration of first dose of GSK3745417 and at Day 8 of each cycle. Additional coagulation samples should be collected in the event of CRS (see Section 6.4.1.4)

	Screening[a]	Cycle (Induction Period)			Follow-Up (post-final dose administered)		
Study Procedure		**Intervention Period (In-Patient-Day1 of cycle 1)**		**Observation Period (Outpatient)**	**TDV[b]**	**Follow-Up**	**Notes**
Week	**≤4**	**1 - 2**		**3 - 4**	**+4**		
Day	**≤28**	**-1**	**1 - 13**	**14 - 28**	**+30d**		
Study Intervention							
Administer GSK3745417			X				GSK3745417 will be administered each cycle on Days 1 – 5 and Days 8 - 12 QD. Participants will receive up to 3 cycles of treatment before moving to Q1W, Q3W, or less frequent dosing schedule (Section 6.1). See Section 4.1 for maximum duration of study intervention. See Section 4.1 for safety and tolerability parameters to be reviewed prior to each daily dose
Non-Azole Antifungal		X	X	X			Non-azole antifungals should be administered if indicated, per local standard, on Day -1 through Day 28 of each cycle.
Tumor Lysis Syndrome Prophylaxis		X					All participants should receive tumor lysis syndrome (TLS) prophylaxis prior to date of first dose of each cycle on Day -1 according to institutional guidelines (e.g., participants should receive IV fluids ± allopurinol and consider alkalization of urine and renal consult). TLS prophylaxis and fluids should be continued over each dosing cycle as clinically indicated. Refer to Section 6.4.1.2 for prophylaxis and management of TLS.
Efficacy Assessments							
Follow-up for survival						Q12W	Participants will be followed Q12W (±2 weeks) for survival and subsequent anticancer therapy. The

	Screening[a]	Cycle (Induction Period)			Follow-Up (post-final dose administered)		
Study Procedure		**Intervention Period (In-Patient-Day1 of cycle 1)**		**Observation Period (Outpatient)**	**TDV[b]**	**Follow-Up**	**Notes**
Week	**≤4**	**1 - 2**		**3 - 4**	**+4**		
Day	**≤28**	**-1**	**1 - 13**	**14 - 28**	**+30d**		
							survival follow-up visit will commence after discontinuation of study intervention.
BM Sample for Disease Assessment	X		D40 (i.e.D12 of Cycle 2)	D84 (i.e. D28 of Cycle 3)	X		BM aspirate and core biopsy samples are required at Screening, Day 12 of Cycle 2 (within EOI+24hr), and Day 28 of Cycle 3 (+2 days is allowed but must be before Day 1 of next cycle). The collection time point is mandatory after the last cycle of intense dosing (i.e. Day 28 of Cycle 3) before moving into maintenance. +2 days is allowed for BM sample collection at each time point provided it occurs before next treatment cycle starts. Both BM aspirate and core biopsy samples should be collected for Disease Assessment and pharmacodynamics.
Pharmacokinetics (PK), Pharmacodynamics and Genomics							
BM Sample	X		D40 (i.e.D12 of Cycle2)	D84 (i.e. D28 of Cycle 3)	X		BM aspirate and core biopsy samples are required at Screening, Day 12 of Cycle2 (within EOI+24hr), and Day 28 of Cycle 3 (+2 days is allowed but must be before Day 1 of next cycle). Consult GSK Medical Monitor if bone marrow samples could not be obtained for any reason during these time points. Alternative on-treatment biopsy timings may be explored, as discussed with GSK Medical Monitor. Additional unscheduled BM aspirate and/or biopsies may be performed any time during the treatment

	Screening[a]	Cycle (Induction Period)			Follow-Up (post-final dose administered)		
Study Procedure		**Intervention Period (In-Patient-Day1 of cycle 1)**		**Observation Period (Outpatient)**	**TDV[b]**	**Follow-Up**	**Notes**
Week	**≤4**	**1 - 2**		**3 - 4**	**+4**		
Day	**≤28**	**-1**	**1 - 13**	**14 - 28**	**+30d**		
							period upon participant consent for this optional procedure.
Progressive Disease BM biopsy					X		Although not required, BM aspirate and core biopsy at the time of disease progression is highly encouraged.
Whole blood (flow cytometry)			X	X	X		**Cycle 1:** Sample collection should be done on Days 1, 5, 9, 12, 13 and 28. • On Days 1 and 9: predose, EOI+4h, EOI+8h, EOI+12h, and EOI+24h time points will be collected. • On Days 5 & 12: predose and EOI+8h will be collected. • For Days 13 & 28: only one time point (any time) will be collected. **Cycle 2:** Sample collection should be done on D12 only (predose, EOI+4h, EOI+8h, EOI+12h, and EOI+24h) **Cycle 3:** D28 (anytime) Sample collection at disease progression is optional.
Serum (cytokines)			X	X	X		**Cycle 1:** Sample collection should be done on Days 1, 5, 9, and 12.

	Screening[a]	Cycle (Induction Period)			Follow-Up (post-final dose administered)		
Study Procedure		**Intervention Period (In-Patient-Day1 of cycle 1)**		**Observation Period (Outpatient)**	**TDV[b]**	**Follow-Up**	**Notes**
Week	**≤4**	**1 - 2**		**3 - 4**	**+4**		
Day	**≤28**	**-1**	**1 - 13**	**14 - 28**	**+30d**		
							• On Days 1 and 9: predose, EOI+4h, EOI+8h, EOI+12h, and EOI+24h time points will be collected; • On Days 5 & 12: predose and EOI+8h time points will be collected. **Cycle 2:** Sample collection should be done on D1 (predose, EOI+8h) and D12 (predose, EOI+4h, EOI+8h, EOI+12h, and EOI+24h) **Cycle 3:** Sample collection should be done on D1 (predose, EOI+8hr) and D12 (predose, EOI+8hr). Sample collection at disease progression is optional.
GSK3745417 plasma PK			X				Cycle 1: PK sample collection times: Day 1 at predose (within 1h prior to dosing), EOI +5m, +15m, +30m, +45m, +1h, +2h, +4h, +6h, +8h, +12h and +24h; Day 4 at predose; Day 5 at predose and EOI+5m, +4h, +8h, +24h; Days 8 at predose (within 1h prior to dosing) and EOI+4h, EOI+8h, EOI+12h and EOI+24h; and Day 12 at predose (within 1h prior to dosing) and EOI+8h and EOI+24h. Cycle 2: PK sample collection times: Day 1 at predose (within 1h prior to dosing), EOI +1h, +4h, +8h; Day 12 at predose (within 1h prior to dosing) and EOI +1h, +4h, +8h, +12h and +24

	Screening[a]	Cycle (Induction Period)			Follow-Up (post-final dose administered)		
Study Procedure		**Intervention Period (In-Patient-Day1 of cycle 1)**		**Observation Period (Outpatient)**	**TDV[b]**	**Follow-Up**	**Notes**
Week	**≤4**	**1 - 2**		**3 - 4**	**+4**		
Day	**≤28**	**-1**	**1 - 13**	**14 - 28**	**+30d**		
							Cycle 3: PK sample collection times: Day 1 predose (within 1h prior to dosing), EOI +1h, +4h, +8h; and Day 12 at predose (within 1h prior to dosing) and EOI +1h, +4h, +8h; and on Day 28 anytime
CCI							

Abbreviations: AE= adverse event; AESI=adverse events of special interest; CBC=Complete blood count; d=day; ECG=electrocardiogram; ECHO=echocardiography; ECOG PS=Eastern Cooperative Oncology Group Performance Score; eGFR= Estimated glomerular filtration rate; EOI=end of injection; h=hour; ICF=informed consent form; m=min; Q1W=Every 1 week; Q3W=Every 3 weeks; Q6W=Every 6 weeks; Q9W=Every 9 weeks; Q12W=Every 12 weeks; SAE=serious adverse event; W=week; TLS = Tumor Lysis Syndrome; TDV=treatment discontinuation visit

Timepoint Definitions for assessments:
X = Anytime during visit (sampling date/time should be recorded)
Predose = within 60 minutes before the start of the GSK3745417 injection
EOI+5m = at 5 minutes ±2 minutes from the end of the GSK3745417 injection
EOI+15m = at 15 minutes ±5 minutes from the end of the GSK3745417 injection
EOI+30m = at 30 minutes ±5 minutes from the end of the GSK3745417 injection
EOI+45m = at 45 minutes ±5 minutes from the end of the GSK3745417 injection
EOI+1h = at 1 hour ±15 minutes from the end of the GSK3745417 injection
EOI+2h = at 2 hours ±30 minutes from the end of the GSK3745417 injection
EOI+4h = at 4 hours ±30 minutes from the end of the GSK3745417 injection
EOI+6h = at 6 hours ±30 minutes from the end of the GSK3745417 injection

EOI+8h = at 8 hours ±1 hours from the end of the GSK3745417 injection
EOI+12h = at 12 hours ±1 hour from the end of the GSK3745417 injection
EOI+18h = at 18 hours ±2 hours from the end of the GSK3745417 injection
EOI+24h = at 24 hours ±2 hours from the end of the GSK3745417 injection and before the next infusion

a. All assessments performed at Screening must be performed within 28 days prior to first dose unless otherwise specified.
b. The assessments required at the study treatment discontinuation visit must be completed within 30 days from the date study treatment was discontinued and must occur prior to the start of subsequent anti-cancer therapy; the window for this visit is +10 days.
c. Procedures scheduled on study treatment administration days can be performed within 3 days prior to dosing day, unless otherwise specified.

1.3.3. Part 1 and Part 2 – GSK3745417 Maintenance Once Weekly

Table 3 Schedule of Activities (GSK3745417 Maintenance Once Weekly- Part 1 & Part 2)

Q1W Cohort	Study Maintenance Period				
Study Procedure	**GSK417 Weekly (Q1W)**		**TDV[a]**	**Follow-Up (post-final dose administered**	**Notes**
Week		**1 and Thereafter**	**+4**		
Day	**-1**	**1 and Thereafter**	**+30d**		
Safety Assessments					
In-House Monitoring	X	Q1W			Participants should be monitored in a medically qualified unit/clinic/hospital starting on Day -1 and 24 hours following the administration of GSK3745417. This requirement may be eliminated as safety data emerge.
Physical Exam		Q1W	X		Brief or targeted physical exams will be performed on Day 1 at predose (within 1h prior to dosing) and as clinically indicated. Refer to Section 8.2.1 for physical examination details.
ECOG PS		Q1W	X		If available, a 3D ECHO is preferred, otherwise a 2D ECHO may be performed. Where the quality of the ECHO examination is sub-optimal, MUGA scans may be used. The modality used at baseline should be repeated throughout the study to ensure comparison to baseline.
Vital Signs		Q1W	X		Vital signs should be collected at least 6 times on Day -1 within 24 hours prior to dosing and on Day 1 at EOI+30m, +1h, +2h, +4h, +6h, +8h, +12h and +24h.
Weight		Q1W	X		

Q1W Cohort	Study Maintenance Period				
Study Procedure	**GSK417 Weekly (Q1W)**		**TDV[a]**	**Follow-Up (post-final dose administered**	**Notes**
Week		**1 and Thereafter**	**+4**		
Day	**-1**	**1 and Thereafter**	**+30d**		
Echocardiogram		Week 1, then Q8W	X		If available, a 3D ECHO is preferred, otherwise a 2D ECHO may be performed. Where the quality of the ECHO examination is sub-optimal, MUGA scans may be used. The modality used at baseline should be repeated throughout the study to ensure comparison to baseline. At TDV, ECHO/MUGA does not need to be performed if an on-study ECHO has been conducted within the 4 weeks prior to visit.
IV Contrast-enhanced Brain MRI (preferred) or IV Contrast-enhanced CT Scan	Conduct if clinically indicated				Brain scans must be performed with IV contrast.
12-lead ECG		Q1W	X		Single ECGs should be obtained at predose (within 1h prior to dosing), within 5 min EOI, and within 2 hours prior to completion of clinic visit. Triplicate ECG should be obtained in case of TLS and participants should have continuous cardiac monitoring. Patients with new onset symptoms consistent with immune-mediated pericarditis or myocarditis should have additional ECGs as clinically indicated.
Holter Monitoring	X				12-lead Holter monitoring will be conducted at Baseline and as clinically indicated on Day -1

Q1W Cohort	Study Maintenance Period				
Study Procedure	**GSK417 Weekly (Q1W)**		**TDV[a]**	**Follow-Up (post-final dose administered**	**Notes**
Week		**1 and Thereafter**	**+4**		
Day	**-1**	**1 and Thereafter**	**+30d**		
					and Day 1 of Week 3 starting at least -24h predose. Holter monitoring will end 24hQ after the first dose followed by normal activity (ambulatory) until -30 min predose, when participant will be lying supine until time 0. Postdose, the participant will by lying supine for at least 3 minutes to align with the PK plasma sampling at EOI +5m, +15m, +30m, +45m, +1h, +2h, +4h, +6h, +8h, +12h, +24h. Holter monitoring will end at 24h after the first study intervention. The Holter will remain with the participant until 24h post-dose and then will be removed. The requirement for Holter monitoring may be waived for individual participants upon approval from GSK.
Neurological Assessment	Conduct if clinically indicated				Refer to Section 6.4.1 for neurological assessment details.
AE/SAE Review	Assess at each visit from first dose until the TDV for AEs and until 90 days after the last dose for AESI and SAEs				
Concomitant Medication Review	Continuous: Assess at each visit from first dose of study intervention				
Follow-Up Phone Call		X			Participants should be contacted by phone 24-72 hours following discharge from clinic to assess for any AEs or cytokine related events

Q1W Cohort	Study Maintenance Period				
Study Procedure	**GSK417 Weekly (Q1W)**		**TDV[a]**	**Follow-Up (post-final dose administered**	**Notes**
Week		**1 and Thereafter**	**+4**		
Day	**-1**	**1 and Thereafter**	**+30d**		
Safety Laboratory Assessments					
Pregnancy Test		X	X	X	Urine pregnancy test will be conducted every 4 weeks for duration of study, on last day of treatment (if possible), at TDV, and at the Follow-Up visit.
CBC with differential	X	Q1W	X		Sample collection times: Day –1 (single sample) and Day 1 at predose, EOI+4h and EOI+24h. At least every 6 hours for the first 48 hours following initiation of daily dosing period, then at least twice daily up to an including Day 5 dosing of each daily dosing period, and more frequently as clinically indicated.
Clinical Chemistry and TLS labs	X	Q1W	X		Sample collection times: Day –1 (single sample) and Day 1 at predose, EOI+6h, +12h, +18h and +24h; see Section 10.2 for complete list of required laboratory assessments.
C-Reactive Protein		Q1W	X		Sample collection times: predose, EOI+8h, and EOI+24h.
Thyroid function[b]		Day 1, then Q8W	X		The first assessment should be done at Week 1 and then Q8W.
Troponin I and T		Q2W	X		Sample will be collected predose and every 2 weeks.
BNP (or NTproNBNP)	X	Repeat as clinically indicated			Repeat test as outlined in management of cardiac events (Section 6.4.1.5)

Q1W Cohort	Study Maintenance Period				
Study Procedure	**GSK417 Weekly (Q1W)**		**TDV[a]**	**Follow-Up (post-final dose administered**	**Notes**
Week		**1 and Thereafter**	**+4**		
Day	**-1**	**1 and Thereafter**	**+30d**		
Urinalysis[b]		Q1W	X		If urinalysis is abnormal, a microscopy should be performed.
Coagulation[b]		Day 1, then Q3W			The first assessment should be done at Day 1 and then Q3W. Additional coagulation samples should be collected in the event of CRS (see Section 6.4.1.4)
Study Intervention					
Administer GSK3745417		Q1W			GSK3745417 must be administered with ±1 day of scheduled visit unless otherwise indicated. Each subsequent dose in a participant should be administered at least 5 days apart. See Section 4.1 duration of study intervention.
Non-Azole Antifungal	X	X	X		Non-azole antifungals should be administered if indicated, per local standard, on Day -1 through Day 28 of each cycle.
Tumor Lysis Syndrome Prophylaxis	X				All participants should receive tumor lysis syndrome (TLS) prophylaxis prior to date of GSK3745417 administration starting on Day -1 and continuing over 24 hours according to institutional guidelines (e.g., participants should receive IV fluids ± allopurinol and consider alkalization of urine and renal consult). Refer to Section 6.4.1.2 for prophylaxis and management of TLS.

Q1W Cohort	**Study Maintenance Period**				
Study Procedure	**GSK417 Weekly (Q1W)**		**TDV[a]**	**Follow-Up (post-final dose administered**	**Notes**
Week		**1 and Thereafter**	**+4**		
Day	**-1**	**1 and Thereafter**	**+30d**		
Efficacy Assessments					
Follow-up for survival				Q4W	Participants will be followed Q4W (±2 weeks) for survival and subsequent anti-cancer therapy. The survival follow-up visit will commence after discontinuation of study intervention.
BM Sample for Disease Assessment		Q6W during the 1st three months, then Q12W			Both BM aspirate and core biopsy samples should be collected for Disease Assessment every 6 weeks during the first three months (2 time points) and then Q12W thereafter until disease progression or initiating another cancer treatment.
Pharmacokinetics (PK), Pharmacodynamics and Genomics					
BM Biopsy		Q6W during the 1st three months, then Q12W			On-treatment BM aspirate and core biopsies are both required during the maintenance phase until disease progression. Sample collection should be performed within EOI+48 hours but allowed window is +7 days after the scheduled visit. Alternative on-treatment biopsy timings may be explored, as discussed with GSK Medical Monitor. Unscheduled BM biopsies may be performed any time during the treatment period upon participant consent for this optional procedure.

Q1W Cohort	Study Maintenance Period				
Study Procedure	**GSK417 Weekly (Q1W)**		**TDV[a]**	**Follow-Up (post-final dose administered**	**Notes**
Week		**1 and Thereafter**	**+4**		
Day	**-1**	**1 and Thereafter**	**+30d**		
Progressive Disease BM biopsy			X		Although not required, a BM aspirate and core biopsy at the time of disease progression is highly encouraged.
Whole blood (flow cytometry)		Weeks 1, 2, 3, 4	X		Sample collection time points: Day 1 (Predose, EOI+4h, EOI+8h, EOI+12h, and EOI+24h), Day 8 (Predose, EOI+8h), Day 15 (Predose, EOI+8h), and Day 22 (Predose only). Collection of samples at disease progression is optional.
Serum (cytokines)		Weeks 1, 2, 3, 4, then Q3W	X		Sample collection time points: Day 1 (Predose, EOI+4h, EOI+8h, EOI+12h, and EOI+24h), Day 8 (Predose, EOI+8h), Day 15 (Predose, EOI+8h), and Day 22 (Predose only). After Day 22, samples will be collected Q3W (predose, EOI+8hr) until disease progression. Collection of serum samples at disease progression is optional.
GSK3745417 plasma PK		Weeks 1, 2, 3, 4, then Q3W			PK sample collection times: Week 3 at predose, EOI +5m, +15m, +30m, +45m, +1h, +2h, +4h, +6h, +8h, +12h, +24h; All other weeks at predose, EOI+1h, EOI +4h, and EOI +8h.

Abbreviations: AE= adverse event; AESI=adverse events of special interest; CBC=Complete blood count; d=day; ECG=electrocardiogram; ECHO=echocardiography; ECOG PS=Eastern Cooperative Oncology Group Performance Score; eGFR= Estimated glomerular filtration rate; EOI=end of injection; h=hour; ICF=informed consent form; m=minQ1W=Every 1 week; Q3W=Every 3 weeks; Q6W=Every 6 weeks; Q9W=Every 9 weeks; Q12W=Every 12 weeks; SAE=serious adverse event; W=week; TLS = Tumor Lysis Syndrome; TDV=treatment discontinuation visit.

Timepoint Definitions for assessments:
X = Anytime during visit (sampling date/time should be recorded)
Predose = within 60 minutes before the start of the GSK3745417 injection
EOI+5m = at 5 minutes ±2 minutes from the end of the GSK3745417 injection
EOI+15m = at 15 minutes ±5 minutes from the end of the GSK3745417 injection
EOI+30m = at 30 minutes ±5 minutes from the end of the GSK3745417 injection
EOI+45m = at 45 minutes ±5 minutes from the end of the GSK3745417 injection
EOI+1h = at 1 hour ±15 minutes from the end of the GSK3745417 injection
EOI+2h = at 2 hours ±30 minutes from the end of the GSK3745417 injection
EOI+4h = at 4 hours ±30 minutes from the end of the GSK3745417 injection
EOI+6h = at 6 hours ±30 minutes from the end of the GSK3745417 injection
EOI+8h = at 8 hours ±1 hours from the end of the GSK3745417 injection
EOI+12h = at 12 hours ±1 hour from the end of the GSK3745417 injection
EOI+18h = at 18 hours ±2 hours from the end of the GSK3745417 injection
EOI+24h = at 24 hours ±2 hours from the end of the GSK3745417 injection and before the next infusion

a. The assessments required at the study treatment discontinuation visit must be completed within 30 days from the date study treatment was discontinued and must occur prior to the start of subsequent anti-cancer therapy; the window for this visit is +10 days.
b. Procedures scheduled on study treatment administration days can be performed within 3 days prior to dosing day, unless otherwise specified.

1.3.5. Part 2 – GSK3745417 Maintenance Every 3 Weeks

Table 4 Schedule of Activities (GSK3745417 Maintenance Every 3 Weeks- Part 2 only)

Q3W Cohort	Study Maintenance Period				
Study Procedure	**GSK417 Every 3 Weeks (Q3W)**		**TDV[b]**	**Follow-Up (post-final dose administered**	**Notes**
Week		**1 and Thereafter[a]**	**+4**	**Q4W**	
Day	**-1**	**1 and Thereafter**	**+30d**		
Safety Assessments					
In-House Monitoring	X	Q3W			Participants should be monitored in a medically qualified unit/clinic/hospital starting on Day -1 and 24 hours following the administration of GSK3745417 on Day 1. This requirement may be eliminated as safety data emerge.
Physical Exam		Q3W	X		Brief or targeted physical exams will be performed on Day 1 at predose (within 1h prior to dosing), and as clinically indicated. Refer to Section 8.2.1 for physical examination details.
ECOG PS		Q3W	X		
Vital Signs	X	Q3W	X		Vital signs should be collected at least 6 times on Day -1 within 24 hours prior to dosing and on Day 1 at predose (within 1 hour prior to dosing) and at EOI+30m, +1h, +2h, +4h, +6h, +8h, +12h and +24h.
Weight		Q3W	X		
Echocardiogram		Week 1, then Q9W	X		If available, a 3D ECHO is preferred, otherwise a 2D ECHO may be performed. Where the quality of the ECHO examination is sub-optimal, MUGA scans may be used. The modality used at baseline should be repeated throughout the study to ensure comparison to baseline. At TDV, ECHO/MUGA does not need to be performed if an on-study ECHO has been conducted within the 4 weeks prior to visit.

Q3W Cohort	**Study Maintenance Period**				
Study Procedure	**GSK417 Every 3 Weeks (Q3W)**		**TDV[b]**	**Follow-Up (post-final dose administered**	**Notes**
Week		**1 and Thereafter[a]**	**+4**	**Q4W**	
Day	**-1**	**1 and Thereafter**	**+30d**		
IV Contrast-enhanced Brain MRI (preferred) or IV Contrast-enhanced CT Scan	Conduct if clinically indicated				Brain scans must be performed with IV contrast.
12-lead ECG		Q3W	X		Single ECGs should be obtained at predose (within 1h prior to dosing), within 5 min EOI, and within 2 hours prior to completion of clinic visit. Triplicate ECG should be obtained in case of TLS. Patients with new onset symptoms consistent with immune-mediated pericarditis or myocarditis should have additional ECGs as clinically indicated.
Holter Monitoring	Day -1	Day 1			12-lead Holter monitoring will be conducted at Baseline on Day-1 and Day 1 of Week 7 starting at least -24h pre-dose. Holter monitoring will end 24h after the first dose, followed by normal activity (ambulatory) until -30 min predose, when participant will be lying supine until time 0. Postdose, the participant will by lying supine for at least 3 minutes to align with the PK plasma sampling at EOI +5m, +15m, +30m, +45m, +1h, +2h, +4h, +6h, +8h, +12, and +24. Holter monitoring will end at 24h after the first study intervention. Holter will remain with the participant until the end of Day 1 and will be removed prior to end of clinic visit. The requirement for Holter monitoring may be waived for individual participants upon approval from GSK.
Neurological Assessment including ICE scoring		Conduct if clinically indicated			Refer to Section 6.4.1 for neurological assessment details.
AE/SAE Review		Assess at each visit from first dose until the TDV for AEs and until 90 days after the last dose for AESI and SAEs			

Q3W Cohort	**Study Maintenance Period**				
Study Procedure	**GSK417 Every 3 Weeks (Q3W)**		**TDV[b]**	**Follow-Up (post-final dose administered**	**Notes**
Week		**1 and Thereafter[a]**	**+4**	**Q4W**	
Day	**-1**	**1 and Thereafter**	**+30d**		
Concomitant Medication Review		Continuous: Assess at each visit from first dose of study intervention			
Follow-Up Phone Call		X			Participants should be contacted by phone 24-72 hours following discharge from clinic to assess for any AEs or cytokine related events
Safety Laboratory Assessments					
Pregnancy Test		X	X	X	Urine pregnancy test will be conducted every 3 weeks for duration of study, on last day of treatment (if possible), at TDV, and at the Follow-Up visit.
CBC with differential	X	Q3W	X		Sample collection times: Day –1 (single-sample) and Day 1 at predose, EOI+4h and EOI+24h. At least every 6 hours for the first 48 hours following initiation of daily dosing period, then at least twice daily up to an including Day 5 dosing of each daily dosing period, and more frequently as clinically indicated.
Clinical Chemistry and TLS labs	X	Q3W	X		Sample collection times: Day –1 (single-sample) and Day 1 at predose, EOI+6h, +12h, +18h and +24h; see Section 10.2 for complete list of required laboratory assessments.
C-Reactive Protein		Q3W	X		Sample collection times: Predose, EOI+8h, and EOI+24h.
Thyroid function[b]		Day 1, then Q6W	X		The first assessment should be done at Week 1 and then Q6W.
Troponin I and T		Q3W	X		Sample will be collected predose and every 3 weeks.
BNP (or NTproNBNP)	X	Repeat as clinically indicated			Repeat test as outlined in management of cardiac events (Section 6.4.1.5)
Urinalysis[b]		Q3W	X		If urinalysis is abnormal, a microscopy should be performed.
Coagulation[b]		Day 1, then Q3W			The first assessment should be done at Day 1 and then Q3W.

Q3W Cohort	Study Maintenance Period				
Study Procedure	**GSK417 Every 3 Weeks (Q3W)**		**TDV[b]**	**Follow-Up (post-final dose administered**	**Notes**
Week		**1 and Thereafter[a]**	**+4**	**Q4W**	
Day	**-1**	**1 and Thereafter**	**+30d**		
Study Intervention					
Administer GSK3745417		Q3W			GSK3745417 must be administered with ±3 day of scheduled visit unless otherwise indicated. Each subsequent dose in a participant should be administered at least 5 days apart. See Section 4.1 duration of study intervention.
Non-Azole Antifungal	X	X	X		Non-azole antifungals should be administered if indicated, per local standard, on Day -1 through Day 28 of each cycle.
Tumor Lysis Syndrome Prophylaxis	X				All participants should receive tumor lysis syndrome (TLS) prophylaxis prior to date of GSK3745417 administration starting on Day -1 and continuing over 24 hours according to institutional guidelines (e.g., participants should receive IV fluids ± allopurinol and consider alkalization of urine and renal consult). Refer to Section 6.4.1.2 for prophylaxis and management of TLS.
Efficacy Assessments					
Follow-up for survival				Q4W	Participants will be followed Q4W (±2 weeks) for survival and subsequent anti-cancer therapy. The survival follow-up visit will commence after discontinuation of study intervention.
BM Sample for Disease Assessment		Q6W during the 1st three months, then Q12W			Both BM aspirate and core biopsy samples should be collected for Disease Assessment every 6 weeks during the first three months (2 time points) and then Q12W thereafter until disease progression or initiating another cancer treatment.
Pharmacokinetics (PK), Pharmacodynamics and Genomics					
BM Biopsy		Q6W during the 1st three months, then Q12W			On-treatment BM aspirate and core biopsies are both required every 6 weeks during the first three months (2 time points) and then Q12W thereafter until disease progression. Sample collection during the maintenance phase should be performed within EOI+48 hours but allowed window is +7 days after the scheduled visit.

Q3W Cohort	**Study Maintenance Period**				
Study Procedure	**GSK417 Every 3 Weeks (Q3W)**		**TDV[b]**	**Follow-Up (post-final dose administered**	**Notes**
Week		**1 and Thereafter[a]**	**+4**	**Q4W**	
Day	**-1**	**1 and Thereafter**	**+30d**		
					Alternative on-treatment biopsy timings may be explored, as discussed with GSK Medical Monitor. Unscheduled BM biopsies may be performed any time during the treatment period upon participant consent for this optional procedure.
Progressive Disease BM biopsy			X		Although not required, a BM aspirate and/or biopsy at the time of disease progression is highly encouraged.
Whole blood (flow cytometry)		Weeks 1, 2, 3, 4	X		Sample collection time points: Day 1 (Predose, EOI+4h, EOI+8h, EOI+12h, and EOI+24h), Day 8 (any time), Day 15 (any time), and Day 22 (Predose only). Collection of samples at disease progression is optional.
Serum (cytokines)		Weeks 1, 2, 3, 4, then Q3W	X		Sample collection time points: Day 1 (Predose, EOI+4h, EOI+8h, EOI+12h, and EOI+24h), Day 8 (any time), Day 15 (any time), and Day 22 (Predose only). After Day 22, samples will be collected Q3W (predose, EOI+8hr) until disease progression. Collection of serum samples at disease progression is optional.
GSK3745417 plasma PK		Weeks 1, 4, 7, 10, then Q3W			PK sample collection times: Week 7 at predose, EOI +5m, +15m, +30m, +45m, +1h, +2h, +4h, +6h, +8h, +12, and +24; All other weeks at predose, EOI+1h, EOI +4h, and EOI +8h.

Abbreviations: AE= adverse event; AESI=adverse events of special interest; CBC=Complete blood count; d=day; ECG=electrocardiogram; ECHO=echocardiography; ECOG PS=Eastern Cooperative Oncology Group Performance Score; eGFR= Estimated glomerular filtration rate; EOI=end of injection; h=hour; ICF=informed consent form; m=min; Q1W=Every 1 week; Q3W=Every 3 weeks; Q6W=Every 6 weeks; Q9W=Every 9 weeks; Q12W=Every 12 weeks; SAE=serious adverse event; W=week; TLS = Tumor Lysis Syndrome; TDV=treatment discontinuation visit.

Timepoint Definitions for assessments:
X = Anytime during visit (sampling date/time should be recorded)
Predose = within 60 minutes before the start of the GSK3745417 injection
EOI+5m = at 5 minutes ±2 minutes from the end of the GSK3745417 injection

EOI+15m = at 15 minutes ±5 minutes from the end of the GSK3745417 injection
EOI+30m = at 30 minutes ±5 minutes from the end of the GSK3745417 injection
EOI+45m = at 45 minutes ±5 minutes from the end of the GSK3745417 injection
EOI+1h = at 1 hour ±15 minutes from the end of the GSK3745417 injection
EOI+2h = at 2 hours ±30 minutes from the end of the GSK3745417 injection
EOI+4h = at 4 hours ±30 minutes from the end of the GSK3745417 injection
EOI+6h = at 6 hours ±30 minutes from the end of the GSK3745417 injection
EOI+8h = at 8 hours ±1 hours from the end of the GSK3745417 injection
EOI+12h = at 12 hours ±1 hour from the end of the GSK3745417 injection
EOI+18h = at 18 hours ±2 hours from the end of the GSK3745417 injection
EOI+24h = at 24 hours ±2 hours from the end of the GSK3745417 injection and before the next infusion

a. The assessments required at the study treatment discontinuation visit must be completed within 30 days from the date study treatment was discontinued and must occur prior to the start of subsequent anti-cancer therapy; the window for this visit is +10 days.
b. Procedures scheduled on study treatment administration days can be performed within 3 days prior to dosing day, unless otherwise specified.

2. INTRODUCTION

2.1. Study Rationale

GSK3745417 is an intravenously delivered STING (STimulator of Interferon Genes) agonist currently under evaluation in solid tumors in the FTIH 208850 dose escalation study. Recent evidence has shown that in addition to immune-mediated activity, GSK3745417 exhibits a cytolytic effect, a second mechanism of action, in AML cells in nonclinical studies. STING is expressed at a higher level on AML cells compared with other tumor types [The Cancer Genome Atlas (TCGA) - National Cancer Institute]. The high level of STING expression combined with preclinical evidence of antitumor activity makes AML a suitable indication to establish proof of mechanism and evaluate the clinical activity of GSK3745417. The goal of the study is to identify an RP2D and schedule with a manageable safety profile. Study 209809 is proposed to evaluate the safety, pharmacokinetics, pharmacodynamics, and preliminary clinical activity of GSK3745417 in relapsed or refractory AML and high-risk myelodysplastic syndrome (HR-MDS).

2.2. Background

Clinical Background: AML and MDS

MDS and AML are clonal neoplasms of myeloid progenitors that arise within the bone marrow. They are typically manifested by peripheral cytopenias (neutropenia, anemia, and/or thrombocytopenia), hypercellularity of the bone marrow (because of ineffective hematopoiesis), molecular and/or karyotypic abnormalities, and an expansion of immature myeloid cells. It is the quantitation of these immature myeloblasts that, in part, differentiates AML from MDS, with a 20% blast percentage marking the transition from MDS to AML. In the US, the estimate for new cases of AML in 2020 was approximately 20,000 and the estimate for deaths from AML was approximately 11,000. For MDS, some estimates indicate around 10,000 cases per year [from American Cancer Society website]. While multiple new targeted agents have been approved to treat AML in patients that have a limited number of genetic mutations, most patients with both MDS and AML are not eligible for these therapies. Despite modern therapies, patients eventually relapse and may become refractory to treatment and have a poor prognosis. Currently, for relapsed/refractory AML patients, there is no standard of care and clinical trial participation is recommended. The median overall survival for relapsed/refractory AML and for high-risk MDS is short, generally less than 6 months. Therefore, new therapies to prolong survival are desperately needed.

GSK3745417 Background:

Preclinical data support the use of STING agonists for the treatment of AML. STING is the key adaptor molecule in the cGAS-STING-TBK1 pathway that mediates the sensing of cytosolic DNA (Chen, 2017; Sun, 2013). Activation of STING generates a distinctive set of type I interferons (IFNα and IFNβ) and pro-inflammatory cytokines that instigate T-cell dependent tumor immunity and tumor vascular collapse (Ishikawa, 2009; Mahadevan, 1990; Woo, 2014). Preclinical studies support the hypothesis that the STING

activation pathway has the potential to boost tumor antigen presentation and tumor immunogenicity. In animal models of AML, STING agonists have demonstrated some activity by improving survival and inducing immune responses via induction of type I interferons and proinflammatory cytokines, suggesting that they may play a role in immune therapy for leukemia and possibly other hematologic malignancies (Curran, 2016). Data demonstrated a second mechanism of action of direct induction of apoptosis in AML cells treated with GSK3745417. Published literature also support a role for STING activation in driving human myeloid and AML cell death (Baba, 2021; Gaidt, 2017). These reports and others suggest cell death driven by a range of mechanisms including lysosomal cell death (Gaidt, 2017), reactive oxygen species (Baba, 2021), and apoptosis (Gulen, 2017).

GSK3745417 is a synthetic STING agonist that is being developed by GlaxoSmithKline as an immune stimulatory agent for the treatment of cancer. It is currently being studied in a Phase 1 first in human trial, 208850, to assess the safety, PK, PD, and preliminary clinical activity of GSK3745417 administered alone and in combination with other immunotherapies in participants with advanced solid tumors. Preliminary data from the 208850 study have shown that administration of GSK3745417 results in increased proinflammatory cytokine production after dosing in participants with solid tumors (GSK3745417 IB). This study is ongoing and clinical activity has not yet been evaluated.

2.3. Benefit/Risk Assessment

2.3.1. Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of GSK3745417 may be found in the IB and Informed Consent document. Table 5 presents an overview of the potential risks associated with GSK3745417 dosing in participants with AML, and the risk mitigation strategies.

Table 5 Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP) GSK3745417		
Cytokine release syndrome (CRS)	**Nonclinical:** The severity of cytokine related symptoms/signs observed in an AML population is not expected to be more severe than that observed to date in the solid tumor population of Study 2008850 and based on the non-clinical data. **Clinical:** In Study 208850, dose dependent cytokine-related symptoms and CRS were observed. Symptoms reported with CRS commonly comprised pyrexia, chills/rigors, tachycardia, hypotension, hypoxia, and headache; these were all Grade 1 or 2 events, with none of the cases being life threatening or fatal. Preliminary analyses suggest that cytokine-related AEs may be more likely associated with drug exposure (AUC-related) than measured cytokine levels.	**General Measures:** • Sites selected based on cytokine release syndrome (CRS) management capabilities (i.e. ICU proximity, staff experience, resuscitation measures, central line placement and medication administration capability). • CRS events are categorized as Adverse Events of Special interest (AESIs) which must be reported to the Medical Monitor within 24 hours regardless of study drug relationship. **Monitoring:** • Careful observation with continuous in-hospital monitoring throughout the 2-week induction daily-dosing period of the cycle, and 24hr hospital observation post-dose for maintenance dosing. **Mitigation:** • Use a starting dose of 12.5 µg that is 1/32nd of the 400 µg MTD (refer to Section 4.4.2). • Dose staggering of participants to allow assessment initial safety data before enrolling next participant. • Guidelines on the management of CRS symptoms is provided in Table 11 and dose modifications in Section 6.4.1.
Tumor Lysis syndrome	In vitro, GSK3745417 shows direct cell killing of AML cells. AML population typically has a high risk for TLS with additional risk factors	**General measures:** • Admission to hospital 24hrs prior to each dose for prophylaxis against TLS (Refer to Section 4.1.1).

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	of large tumor burden (high blast count in AML), impaired renal function and inadequate hydration.	• TLS events are categorized as adverse events of special interest (AESIs) which must be reported to the Medical Monitor within 24 hours regardless of study drug relationship. **Monitoring:** • Careful observation with continuous in-hospital monitoring throughout the 2-week induction daily-dosing period of the cycle, and 24hr hospital observation post-dose for the maintenance dosing. • Frequent monitoring of clinical chemistry including uric acid and phosphate as per schedule of activities (SOA), Section 1.3. **Mitigation:** • Participants must have: ▪ white cell counts <25,000/µL ▪ eGFR (CKD-EPI) >60 ml/min/1.73m^2 • Guidelines on the management of TLS symptoms is provided in Table 11, holding of dosing and stopping criteria outlined in Section 6.4.1.
Renal toxicity	**Nonclinical:** In monkeys given doses of GSK3745417 renal changes considered secondary to significant cytokine release, were observed in some animals (refer to IB). **Clinical:** No significant renal adverse events have been observed in the first 3 dose levels of Study 208850. The risk of TLS may potentially lead to additional renal toxicity.	**Monitoring:** • Frequent monitoring of clinical chemistry including serum creatinine and eGFR as per schedule of activities (SOA), Section 1.3. **Mitigation:** • Inclusion criteria of eGFR (CKD-EPI) >60 ml/min/1.73m^2 • Specific renal stopping criteria and dose modification management guidelines outlined in Section 7.1.2

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Cardiac effects	**Nonclinical:** There were dose-related increases in the heart rate (26-114 bpm) observed in monkeys given ≥0.6 mg/kg/dose of GSK3745417 (fourth weekly dose) between 1- and 20-hour post-dose, and in the number of ventricular ectopic arrhythmia in monkeys given 1 mg/kg/dose (second administration of this dose). Inflammatory cytokines have been shown to contribute to increased heart rate and ventricular arrhythmias. **Clinical:** Tachycardia and changes in blood pressure associated with cytokine release have been observed in Study 208850 in solid tumors. One likely immune-mediated event of myocarditis has been observed in Study 208850 to date and therefore cardiac monitoring on study is required.	**Monitoring:** • Frequent study cardiac monitoring with EKG, ECHO, and troponin (see SOA and Section 6.4.1.5). • Holter monitoring per SOA. **Mitigation:** • Inclusion of those with adequate LF function (Section 5.1) • Exclusion of patients with a history or evidence of cardiovascular risk including a history of immune myocarditis and/or pericarditis (Section 5.2). • Specific dose modification and management guidelines, including when cardiac consult needed outlined in Section 7.1.3.
Immune-related AEs	Inflammatory AEs such as diarrhea/colitis, pneumonitis, nephritis, and hepatotoxicity are well established as treatment emergent AEs with immune-modulating agents and are a potential risk for GSK3745417 based on the immune-stimulatory mechanism of action. **Clinical:** One likely immune mediated event of myocarditis has been observed in Study 208850 to date.	**General measures:** • AEs are categorized as AESIs which must be reported to the Medical Monitor within 24 hours regardless of study drug relationship. **Mitigation:** • Exclusion of patients with active immune disease or unresolved immune-related toxicity from prior treatment as per Section 5.2. • Guidelines on the management of potential immune-related AEs is provided in Section 6.4.1.7.
Hepatic toxicity	**Nonclinical:** Hepatic toxicity considered secondary to high cytokine levels was observed after repeat dosing in mice and monkeys (Refer to the IB of GSK3745417). **Clinical:** No participants have met liver stopping criteria in Study 208850 over the first 3 dose levels. There have been a small	**General measures:** • Inclusion criteria for ALT≤2.5x ULN and bilirubin≤1.5x ULN. **Mitigation:** • Inclusion criteria for ALT ≤2.5x ULN and bilirubin ≤1.5x ULN. • Guidelines on the management of potential immune-related AEs is provided in Section 6.4.1.7.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	number of transient mild ALT and AST elevations though cases are generally confounded by liver metastases.	• Standard phase 1 oncology Liver Chemistry Stopping Criteria. (See Section 7.1.5).
Hematologic Toxicity	**Nonclinical:** Nonclinical models showed a transient and dose dependent decrease in red blood cells after dosing. **Clinical:** Drug-related anemia was observed in Study 208850. AML risks to pancytopenia manifesting as anemia, neutropenia, and thrombocytopenia.	**Measures** • Full supportive care including transfusions are permitted. on study. There are no Hb or platelet inclusion criteria in the protocol as AML patients are generally dependent on regular red blood cell and platelet transfusions. Haemato-oncologists are well experienced in managing hematological toxicity.
Reproductive toxicity	No reproductive organ toxicity was observed with GSK3745417 in mice and monkeys. Based on the immune activation mechanism of action, GSK3745417 may affect establishment or maintenance of a pregnancy. There is also a potential risk for embryofetal toxicity.	**Mitigation:** • Exclusion of lactating and pregnant women • Contraception guidelines will be included as inclusion criteria for females (Section 5.1). • Additional male and female contraceptive requirements if patients are taking a permitted concomitant medication, hydroxyurea, to control blast count (Section 10.5.2).

2.3.2. Benefit Assessment

The high level of STING expression combined with sensitivity to dual mechanisms of action of direct cell killing and immune activation as well as intravenous (IV) administration of GSK3745417 make AML a suitable indication to establish proof of mechanism and clinical activity of GSK3745417 with possible benefit that may include complete/partial remission, independence from transfusion, and competent immune function for an indication with unmet medical need.

2.3.3. Overall Benefit: Risk Conclusion

Upon review of the nonclinical and available clinical safety data from the ongoing 208850 solid tumor study, there are currently no known risks associated with GSK3745417 which would preclude further development. Given the disease under study (relapsed/refractory AML with no other effective treatment options) and the mitigation measures specified in the protocol to reduce the potential risks, the benefit:risk for commencing development of GSK3745417 in AML is considered favorable.

3. OBJECTIVES AND ENDPOINTS

Dose Escalation (Part 1)		
	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 (Part 1)		
	Objectives	**Endpoints**
	CCI [redacted]	

Dose Expansion (Part 2)		
	Objectives	**Endpoints**
Primary	• To evaluate clinical efficacy following the daily dosing “induction” period of GSK3745417 in participants with relapsed/refractory AML and HR-MDS.	• Objective response rate (ORR) after the daily dosing “induction” period of GSK3745417

Dose Expansion (Part 2)		
	Objectives	**Endpoints**
	• To determine the safety, tolerability, and recommended Phase 2 dose (RP2D) for "maintenance"	• Frequency and severity of Adverse Events (AEs), Serious Adverse Events, (SAEs), Dose Limiting Toxicity (DLT), withdrawals due to AEs during "maintenance" dosing
Secondary	• To further evaluate the safety, tolerability of one or more RP2D for maintenance	The following may be included based on the availability of data and appropriateness: • AEs, SAE, AESIs leading to dose modifications or delays
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 Expansion (Part 2)		
	Objectives	**Endpoints**
	CCI	

4. STUDY DESIGN

4.1. Overall Design

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. Dosing in Part 1 will include 3 initial cycles followed by "maintenance" at a weekly dosing schedule. Part 2 represents an expansion cohort at the recommended induction dose/doses and schedule from Part 1 for 3 cycles, followed by either a weekly, every 3 weeks, or less frequent dosing schedule for "maintenance." Approximately 72 participants will be enrolled: approximately 22 participants in Part 1 and 50 participants in Part 2.

Part 1

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. The first participant at the starting dose level(s) of each cohort will begin treatment after review of safety data and DEM to allow assessment of initial safety data before beginning the next participant's treatment. The dosing of subsequent participants will be staggered by ≥5 days.

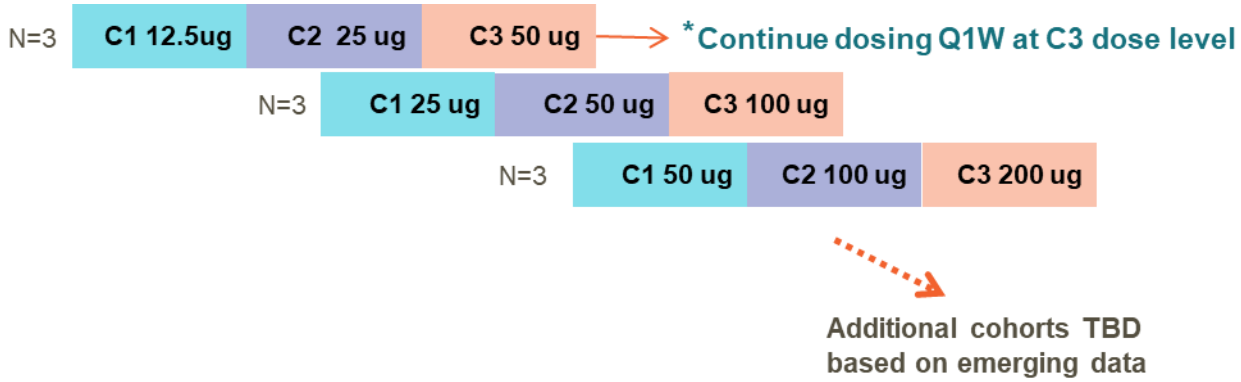
Table 6 Dosing and Hospitalization Schedule for Cycles 1 - 3

Day	-1	1	2	3	4	5	6	7	8	9	10	11	12	13	14-28
GSK3745417		X	X	X	X	X			X	X	X	X	X		
In-patient	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Non-azole antifungal	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Dose escalation will initiate with Cycle 1 at 12.5 µg GSK3745417 as the first cohort and the Cycle 1 dose will increase by 2-fold between cycles (3 dose levels). The starting dose of subsequent cohorts will increase by 2-fold from Cycle 1 of the previous cohort. Patients may be dose reduced for subsequent cycles if there is lack of tolerability in the previous cycle (Section 6.4). The DLT period will be 28 days starting at Day 1 of Cycle 1 of each cohort. After 3 induction cycles, if a CR or PR (IWG) is observed (See Appendix 9), 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 if the assessment by the investigator determined a benefit and GSK Medical Monitor agrees.

In Part 1, participants will receive dosing in the hospital on a 5 days on/2 days off schedule for 2 weeks, and then have an additional 2 weeks off dose for observation. The participant will be observed for at least 24 hours after the final dose in each cycle. All participants will be hospitalized the day before a new dosing cycle starts to receive tumor lysis syndrome (TLS) prophylaxis in line with institutional guidelines (all participants should receive IV fluids ± allopurinol as well as alkalinization of urine with renal consult if this is in line with institutional guidance). TLS prophylaxis will continue alongside daily dosing as clinically indicated. To further reduce the risk of TLS, guidance in Section 6.4.1.2 must be followed to determine when daily dosing should be held.

Figure 4 Part 1 Intense Dosing Regimen (Intra-patient Dose-Escalation Study)

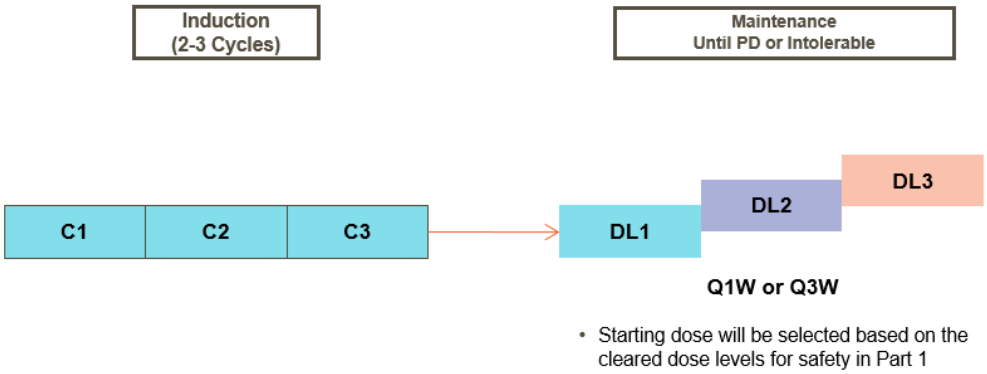


* Patients in C3 dose level in all cohorts will be continuing dosing Q1W at C3 dose level

Part 2

Part 2: Efficacy will be evaluated after an induction phase in approximately 50 participants, 25 AML participants and 25 HR-MDS participants. The induction phase consists of a treatment regimen at the dose/doses determined to be safe in Part 1 (RP2D). The number of cycles, number of doses investigated in the induction phase, and/or dosing schedule of 5 / 2 / 5 q28d treatment will be determined and may be modified based on a review of safety and PK data generated from Part 1. After the induction phase, patients will continue to either a weekly (Q1W), every 3 weeks (Q3W), or less frequent dosing schedule for maintenance treatment, if a CR or PR is observed (See Response Criteria for Participants with AML Appendix 9; See IWG Criteria for Response for Participants with MDS Appendix 8). Participants with stable disease or PR after 3 induction cycles might receive additional cycles if the assessment by the investigator determined a benefit and GSK Medical Monitor agrees. Up to three dose levels for maintenance treatment will be evaluated in the maintenance dose escalation. The DLT period for the maintenance dose escalation portion of Part 2 will be 28 days starting at Day 1 of each cycle. Dose escalation for the maintenance schedule will start at the highest dose cleared for safety in Part 1. Part 2 will evaluate the efficacy of the induction regimen separately for AML and HR-MDS as well as the tolerability and duration of response of the Q1W or Q3W maintenance schedules to determine the best dose and schedule for further studies.

Figure 5 Part 2 Dose Escalation for Maintenance Dosing MTD and Expansion



Each part of the study includes a screening period, a treatment period, and a follow up period. Participants will be screened for eligibility beginning 4 weeks (or 28 days) before the start of treatment.

Dose Escalation

To complete dose escalation in Part 1, it is estimated that up to 22 participants will be enrolled. Dose escalation for Part 1 will use the N-CRM. This method utilizes a 2parameter logistic model, with parameters α and β, to describe the relationship between DLT and dose (12.5, 25, 50, 100, 200 µg). The N-CRM estimates, for each potential dose, the posterior probabilities that the DLT rate lies in each of 4 toxicity intervals:

- [0%,16%)=Underdosing range;
- [16%,33%)=Target toxicity range;
- [33%,50%)=Excessive toxicity range;
- [50%,100%)=Unacceptable toxicity range.

Additionally, the following constraints for the recommended dose will be maintained:

The posterior probability of the DLT rate lying in the Excessive Toxicity or Unacceptable Toxicity range is less than 25%.

Dose escalation will continue until:

i. An MTD is found:

At least 9 participants have been treated at the current target dose

AND

The posterior probability that the DLT rate for the current dose lies in either the excessive toxicity or unacceptable toxicity range is less than 25%.

AND

The posterior probability that the DLT rate for the next higher dose lies in either the excessive toxicity or unacceptable toxicity range is greater than or equal to 25%.

OR

ii. The RP2D has been reached and at least 9 participants have been dosed at that dose level.

OR

iii. All doses have a posterior probability of lying in either the excessive toxicity or unacceptable toxicity range of greater than or equal to 25%

AND

At least 2 DLTs have been observed.

All available data, including safety, PK, and pharmacodynamic data from current and prior cohorts will be reviewed at dose escalation meetings after each cohort in Part 1. Clinical judgment by the Medical Monitor, recommendation from GSK clinical pharmacologist, GSK scientist and GSK statistician, and in consultation with the investigators can decide dose escalation or reduce the recommended dose as deemed appropriate at any time during the trial.

Maximum Tolerated Dose: The MTD will be defined as the dose within cycle that has the highest probability of having a DLT rate within the target toxicity interval, and for which the probability that the DLT rate lies within the excessive toxicity, or the unacceptable toxicity window is less than 25%. The DLT observation period will be 28 days.

Recommended Phase 2 Dose: RP2D of GSK3745417 will be determined after review of all available safety, PK, pharmacodynamics, and clinical efficacy data. The RP2D will be equivalent with the MTD or a lower GSK3745417 dose and regimen that provides adequate PK exposure and biologic activity with acceptable safety and tolerability.

Maintenance dose escalation for Part 2 will use the mTPI method as described in Section 9.2. Dose escalation will proceed until the MTD for GSK3745417 for a specific maintenance dosing schedule is determined.

4.1.1. Dose Limiting Toxicities (DLT)

All toxicities will be graded using National Cancer Institute – Common Toxicity Criteria for AEs (NCI-CTCAE), version 5.0.

An AE is considered to be 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 the table below. 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. Participants unable to receive at least 70% of scheduled doses within the DLT

period for reasons other than toxicity (e.g., acute illness, disease progression) will not be considered evaluable.

Table 7 Dose-Limiting Toxicities

Toxicity	DLT Definition
Cytokine Release Syndrome (CRS)	Grade 3 or 4 (See Section 10.4)
TLS	• Grade 3 or Grade 4 TLS (Cairo Bishop criteria, Appendix 11) that cannot be managed/ is not resolved within 72 hours
Liver Toxicity	ALT ≥3x upper limit of normal (ULN), plus bilirubin ≥2x ULN (>35% direct) or plus international normalized ratio (INR)>1.5 (Possible Hy's law)
Other	Grade ≥3 non-hematologic toxicity of any duration with the following exceptions: • Transient (≤ 72 hours) abnormal laboratory value without associated clinically significant signs or symptoms • Individual parameters of CRS which collectively constitute <Grade 3 CRS • Nausea, vomiting, or diarrhea that improves with supportive care within 72 hours • Alopecia of any grade • Grade 3 fatigue with duration <7 days • Grade 3 headache that resolves with supportive treatment to ≤Grade 2 within 24 hours • G3 acute renal injury considered related to TLS which improves or resolves with appropriate fluids and management of TLS Grade ≥3 immune-related toxicity that does not resolve to Grade ≤1 or baseline within 8 days despite adequate immune suppressive therapy. Any other event which in the judgment of the investigator and GSK Medical Monitor is considered to be a DLT.

Participants who withdraw from the study before completing DLT period for reasons other than DLT may be replaced. If a participant experiences a DLT during the DLT period of treatment, the participant will be discontinued from study treatment unless the investigator considers it in the best interest of the participant to continue on study (e.g., in case of symptomatic disease improvement, and/or if the DLT is viewed as preventable in subsequent doses/visits, etc.) and the sponsor approves of the decision.

Guidance for the management of toxicity, including dose modification algorithms, is provided in Section 6.4.

4.1.2. Dose Escalation Decisions

The Dose Escalation committee, in joint discussion with the participating investigators, will be responsible for determining whether cohort level dose escalation or de-escalation during the study should continue as recommended by the N-CRM approach for Part 1 and the mTPI approach for Part 2. Prior to the dose escalation/de-escalation decision, the medical monitor, clinical scientist, safety physician/scientist, clinical pharmacologist,

statistician, and investigators will review critical safety data defined in the Dose Escalation Plan, including data on all adverse events including non-DLT toxicities, laboratory assessments and other safety evaluations, as well as any available PK and/or PD data. The quality review of critical safety data will be described in the Dose Escalation Plan, which includes ongoing study monitoring visits along with data review of the clinical database.

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

Intra-patient dose escalation

In Part 1, participants are permitted to dose escalate between the 2-3 induction 5 / 2 / 5 q28d cycles based on discussion and agreement with Medical Monitor and the Investigator after reviewing available safety and laboratory data, and in line with the following safety and tolerability parameters:

- Investigator and MM must both consider that dose escalation is in the best interests of the participant
- Participant must have received at least 7 of the 10 doses in the prior cycle
- Participant must not have experienced:
    - Any Grade ≥3 adverse event
    - Grade ≥3 TLS
    - A DLT (which includes Grade 3 CRS, all non-hematologic Grade 3 events with a few exceptions as per Table 7)
    - More than 1 episode of Grade 2 CRS in the previous cycle
    - Evidence of ongoing immune related AEs during the observation period (sustained or intermittent Grade ≥2 fever ongoing after the first week of the observation period, in which infectious cause is ruled out).

4.2. Number of Participants

Approximately 22 participants may be enrolled in Part 1, and approximately 50 participants may be enrolled in Part 2. The total number of participants to be enrolled is an estimate and will depend on the number needed to adequately characterize the DLT and PD profile and determine the MTD(s)/RP2D(s). All participants who take at least one dose of study intervention will be considered evaluable for analysis. See the statistical considerations, Section 9.2, for justification of the sample size.

4.3. Scientific Rationale for Study Design

Preclinical data support the use of STING agonists for the treatment of AML. A study evaluating the effect of a STING agonist on 144 different cancer cell lines spanning 14 different histologies revealed that GSK3745417 induced cell growth inhibition in two out of two AML cell lines tested and one large cell lymphoma cell line. In a subsequent study focused on 12 additional AML cell lines, GSK3745417 induced cytotoxicity in 3 of 12 cell lines, cytostaticity in 5 of 12 cell lines, or modest to no effect in 4 of 12 cell lines.

Even with these "cytostatic" lines, apoptosis was induced. Over both studies, GSK3745417 induced cytotoxicity or cytostaticity in 64% (9 of 14) of all AML cell lines tested. Mechanistically, GSK3745417 activates caspases 3/7 in highly sensitive AML cell lines, suggesting a role for STING mediated apoptosis in driving AML cell death. In addition to STING driven cytotoxicity or cytostaticity of AML, a recent publication also suggests STING agonists stimulate potent anti-AML immunity in a mouse model via induction of type I interferons and proinflammatory cytokines (Curran, 2016). A 5 / 2 / 5 q28d dosing regimen is being evaluated in Part 1 since it is hypothesized that increased dosing frequency, and therefore average concentration, of GSK3745417 will enhance the direct cell killing effect.

The proposed Phase 1 study will evaluate the safety and tolerability, PK, PD, and preliminary clinical activity of increasing doses of GSK3745417 administered IV in adult participants with relapsed or refractory AML or high-risk MDS and will determine a dose and schedule of GSK3745417 for future clinical studies.

4.4. Justification for Dose

4.4.1. Human Experience with GSK3745417 Dosing in Participants with Solid Tumors

For the ongoing first time in human study (Study 208850), the minimally anticipated biological effect level (MABEL) approach was used in conjunction with the ICH S9 guidance on selection of starting dose for a biopharmaceutical with immune agonistic properties to select a safe starting dose of GSK3745417 for use in cancer patients with advanced tumors with due consideration of relevant in vitro, ex vivo, and in vivo nonclinical data. A dose level of 100 µg QW was used as a starting dose following a 10-fold safety factor from the identified MABEL dose of 1000 µg and was tolerated in humans. The 100 µg was considered safe and tolerated as no DLTs were observed during the DLT determination period of 21 days. To date, three dose levels (100, 200, and 400 µg) have been investigated in the solid tumor population, with further detail in the human PK section below. MTD was identified as 400 ug for Q1W mono therapy. Study 208850 is ongoing with further investigations into Q3W dosing of GSK3745417 monotherapy, and eventually Q1W or Q3W in combination therapy with dostarlimab.

4.4.2. Selected Human Starting Dose and Discussion

It is unclear how the observed solid tumor effects of GSK3745417 in BALB/c mice will translate into the human AML disseminated tumor setting or the current human experience in solid tumors, though it is noted that the C_{max} in the 200 and 400 µg dose levels in human approximates the 3 h concentration in the BALB/c tumor model where tumor regression was observed. Regarding the direct cell killing mechanism, to match the geometric mean of the gIC_{50} values of 5.14 ng/mL for growth inhibition, and assuming linear PK, a predicted dose level of ~16 µg would be required to achieve a C_{max} of ~5.14 ng/mL.

Therefore, with the lower dose goal of achieving direct cell killing, the recommended starting dose in the AML population is 12.5 µg, which is approximately 1× of the geometric mean of the gIC_{50} in AML cell lines, $1/8^{th}$ of the lowest dose studied to date in the solid tumor population (Study 208850), and $1/16^{nd}$ of the maximum tolerated dose in the solid tumor population (Study 208850). The 100-µg starting dose in the solid tumor study was dosed weekly; 12.5 µg daily for 5 days is still cumulatively a lower dose than the 100-µg single dose used in the solid tumor study. This starting dose would be predicted to result in a C_{max} of ~4 ng/mL and an AUC of ~8 hr*ng/mL. This approach relies on the finding in bone marrow that the AML population would have no higher cytokine induction through the innate immune system response, and therefore represents an additional three low-dose cohorts compared to the solid tumor study (Study 208850). This low starting dose of 12.5 µg also provides an important safety margin given the preliminary non-clinical data which suggest that there may be some accumulation of cytokine related symptoms/immune system activation with daily dosing. Given the available safety profiles with human dosing in 21 participants in Study 208850, and absence of significant cytokine related symptoms at the starting dose of 0.1 mg in Study 208805 this would appear to be a reasonable risk/benefit trade-off because of the potential benefit of cell killing at lower dose levels.

4.5. End of Study Definition

The end of the study is defined as the date of the last visit of the last participant in the study or last scheduled procedure shown in the Schedule of Activities (SoA) for the last participant in the trial globally.

A participant is considered to have completed the study if he/she has completed all phases of the study including the last visit or the last scheduled procedure shown in the Schedule of Activities. 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.

Participant would be considered off study in the event of death, withdrew consent, or lost to follow-up.

5. STUDY POPULATION

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

5.1. Inclusion Criteria

Participants are eligible for inclusion in this study if all the following criteria apply:

1. Must be ≥18 years of age and ≤75 years of age at the time of signing the informed consent for dose escalation and >18 years of age at the time of signing the informed consent for the dose expansion.

2. Capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in the protocol.

3. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.

4. Participants with AML/High Risk MDS are eligible for participation in Part 1 and Part 2 if they have:

   - A diagnosis of AML according to the World Health Organization 2016 criteria (Arber, 2016) with relapsed or refractory disease and ineligible for or have exhausted standard therapeutic options.

   - Have high-risk or high/very high by IPSS-Revised [IPSS-R] criteria [Greenberg] MDS (restricted to Part 1) that has relapsed after or been refractory to prior therapy with hypomethylating agent.

5. Adequate organ function:

Organ system	Laboratory Values
Hematologic	
White blood cell count (absolute)	≤25,000/µL (both at screening and prior to study drug administration on Day 1) (hydroxyurea is permitted to reduce white cell count prior to screening). Hydroxyurea or leukapheresis may be used prior to and throughout study to control white cell count
PT/INR and PTT in patients not receiving therapeutic anticoagulants	≤1.5 x ULN
PT/INR and PTT in patients receiving therapeutic anticoagulants	Within the intended therapeutic range of the anticoagulant
Hepatic	
Total bilirubin *For participants with Gilbert's Syndrome (only if direct bilirubin 35%)*	≤1.5 x ULN *≤3.0 x ULN*
ALT	≤2.5 x ULN
Renal	
eGFR by CKD-EPI	≥50mL/min/1.73m^2
Endocrine	
TSH[1]	WNL
Cardiac	
Ejection fraction	≥Lower limit of normal (LLN) (minimum of 50%)

1. If TSH is not within normal limits at baseline, the participant may still be eligible if total T3 or free T3 and free T4 are within the normal limits

6. Participants with a prior history of stem cell transplant (autologous and/or allogeneic) are allowed if:

- No clinical signs or symptoms of graft versus host disease (other than Grade 1 GVHD (<25% skin surface affected) and the participant is off all systemic immunosuppression. (**Note**: topical steroids for G1 skin GVHD are permitted on study)

7. Agree to abide by the gender specific contraceptive requirements below:

    - Female participants are eligible to participate if they are not either pregnant or breastfeeding, and at least one of the following conditions applies:

        - Is not a woman of childbearing potential (WOCBP), or

        - Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), with low user dependency during the study treatment period and for at least 7 days after the last dose of study treatment and agrees not to donate eggs (ova, oocytes) for the purpose of reproduction during this period. The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study treatment.

        - A WOCBP must have a negative highly sensitive pregnancy test (urine or serum) as required by local regulations) within 7 days before the first dose of study intervention. If a urine test cannot be confirmed as negative (e.g., an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.

        - Additional requirements for pregnancy testing during and after study treatment will be described in the protocol.

        - The investigator is responsible for a review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

    - Male participants and WOCBP taking hydroxyurea during the study must follow contraceptive guidance in the hydroxyurea prescribing information

5.2. Exclusion Criteria

1. Diagnosis of acute promyelocytic leukemia (APML or t(15;17) PML-RARA fusion). Patients with biphenotypic disease are excluded.

2. Active central nervous system involvement or disorder:

    a. Participants with a history of CNS disease are permitted to enroll if they have previously received appropriate therapy and CNS remission has been

documented and are symptom/progression free and off therapies that are controlling symptoms for at least 4 weeks prior to enrollment. **Note*:*** In the absence of CNS symptoms, a lumbar puncture is not required for study entry.

b. Active CNS disorder, such as seizure, cerebrovascular ischemia/hemorrhage, dementia, cerebellar disease, or any autoimmune disease with CNS involvement, unless considered stable and well-controlled with ongoing treatment

3. Immediate life-threatening, severe complications of leukemia (sepsis, hemorrhage).

4. Participants with extramedullary disease as the sole site of AML

5. Active severe or uncontrolled infection, known human immunodeficiency virus infection, or presence of hepatitis B surface antigen (HBsAg) or positive hepatitis C antibody test at screening. **Note:** Participants with positive hepatitis C antibody due to prior resolved disease can be enrolled only if a confirmatory negative hepatitis C RNA polymerase chain reaction (PCR) (or comparable test) is obtained.

6. Participants with signs/symptoms suggestive of COVID-19 within 14 days of study entry, or with known exposure to COVID-19 within 14 days prior to study entry

7. Active autoimmune disease that has required systemic disease modifying or immunosuppressive treatment within the last 2 years.

8. Concurrent medical condition requiring the use of systemic immunosuppressive treatment within 28 days before the first dose of study treatment.
Note: Physiologic doses of corticosteroids for treatment of endocrinopathies or steroids with minimal systemic absorption, including topical, inhaled, or intranasal corticosteroids may be continued if the participant is on a stable dose.

9. History of vasculitis at any time prior to study treatment.

10. Participant has a history of other malignancies less than 2 years prior to study entry, with the exception of:

    - Adequately treated in situ carcinoma of the cervix uteri or carcinoma in situ of breast;

    - Basal cell carcinoma of the skin or localized squamous cell carcinoma of the skin;

11. QTcF >450 msec for male participants, >470 msec for female participants, or >480 msec for participants with bundle branch block. QTcF is QT corrected for

heart rate according to Fridericia's formula and can be machine calculated or manually over-read.

12. Recent history of allergen desensitization therapy within 4 weeks of starting study treatment.

13. History or evidence of cardiovascular (CV) risk including any of the following:

    - Clinically significant uncontrolled hypertension
    - Recent (within the past 6 months) history of serious uncontrolled cardiac arrhythmia or clinically significant ECG abnormalities including second degree (Type II) or third-degree atrioventricular block.
    - Cardiomyopathy, myocardial infarction, acute coronary syndromes (including unstable angina pectoris), coronary angioplasty, stenting, or bypass grafting within the past 6 months before enrollment.
    - Congestive heart failure (Class II, III, or IV) as defined by the New York Heart Association functional classification system [NYHA, 1994].
    - History of immune myocarditis or pericarditis.

14. Prior STING therapy.

15. Prior solid organ transplantation.

16. Recent prior therapy defined as follows:

    - Any non-monoclonal anti-cancer therapy within 14 days or 5 half-lives, whichever is longer, prior to start of study treatment
    - Prior therapy with biological agents (including monoclonal antibodies) within 28 days prior to start of study treatment
    - Any radiotherapy or major surgery within 14 days prior to start of study treatment
    - Currently receiving investigational therapy in a clinical trial

      Note: Hydroxyurea may be used prior to and throughout study to control white cell count.

17. Receipt of any live vaccine within 30 days of start of study treatment. Inactivated vaccines such as the inactivated flu intramuscular vaccine are permitted. Live attenuated vaccines including herpes zoster, nasal flu, and coronavirus vaccines should be avoided. Recombinant human or non-human primate adenoviral vector vaccines are also excluded.

18. Immune-related toxicity related to prior treatment that has not resolved to Grade ≤1 (except alopecia, hearing loss or Grade ≤2 neuropathy or endocrinopathy managed with replacement therapy).

19. Concomitant administration of drugs that are sensitive substrates or narrow therapeutic range substrates for cytochrome p450 (CYP)3A4 enzyme, P-gp, BCRP, OATP1B1 and OATP1B3 transporter, and moderate to strong inducers and inhibitors of CYP3A4, P-gp, OATP1B1 and OATP1B3 should be excluded during the study and for 7 days prior to and following treatment with GSK3745417 (14 days for itraconazole). Note: any medications (including antibacterials, antifungals, and antivirals) which are necessary for the health, well-being, or standard clinical care of patients with hematologic malignancies are exempt from this restriction. Any medications potentially interacting with GSK3745417 will require a pause in GSK3745417 dosing unless allowed through consultation with Sponsor.

20. Ongoing drug or alcohol abuse.

5.3. Lifestyle Considerations

5.3.1. Meals and Dietary Restrictions

- Refrain from consumption of red wine, Seville oranges, grapefruit or grapefruit juice, pomelos, exotic citrus fruits, grapefruit hybrids, or fruit juices from at least 7 days before the start of study intervention until after the final dose.

5.3.2. Caffeine, Alcohol, and Tobacco

- During each dosing session, participants will abstain from ingesting caffeine- or xanthine-containing products (e.g., coffee, tea, cola drinks, and chocolate) for 4 hours before the start of dosing until after collection of the final PK and/or pharmacodynamic sample.

- During each dosing session, participants will abstain from alcohol for 24 hours before the start of dosing until after collection of the final PK and/or pharmacodynamic sample.

- Participants who use tobacco products will be instructed that use of nicotine-containing products (including nicotine patches and other delivery devices such as vaporizers) will not be permitted while they are in the clinical unit.

5.3.3. Activity

- Participants will abstain from strenuous exercise for 8 hours before each blood collection for clinical laboratory tests. Participants may participate in light recreational activities during studies (e.g., watching television, reading).

5.4. Screen Failures

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

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

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

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

6.1. Study Intervention(s) Administered

GSK3745417 will be administered to participants at each study site under medical supervision of an investigator or designee. Cytokine-related AEs including changes in vital signs may begin within several hours of administration of GSK3745417. Participants must be monitored in the clinic/hospital throughout dosing in the initial cycles and for up to 24 hours after administration of the Q1W or Q3W maintenance doses, or longer as clinically indicated. Guidelines for monitoring cytokine-related AEs and tumor lysis syndrome are summarized in Section 6.4.

For Part 1, the dosing schedule each Cycle from 1 – 3 is 5 days on / 2 days off / 5 days on followed by observation for 2 weeks. After 3 cycles, participants will move to a dosing schedule of once every week (Q1W). For Part 2, after the induction regimen determined from Part 1, participants will enter a maintenance phase at a dose and schedule determined by emerging FIH data.

The specific time of study treatment administration (e.g., time of the week for first administration; time of the day for each administration) should take into consideration PK sampling time points and study visit procedures and will be recorded in the source documents and in the eCRF.

Weekly dosing may be done ±24 hours and Q3W dosing may be done ±72 hours.

ARM Name	Intervention
Intervention Name	GSK3745417
Type	Drug
Dose Formulation	To be provided in the study reference manual
Dosage Form	Powder for Solution for Injection
Unit Dose Strength(s)	2 mg/vial

Dosage Level(s)	12.5 µg – 800 µg (to be determined)
Route of Administration	IV injection through a central or PICC line
Use	experimental
IMP and NIMP	GSK3745417
Sourcing	Provided centrally by the Sponsor
Packaging and Labeling	Study Intervention will be provided as 1 vial in a carton. Each vial and carton will be labeled as required per country requirement.
Current/Former Name(s) or Alias(es)	N/A

6.2. Preparation/Handling/Storage/Accountability

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

2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

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

4. Further guidance and information for the final disposition of unused study intervention are provided in the Study Reference Manual.

- Under normal conditions of handling and administration, study intervention is not expected to pose significant safety risks to site staff. Take adequate precautions to avoid direct eye or skin contact and the generation of aerosols or mists. In the case of unintentional occupational exposure notify the monitor, Medical Monitor and/or GSK study contact.

- A Material Safety Data Sheet (MSDS)/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or is available upon request from GSK.

Precaution will be taken to avoid direct contact with the study intervention. A Material Safety Data Sheet (MSDS)/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or is available upon request from GSK. In the case of unintentional occupational exposure notify the monitor, Medical Monitor and/or GSK study contact.

6.3. Measures to Minimize Bias: Randomization and Blinding

This is an open-label study. Investigators and study team will have direct access to individual participant's study intervention. All screened participants will be identified by a unique participant number that will remain consistent for the duration of the study.

In Part 1, at least 3 participants will be enrolled at a particular dose level. For the first cohort, the first participant will be enrolled, treated with 10 planned doses, and observed for 2 more days before subsequent participants are enrolled into that cohort to allow assessment of initial safety data. The next 2 participants in the first cohort will receive study treatment at least 5 days apart. Study Intervention Compliance

- When the individual dose for a participant is prepared from a bulk supply, the preparation of the dose will be confirmed by a second member of the study site staff.

- When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

6.4. Dose Modification

6.4.1. Participant-Level Dose Modifications due to Adverse Events

GSK3745417 dose reduction or alternative dosing schedules at a participant or cohort level may be considered based on emerging data.

Holding daily dosing

Daily dosing will be continued unless there is evidence of ongoing TLS or immune activation in line with the criteria below.

Daily dosing held if:

- Ongoing Grade 3 TLS (see Appendix 11 for Cairo Bishop grading) or Grade 3 electrolyte abnormalities that are not responding to treatment
- Failure of any CRS, fevers, or chills to resolve to Grade ≤1 (with supportive treatment) within 24 hours
- Any new neurological adverse events (except for Grade ≤2 headache which responds to analgesia), until assessment and cause of neurological event is identified
- Investigator judgement that dosing should be held based on the clinical status of patient

Dose reduction for CRS

In the event of Grade 2 CRS, further dosing can be given with prophylaxis against CRS with steroids, paracetamol/acetaminophen, and antihistamines (as agreed between investigator and MM). Patients with more than one episode of Grade 2 CRS within the same cycle despite prophylaxis should be dose reduced to the next dose level down once dosing resumes. Participants will come off study if more than 2 dose reductions required, or if they require dose reduction below the lowest study dose of 12.5 µg.

In participants who develop CRS requiring holding of daily dosing, Investigators should perform additional LFT and clinical chemistry tests during the dose hold as clinically indicated, and perform the additional investigations outlined in Section 6.4.1.4.

6.4.1.1. Intra-Patient Dose Escalation

Intra-patient dose escalation is permitted for induction treatment cycles 2 and 3 depending on safety and tolerability of the first dosing cycle. To allow intra patient dose escalation for the next dosing cycle:

- Investigator and MM must both consider that dose escalation is in the best interests of the participant
- Participant must have received at least 7 of the 10 doses in the prior cycle
- Participant must not have experienced:
  - Any Grade ≥3 AE
  - Grade ≥3 TLS
  - A DLT (which includes Grade 3 CRS, all non-hematologic Grade 3 events with a few exceptions as per Table 7)
  - More than 1 episode of Grade 2 CRS in the previous cycle
  - Evidence of ongoing immune activation during the observation period (sustained or intermittent Grade ≥2 fever ongoing after the first week of the observation period)

6.4.1.2. Tumor Lysis Syndrome

Tumor lysis syndrome (TLS) may occur in participants treated with GSK3745417 as it has demonstrated a direct cell killing mechanism in AML cells. Laboratory or Clinical TLS should be diagnosed according to the Cairo Bishop criteria (Cairo, 2004). In the event of TLS, Investigators should use clinical judgement and follow institutional guidelines for prophylaxis and symptom management of TLS.

Participants should be assessed for TLS risk prior to each dose, including evaluation of tumor burden, comorbidities, and renal function, and prior to each dosing with GSK3745417 should be admitted to hospital the day before first dose of each induction cycle or maintenance dose, and receive prophylaxis for TLS in line with institutional guidance. Blood clinical chemistry must be monitored every 6 hours for the first 48 hours of the first dosing cycle, and each cycle with a dose increase. Participants are hospitalized throughout the 2-week dosing period of each induction treatment cycle and TLS prophylaxis should continue alongside daily dosing of GSK3745417 as clinically indicated.

Table 8 Cairo Bishop Definition of Laboratory TLS

Assessment	Result Range
Uric acid	≥476 µmol/L (≥8.0 mg/dL) or 25% increase from baseline
Potassium	≥6.0 mmol/L or 25% increase from baseline
Phosphorus	≥1.45 mmol/L (≥4.5 mg/dL; adults) or 25% increase from baseline
Calcium	≤1.75 mmol/L (≤7.0 mg/dL) or 25% decrease from baseline

Table 9 Cairo Bishop Definition of Clinical TLS

Creatinine: x ≥1.5 ULN
Cardiac arrythmia/sudden death
Seizure

For grading of TLS, refer to Cairo Bishop grading in Appendix 11.

6.4.1.3. Infusion Reaction

Infusion reactions typically develop within 30 minutes to two hours after initiation of drug infusion, although symptoms may be delayed for up to 48 hours. There are multiple mechanisms known to lead to infusion-related reactions including both IgE-dependant anaphylactic and non-IgE dependent anaphylactoid hypersensitivities. Infusion reactions may affect any organ system in the body. Most are mild in severity, although severe and fatal reactions can occur. As a group, infusion reactions (including both cytokine-mediated and allergic) usually occur during or within a few hours of drug infusion. Occasionally, a reaction may occur one to two days after administration. The NCI-CTCAE (version 5.0) [NCI, 2017] for grading adverse reactions during the infusion of a pharmacological or biological substance has a term for grading the severity of infusion reactions and separate terms for grading allergic reactions, anaphylaxis, and cytokine release syndrome. The use of these separate terms in grading severity of the event may be useful for classifying the nature of an infusion reaction for research purposes; they are less useful for clinical care, since it may not be obvious if the participant is having an allergic infusion reaction or a non-allergic infusion reaction.

Clinically, infusion reactions may present with fever, chills, flushing, itching, urticaria, and/or angioedema, repetitive cough, sudden nasal congestion, shortness of breath, chest tightness, wheeze, sensation of throat closure or choking, and/or change in voice quality, faintness, tachycardia (or less often bradycardia), hypotension, hypertension and/or loss of consciousness, nausea, vomiting, abdominal cramping, and/or diarrhea, sense of impending doom, tunnel vision, dizziness, and/or seizure, severe back, chest, and pelvic pain.

6.4.1.4. Cytokine Release Syndrome

Cytokine release syndrome, and severe, cytokine “storm”, has been identified as a sequelae of immune system activation associated with infusion reactions.

Prophylaxis for CRS is not mandated. However, if a participant experiences CRS, prophylaxis with antihistamines and paracetamol is permitted on subsequent infusions. Steroids may also be considered after discussion with the Medical Monitor.

Table 11 provides the recommended management of CRS according to grade, which has been further adapted from CTCAE for use with immunotherapy and should be implemented in accordance with institutional guidelines. Symptoms can mimic those seen with infection. The diagnosis of CRS is clinical and is supported by the exclusion of infection as well as the presence of increased cytokine levels and other biomarkers. Assessment and treatment guidelines are provided below in alignment with (the Society for Immunotherapy of Cancer SITC) guidelines (Maus, 2020). In the event of CRS, Investigators may also follow institutional guidelines for symptom management; additional guidance can be found in the published literature (Lee, 2019).

If CRS is suspected, in addition to assessment for infection, the following tests should be conducted **every day for the first week** and approximately **every other day thereafter** until symptoms are improving or an alternative diagnosis is confirmed:

- Local tests:
    - Clinical chemistry including LFTs, hematology, ferritin and coagulation, as well as C-reactive protein (CRP) labs;
    - Troponin, and *N*-terminal pro B-type natriuretic peptide (NT-proBNP) / BNP tests;
- Central tests: See Table 10 for central or local biomarker testing

CCI

    - cytokine-profiling as described in Section 8.6.

Table 11 Management Guidelines for Cytokine Release Syndrome

Grade	Clinical Presentation for Grading Assessment[1,2]	Management Guidelines
1	Temperature ≥38.0 °C	Vigilant supportive care[4] Assess for infection and treat[5]
2	Temperature ≥38.0 °C with hypotension not requiring vasopressors and/or hypoxia requiring the use of oxygen delivered by low-flow nasal cannula (≤6 L/minute) or blow-by.	Monitor cardiac and other organ function Vigilant supportive care[4] Assess for infection and treat[5] Treat hypotension with fluid Administer O_2 for hypoxia[6] Consider administering tocilizumab ± corticosteroids[7]
3	Temperature ≥38.0 °C with hypotension requiring a vasopressor with or without vasopressin and/or hypoxia requiring high-flow nasal cannula (>6 L/minute), facemask, non-rebreather mask, or venturi mask not attributable to any other cause[3]	Monitor participant very closely for cardiac and other organ dysfunction. Most likely will require monitoring in an intensive care unit (ICU). Vigilant supportive care[4] Assess for infection and treat[5] Treat hypotension with fluid and pressors[6]. Administer O_2 for hypoxia. Administer tocilizumab ± corticosteroids[7]
4	Temperature ≥38.0 °C with hypotension requiring multiple vasopressors (excluding vasopressin) and/or hypoxia requiring positive pressure (eg: CPAP, BiPAP, intubation and mechanical ventilation)	Manage participant in ICU Intensive supportive care including mechanical ventilation, fluids, pressors, antibiotics and other measures as required[6] Administer tocilizumab ± corticosteroids[7]
5	Death	

1. Fever is defined as temperature ≥38°C not attributable to any other cause. In patients who have CRS then receive antipyretic or anti-cytokine therapy such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.
2. CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause. For example, a patient with temperature of 39.5°C, hypotension requiring 1 vasopressor, and hypoxia requiring low-flow nasal cannula is classified as grade 3 CRS.
3. Low-flow nasal cannula is defined as oxygen delivered at ≤6 L/minute. Low flow also includes blow-by oxygen delivery, sometimes used in pediatrics. High-flow nasal cannula is defined as oxygen delivered at >6 L/minute.
4. Supportive care includes monitor fluid balance, maintain adequate hydration and blood pressure
5. Assessment and treatment to include history and physical, blood and urine cultures, imaging studies, administration of antimicrobial agents for concurrent bacterial infections, and for treatment of fever and neutropenia as per institutional practice; and antipyretics, analgesics as needed.
6. Given that prolonged fluid resuscitation without pressor use is associated with worse outcome and because early and aggressive supportive care, early use of vasopressors, and timely anti-cytokine therapy are paramount to mitigating life-threatening CRS.
7. Other immunosuppressor agents may be used, including TNFα and IL-1R inhibitors.

Source: (Lee, 2019)

6.4.1.5. Cardiac Monitoring

6.4.1.6. Cardiac Monitoring and Dose Modification Guidelines

In Study 208850 examining GSK3745417 in participants with advanced solid organ tumors, one case of immune-mediated perimyocarditis has been observed, with a likely causal relationship to GSK3745417. On-study monitoring of cardiac symptoms (myocarditis or pericarditis), troponins and cardiac function (using ECHO or MUGA) will be therefore required in this study.

BNP will be measured at screening and then on study as clinically indicated. Troponin should be measured at baseline and then every 2-3 weeks on study as per the schedule in Section 1.3. Troponin T will be assessed at a central laboratory as a means of consistent evaluation across all subjects. A second troponin sample will be assessed at a local laboratory for purposes of subject management. Whenever possible, troponin T will be assayed by the local laboratory. However, troponin I may be assessed at a local laboratory if troponin T is not available. The same local laboratory test (troponin I or troponin T) should be used consistently for an individual subject throughout the study.

Participants should receive a screening ECHO which should be a 3D ECHO if available. If not, a 2D ECHO should be used, and MUGA may be used where ECHO is considered sub-optimal e.g., large body habitus. The same modality should then be used throughout the study to enable comparison to baseline (ideally by the same reader at study center). Global longitudinal strain will be assessed via ECHO. All ECHO/MUGA data will be transferred and reviewed by an independent cardiologist.

GSK3745417 should be withheld, and participant referred for cardiology consult if:

- Troponin is elevated ≥2× ULN
- patient experiences symptoms consistent with pericarditis or myocarditis
- ECHO – on-study decrease in left ventricular ejection fraction ≥ 10% AND falling below the LLN, OR
- Absolute decrease in left ventricular ejection fraction ≥ 15%, even if LVEF remains in the normal range for the institution

Elevation of troponin ≥2× ULN without symptoms requires withholding GSK3745417 while awaiting repeat troponin value. A repeat troponin ≥2× ULN requires withholding GSK3745417 and awaiting cardiology consult. In participants with asymptomatic troponin elevations, GSK3745417 may be restarted in discussion with medical monitor, depending on benefit/risk.

Participants with suspected myocarditis should be diagnosed and managed in line with institutional guidelines and cardiology advice. For a detailed review of diagnosis and management of myocarditis, and to guide treatment principles, the ASCO guidelines (Brahmer, 2018) and a recent review of myocarditis in patients treated with checkpoint

inhibitors (Palaskas, 2020) may be used, which include treatment principles around use of high dose steroids with a slow, monitored taper.

6.4.1.7. Immune mediated events on study

In Study 208850 examining GSK3745417 in participants with advanced solid organ tumors, one case of immune-mediated perimyocarditis has been observed, with a likely causal relationship to GSK3745417. Participants with new cardiac or respiratory symptoms should be assessed for potential pericarditis or myocarditis, with cardiology consult and cardiac imaging as clinically indicated. Other immune-mediated events may be a potential risk of GSK3745417 based on the anticipated pharmacology.

Table 12 Dose Modification and Toxicity Management Guidelines for Immune Related- Aes

General instructions: 1. Corticosteroid taper may be initiated upon AE improving to Grade 1 or less as per investigator judgement and institutional treatment guidelines 2. For severe and life-threatening irAEs, IV corticosteroid should be initiated first followed by oral steroid. Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids.				
Immune-related Aes	**Toxicity grade or conditions (CTCAEv5.0)**	**Action taken±**	**irAE management with corticosteroid and/or other therapies**	**Monitor and follow-up**
Pneumonitis	Grade 2	Restart dosing when toxicity resolves to Grade 0-1. If Grade 2 recurs, permanently discontinue.	• Administer corticosteroids (initial dose of 1-2 mg/kg methylprednisolone or equivalent) followed by taper	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment • Add prophylactic antibiotics for opportunistic infections
	Grade 3 or 4, or recurrent grade 2	Permanently discontinue		
Diarrhea / colitis	Grade 2 or 3	Restart dosing when toxicity resolves to Grade 0-1.	• Administer corticosteroids (initial dose of 1-2 mg/kg methylprednisolone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (i.e., diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (i.e., peritoneal signs and ileus). • Participants with ≥ Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis. • Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
	Grade 4	Permanently discontinue		
AST / ALT elevation or increased bilirubin	Grade 2	Restart dosing when toxicity resolves to Grade 0-1.	• Administer corticosteroids (initial dose of 0.5- 1 mg/kg methylprednisolone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable • See Section 10.7 for additional details on Liver Event Follow-Up Assessments
	Grade 3 or 4	Permanently discontinue[3]	• Administer corticosteroids (initial dose of 1-2 mg/kg methylprednisolone or equivalent) followed by taper	
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	Grade 3-4 hyperglycemia or T1DM (associated with	Restart dosing in appropriately managed, clinically and metabolically stable patients; insulin replacement therapy is required.	• Initiate insulin replacement therapy for participants with T1DM • Administer antihyperglycemic in participants with hyperglycemia	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes.

General instructions:
1. Corticosteroid taper may be initiated upon AE improving to Grade 1 or less as per investigator judgement and institutional treatment guidelines
2. For severe and life-threatening irAEs, IV corticosteroid should be initiated first followed by oral steroid. Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids.

Immune-related Aes	Toxicity grade or conditions (CTCAEv5.0)	Action taken±	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
	metabolic acidosis or ketonuria)β			
Hypophysitis	Grade 2 or 3	For Grade 2-3, hold until administration of hormonal therapy results in return to adequate hormone levels based on laboratory values and restart dosing when toxicity resolves to Grade 0-1. For recurrence or worsening of ≥ Grade 2 hypophysitis after steroid taper has been completed and patient is on adequate hormone replacement therapy, permanently discontinue.	• Administer corticosteroids and initiate hormonal replacements as clinically indicated.	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 4	Permanently discontinue		
Hyperthyroidism	Grade 3	Hold until administration of hormonal therapy results in return to adequate hormone levels based on laboratory values and restart dosing when toxicity resolves to Grade 0-1.	• Treat with non-selective beta-blockers (e.g., propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders.
	Grade 4	Permanently discontinue[1]		
Hypothyroidism	Grade 2-4	Grade 3: Hold until administration of hormonal therapy results in return to adequate hormone levels based on laboratory values and restart dosing when toxicity resolves to Grade 0-1.	• Initiate thyroid replacement hormones (e.g., levothyroxine or liothyroinine) per standard of care	• Monitor for signs and symptoms of thyroid disorders. • Monitor TFTs • Ensure adequate evaluation (eg., endocrine consultation) • Exclude concomitant adrenal insufficiency (AM cortisol level)
	Grade 3-4	Grade 4: Permanently discontinue		
Myocarditis or pericarditis	Grade 1 or 2	Withhold. Seek cardiology consult. Ensure complete resolution after steroid treatment before considering re-start of GSK3745417 depending on benefit/risk of further study drug	• Based on severity of AE administer corticosteroids. Consider high dose steroids with slow taper, as per cardiology advice / institutional guidelines for myocarditis. • Treat until cardiac function returns to baseline	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		

General instructions:
1. Corticosteroid taper may be initiated upon AE improving to Grade 1 or less as per investigator judgement and institutional treatment guidelines
2. For severe and life-threatening irAEs, IV corticosteroid should be initiated first followed by oral steroid. Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids.

Immune-related Aes	**Toxicity grade or conditions (CTCAEv5.0)**	**Action taken±**	**irAE management with corticosteroid and/or other therapies**	**Monitor and follow-up**
Adrenal insufficiency	Grade 2 or 3	Hold until administration of hormonal therapy results in return to adequate hormone levels based on laboratory values and restart dosing when toxicity resolves to Grade 0-1. For recurrent or worsening ≥ Grade 2 adrenal insufficiency while adequate hormonal replacement is continuing, permanently discontinue study drug.	• Start treatment with corticosteroids before other hormone replacement to avoid adrenal crisis (hydrocortisone slowly titrating doses down according to symptoms OR prednisone and fludrocortisone titrating up or down based on BP, other symptoms, and labs); patient with severe symptoms may require additional fluids (e.g., saline >2 L).	• Monitor for cortisol level (AM), comprehensive metabolic panel (Na, K, CO^2, glucose) and renin.
	Grade 4	Permanently discontinue		
Uveitis	Grade 2	Withhold	• Urgent ophthalmology consultation • Administer treatment with ophthalmic and systemic prednisone/methylprednisolone	• Ensure adequate evaluation (e.g., urgent ophthalmology consultation)
Immune-related Encephalitis	Any grade	Permanently discontinue	• Consider IV acyclovir until PCR results obtained • Trial with methylprednisolone; if severe, treatment with methylprednisolone • If positive for autoimmune encephalopathy antibody or no improvement after 7-14 days, consider rituximab	• Ensure adequate evaluation to confirm etiology and/or exclude other causes.
Rash	Grade 3	Withhold	• Treat with high potency topical steroids to affected areas • Treat with prednisone	• Ensure adequate evaluation (eg., urgent dermatology consultation) to confirm etiology and/or exclude other causes.
	Grade 4	Permanently discontinue		
Renal failure or nephritis	Grade 2	Restart dosing when toxicity resolves to Grade 0-1.	• Start treatment with prednisone; if persistent G2 beyond 1 week, prednisone/methylprednisone	• Monitor participants for signs and symptoms, including monitoring of creatinine and urine protein every 3-7 days. • Ensure adequate evaluation (eg., nephrology consultation) to confirm etiology and/or exclude other causes.

General instructions:

1. Corticosteroid taper may be initiated upon AE improving to Grade 1 or less as per investigator judgement and institutional treatment guidelines
2. For severe and life-threatening irAEs, IV corticosteroid should be initiated first followed by oral steroid. Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids.

Immune-related Aes	**Toxicity grade or conditions (CTCAEv5.0)**	**Action taken±**	**irAE management with corticosteroid and/or other therapies**	**Monitor and follow-up**
	Grade 3 or 4	Permanently discontinue	• Start treatment with prednisone; if persistent G2 beyond 1 week, prednisone/methylprednisone • Consider adding one of the following after 1 week of steroids: azathioprine, cyclosporine, cyclophosphamide, infliximab, mycophenolate	• Ensure adequate evaluation (eg., nephrology consultation, renal biopsy) to confirm etiology and/or exclude other causes. • Consider inpatient care
Recurrence of Aes after resolution to ≤Grade 1	Grade 1 or 2	Withhold	• Based on severity of Aes, administer appropriate treatment until symptoms improve to ≤Grade 2	
	Grade 3 or 4	Permanently discontinue		

NOTES:

1. The decision whether to withhold or permanently discontinue GSK3745417 is at the discretion of the investigator or treating physician.
2. For participants with Grade 3 or 4 immune-related endocrinopathy where interruption of GSK3745417 is required, treatment with GSK3745417 may be resumed when the event resolves to Grade ≤2 and is controlled with hormonal replacement therapy or, for T1DM, metabolic control has been achieved.

6.5. Continued Access to Study Intervention after the End of the Study

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

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

6.6. Treatment of Overdose

For this study, any dose of GSK3745417 greater than 50% within a 24-hour period will be considered an overdose.

GSK does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator/treating physician should:

1. Contact the Medical Monitor immediately.

2. Closely monitor the participant for AE/SAE, vital signs, and laboratory abnormalities for at least 24 hours, and longer if clinically indicated or recommended by the medical monitor based on safety data obtained from the study

3. Obtain a blood sample for PK analysis as soon as possible following the study intervention if requested by the Medical Monitor (determined on a case-by-case basis)

4. Document the quantity of the excess dose as well as the duration of the overdosing in the CRF.

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

6.7. Concomitant Therapy

6.7.1. Permitted Medications

Participants considered to have an increased risk of thrombosis (e.g., history of catheter related clots, DVT) can be considered for prophylactic anticoagulation per local practice and/or clinical judgement.

Prophylaxis for CRS is not mandated. However, if a participant has CRS, prophylaxis with antihistamines and paracetamol /acetaminophen is permitted on subsequent infusions. NSAIDs for fever or symptoms control should be avoided due to risk of renal injury.

Participants receiving hormonal therapy for a definitively treated malignancy (e.g., adjuvant therapy of localized breast or prostate cancer) may continue to receive therapy during study, after discussion with the medical monitor.

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

6.5.2. Prohibited Medications and Non-Drug Therapies

The following medications are prohibited before the first dose of study treatment (see Section 5.2 for specific time requirements) and while on treatment in this study:

- Any investigational drug(s)
- Other anticancer therapy (chemotherapy, radiation therapy [unless administered palliatively], immunotherapy, biologic therapy, or hormone therapy other than for replacement).
    - Note: participants receiving hormonal therapy for a definitively treated malignancy (e.g., adjuvant therapy of localized breast or prostate cancer) may continue to receive therapy during study, after discussion with the medical monitor.
- Live vaccines or live attenuated vaccines including herpes zoster, nasal flu, and coronavirus vaccines, as well as recombinant human or non-human primate adenoviral vector vaccines.

Concomitant administration of drugs that are sensitive substrates or narrow therapeutic range substrates for cytochrome p450 (CYP) 3A4 enzyme, P-gp, BCRP, OATP1B1 and OATP1B3 transporter, and moderate to strong inducers and inhibitors of CYP3A4, P-gp, OATP1B1 and OATP1B3 should be excluded during the study and for 7 days prior to and following treatment with GSK3745417 (14 days for itraconazole),. Note: any medications (including antibacterials, antifungals, and antivirals) which are necessary for the health, wellbeing, or standard clinical care of patients with hematologic malignancies are exempt from this restriction. Any medications potentially interacting with GSK3745417 will require a pause in GSK3745417 dosing unless allowed through consultation with the Sponsor. Refer to the Study Reference Manual for a detailed list of excluded drugs.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

In some instances, it may be necessary for a participant to permanently discontinue study intervention. If study intervention is permanently discontinued, the participant will remain in the study to be evaluated for disease status / progression and survival. See the SOA for data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed.

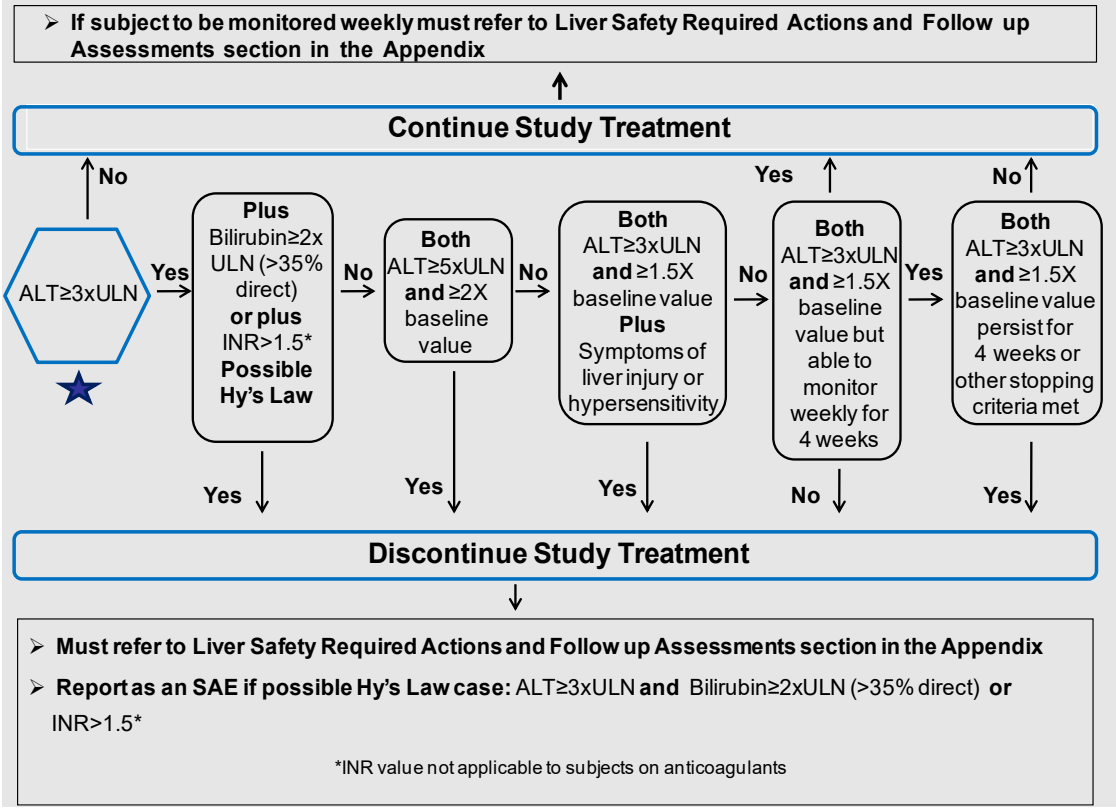
7.1. Discontinuation of Study Intervention

7.1.1. Liver Chemistry Stopping Criteria

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

Discontinuation of study intervention for abnormal liver tests is required when a participant meets one of the conditions outlined in Figure 6.

Figure 6 Liver Stopping and Monitoring Event Algorithm



Refer to Section 10.7 for required Liver Safety Actions and Follow up Assessments and for required process for study intervention restart/rechallenge if considered for the participant.

7.1.2. Renal Stopping and Increased Monitoring Guidelines

Renal events are to be managed as outlined in Table 13.

Table 13 Guidelines for Dose Modification and Management of Renal Events

Adverse Event	Management
Serum Creatinine Increase by >0.3 mg/dL or 26.5 μmol/L Compared to Baseline	• Hold Study Treatment unless considered related to TLS (see Section 6.4.1.2) • Repeat serum creatinine levels at least every 24 hours, monitor urine output • Perform diagnostics to identify root cause • Nephrology consultation is highly recommended • Discuss with Sponsor/Medical Monitor if considering resuming study drug treatment after initial hold • If serum creatinine is Grade 2 or higher for more than 7 days without a known cause, permanently discontinue treatment (unless continued dosing is approved by Medical Monitor) • If renal injury is considered secondary to TLS (for example, an increase in creatinine in association with increasing blood phosphate and uric acid levels), treatment may be continued (without hold) with the agreement of the Medical Monitor. In such cases, consider close monitoring of urine output and urinary pH, and early nephrology consultation
Abnormal urinalysis findings, including hematuria	• Perform diagnostics to identify root cause • Consider holding study treatment (though patients with abnormal findings consistent with TLS such as urate crystals may continue dosing as agreed by investigator and Medical Monitor) • Nephrology consultation is highly recommended if cause is not known

7.1.3. QTc Stopping Criteria

The QTcF correction formula will be used for *each individual participant* to determine eligibility for and discontinuation from the study. This formula may not be changed or substituted once the participant has been enrolled. If an ECG demonstrates a prolonged QTcF interval, then obtain 2 more ECGs over a brief period and then use the averaged QTcF values of the 3 ECGs to determine whether the participant should be discontinued from the study.

If a participant meets either of the following criteria, they must be discontinued from study treatment.

- QTcF >500 msec

OR

- Change from baseline of QTcF >60 msec

For participants with underlying **bundle branch block**, proceed with the following discontinuation criteria:

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

QTcF = QT duration corrected for heart rate by Fridericia's formula

If a clinically significant finding is identified (including, but not limited to changes from baseline in QT interval corrected using [Bazett's formula [QTcB] or Fridericia's formula [QTcF]]) after enrollment, the investigator or qualified designee will determine if the participant can continue in the study and if any change in participant management is needed. This review of the ECG printed at the time of collection must be documented. Any new clinically relevant finding should be reported as an AE.

7.1.4. Temporary Discontinuation

Please refer to Section 7.1.5 for information on rechallenge following a liver stopping event.

7.1.5. Rechallenge

7.1.5.1. Study Intervention Restart After Liver Stopping Criteria Met

Study intervention restart after liver chemistry stopping criteria are met is allowed in this study. Study intervention rechallenge after liver chemistry stopping criteria are met by any participant in this study is not allowed.
If participant meets liver chemistry stopping criteria, do not restart participant with study intervention unless:

- GSK Medical Governance approval **is granted**
- Ethics and/or IRB approval is obtained, if required, and
- Separate consent for intervention restart is signed by the participant and participant is informed of any associated risks Refer to Appendix 7 for details on restart process.

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

7.1.5.2. Study Intervention Restart When Renal Toxicity Stopping Criteria Met

If the patient meets renal toxicity stopping criteria (serum creatinine is Grade ≥2 for >7 days without a known cause), permanently discontinue treatment unless the benefits of therapy outweigh the risk of rechallenge in the opinion of the investigator, the Medical Monitor, as well as GSK medical governance. In this situation, rechallenge may be permitted.

7.1.5.3. Study Intervention Restart When QTc Stopping Criteria Met

- If the patient meets the QTc stopping criteria, patient should not be rechallenged.

7.2. Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, or compliance reasons. This is expected to be uncommon.

- At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA. See the SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

7.3. Lost to Follow-Up

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

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study.

- Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.

- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

- Site personnel, or an independent third party, will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants randomized, including those who did not get study intervention. Public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented, and the participant will not be considered lost

to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.

Discontinuation of specific sites or of the study are handled as part of Appendix 1.

8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA.
- Protocol waivers or exemptions are not allowed
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and was performed within the time frame defined in the SoA.
- The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed 275 mL in a 4-week period.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1. Efficacy Assessments

Bone marrow biopsies for response assessments will be performed as outlined in the SoA tables. Participants will have responses graded per IWG criteria, as described in Appendix 8. Note that for clear cases of progression (e.g., emergence of blasts in the peripheral blood) that bone marrow biopsy may not be needed to document progression.

Participants will be followed every 12 weeks (±2 weeks) for survival and subsequent anticancer therapy. The survival follow-up visit will commence after discontinuation of study intervention.

8.2. Safety Assessments

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

8.2.1. Physical Examinations

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

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

8.2.2. Performance Status

The performance status will be assessed using the ECOG scale in Section 10.10 at the timepoints specified in the SoA.

8.2.3. Vital Signs

- Vital sign measurements to be measured, in a consistent fashion, per institutional standard (e.g., in a seated or semi-supine position after 5 minutes rest), will include temperature, systolic and diastolic blood pressure, pulse rate, and respiratory rate.
- In case of an abnormal first reading, three readings of blood pressure and pulse rate should be taken and averaged to give the measurement to be recorded in the CRF.
- Vital signs will be measured more frequently if warranted by clinical condition of the participant.

Refer to the SRM for further details.

8.2.4. Electrocardiograms

Triplicate 12-lead ECG will be obtained as outlined in the SoA (see Section 1.3) using an ECG machine that automatically or manually calculates the heart rate and measures PR, QRS, QT, and QTc intervals. Refer to Section 7.1.2 for QTc withdrawal criteria and additional QTc readings that may be necessary.

8.2.5. Holter Monitoring

Digital Holter ECG data will be obtained from 12-lead continuous Holter monitoring device supplied by the Sponsor. ECG acquisition via the Holter monitoring device will be performed (Section 1.3) and may be waived for individual participants upon approval from GSK.

Analysis of intervals and morphology from the continuous digital ECG data will be acquired and stored electronically and may be manually over-read by an external central validated ECG laboratory.

Refer to the Study Reference Manual (SRM) for details regarding Holter monitoring procedures.

8.2.6. Clinical Safety Laboratory Assessments

- See Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.
- The investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory reports must be filed with the source documents.
- Abnormal laboratory findings associated with the underlying disease are not considered clinically significant, unless judged by the investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 30 days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered significantly abnormal by the investigator or medical monitor.
    - If clinically significant values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified, and the sponsor notified.
- All protocol-required laboratory tests, as defined in Section 10.2, must be conducted in accordance with the laboratory manual and the SoA (Section 1.3).
- If laboratory values from non-protocol specified laboratory tests performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification), then the results must be recorded.

8.2.7. Pregnancy Testing

- Refer to Section 5.1 for pregnancy testing entry criteria.
- Pregnancy testing (urine or serum as required by local regulations) should be conducted at monthly intervals during study intervention period.
- Pregnancy testing (urine or serum as required by local regulations) should be conducted at the end of relevant systemic exposure plus an additional 30 days and correspond with the time frame for female participant contraception in Section 5.1.
- Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the participant's participation in the study.

8.3. Adverse Events (AEs), Serious Adverse Events (SAEs) and Other Safety Reporting

The definitions of adverse events (AE) or serious adverse events (SAEs) can be found in Section 10.3.

The definitions of unsolicited and solicited AEs can be found in Section 10.3.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

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

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 10.3.

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

- All SAEs will be collected from the signing of the informed consent form (ICF) OR start of intervention until the follow-up visit at the time points specified in the SoA (Section 1.3). However, any SAEs assessed as related to study participation (e.g., study intervention, protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product will be recorded from the time a participant consents to participate in the study.

- All AEs will be collected from the signing of the ICF OR start of intervention until the follow-up visit at the time points specified in the SoA (Section 1.3).

- Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded as Medical History/Current Medical Conditions not as AEs.

- All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

- Investigators are not obligated to actively seek information on AEs or SAEs after the conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.3.2. Method of Detecting AEs and SAEs

- Care will be taken not to introduce bias when detecting AE and/or SAE. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, and non-serious AEs of special interest (as defined in Section 8.3.8]), will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is given in Appendix 3.

8.3.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.

- An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

8.3.5. Pregnancy

- Details of all pregnancies in female participants and, if indicated, female partners of male participants will be collected after the start of study intervention and until time for reporting pregnancies should align with the time for post-intervention contraception determined in Section 5.1.

- If a pregnancy is reported, the investigator will record pregnancy information on the appropriate form and submit it to GSK within 24 hours of learning of the female participant or female partner of male participant (after obtaining the necessary signed informed consent from the female partner) pregnancy. 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.

- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.

- The participant/pregnant female partner will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant/pregnant female partner and the neonate, and the information will be forwarded to the sponsor.

- Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.3.4. While the investigator is not obligated to actively seek this information in former study participants /pregnant female partner, he or she may learn of an SAE through spontaneous reporting.

- Any female participant who becomes pregnant while participating in the study will discontinue study intervention or be withdrawn from the study OR may request continuation of study intervention.

Prior to continuation of study intervention following pregnancy, the following must occur:

The sponsor and the relevant IRB/IEC give written approval.

The participant gives signed informed consent.

The investigator agrees to monitor the outcome of the pregnancy and the status of the participant and her offspring.

8.3.6. Cardiovascular and Death Events

For any cardiovascular events and all deaths, whether they are considered SAEs, specific Cardiovascular (CV) and Death sections of the CRF will be required to be completed. These sections include questions regarding cardiovascular (including sudden cardiac death) and non-cardiovascular death.

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

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

8.3.7. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as SAEs

The following disease related events (DREs) are common in participants with AML and can be serious/life threatening:

- Disease Progression

Disease progression does not need to be reported as a serious adverse event (SAE). Death due to disease under study is to be recorded on the Death form of the electronic case report form (eCRF). Because these events are typically associated with the disease under study, they will not be reported according to the standard process for expedited reporting of SAEs to GSK (even though the event may meet the definition of an SAE). These events will be recorded within 7 days and monitored by the GSK study team.

Note: However, if either of the following conditions apply, then the event must be recorded and reported as an AE/SAE (instead of a DRE):

- The event is, in the investigator's opinion, of greater intensity, frequency, or duration than expected for the individual participant,

  OR

- The investigator considers that there is a reasonable possibility that the event was related to intervention with the investigational product

8.3.8. Adverse Events of Special Interest

Adverse events of special interest designated in this protocol include events that may be immune-related or related to CRS or TLS. AESIs must be reported to the GSK medical monitor within 24 hours regardless of relationship to study treatment. The severity of AEs will be graded utilizing the NCI-CTCAE, version 5.0. Guidelines for dose modifications and interruptions for management of common toxicities associated with the study treatment are provided in Section 6.4. Please also refer to Appendix 4 for AEs of special interest.

8.4. Pharmacokinetics

Blood samples of approximately 2 mL will be collected for measurement of plasma concentrations of GSK3745417 as specified in the SoA (Section 1.3).

- A maximum of 10 samples may be collected at additional time points during the study if warranted and agreed upon between the investigator and the sponsor. The timing of sampling may be altered during the study based on newly available data to ensure appropriate monitoring.

- Instructions for the collection and handling of biological samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

- Samples will be used to evaluate the PK of GSK3745417. Each plasma sample will be divided into 2 aliquots (1 each for [PK, other analyses, and a back-up]). Samples collected for analyses of GSK3745417 plasma concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.
- CCI [redacted]
- Plasma samples may be analyzed for other compound-related metabolites and the results reported under a separate DMPK, GlaxoSmithKline protocol.
- Details on PK blood sample collection, processing, storage, and shipping procedures are provided in the SRM.

8.5. Genetics and Pharmacogenomics

CCI [redacted]

8.6. Biomarkers

CCI [redacted]

CCI

[redacted]

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

With respect to the primary objectives and endpoints of Part 1 and the maintenance dosing of Part 2, no specific statistical hypotheses are being tested. The primary focus of Part 1 and maintenance dosing of Part 2 will be on determining the RP2D for both induction and maintenance for further exploration based upon the safety, PK, and anticancer activity profiles of GSK3745417 alone.

The primary efficacy objective of the expansion cohort in Part 2 is to demonstrate that GSK3745417 is clinically active at the proposed induction RP2D(s) in participants with R/R AML and separately in participants with HR-MDS.

Specifically, the first half of Part 2 is designed to provide evidence with regards to ORR to support the null hypothesis:

H_0: $p \leq 10\%$

or to reject it in favor of the alternative hypothesis:

H_A: $p \geq 30\%$

where p is the overall response rate.

9.2. Sample Size Determination

Approximately 72 participants will 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 will be recruited.

Part 1:

To complete dose escalation, it is estimated that up to approximately 22 participants will be enrolled in Part 1, assuming scenario 2 (described below) is most likely to occur.

Dose escalation for Part 1 will use the N-CRM. This method utilizes a 2-parameter logistic model, with parameters α and β, to describe the relationship between DLT and dose. The N-CRM estimates, for each potential dose, the posterior probabilities that the DLT rate lies in each of 4 toxicity intervals:

- [0%,16%)=Underdosing range;
- [16%,33%)=Target toxicity range;
- [33%,50%)=Excessive toxicity range;
- [50%,100%)=Unacceptable toxicity range.

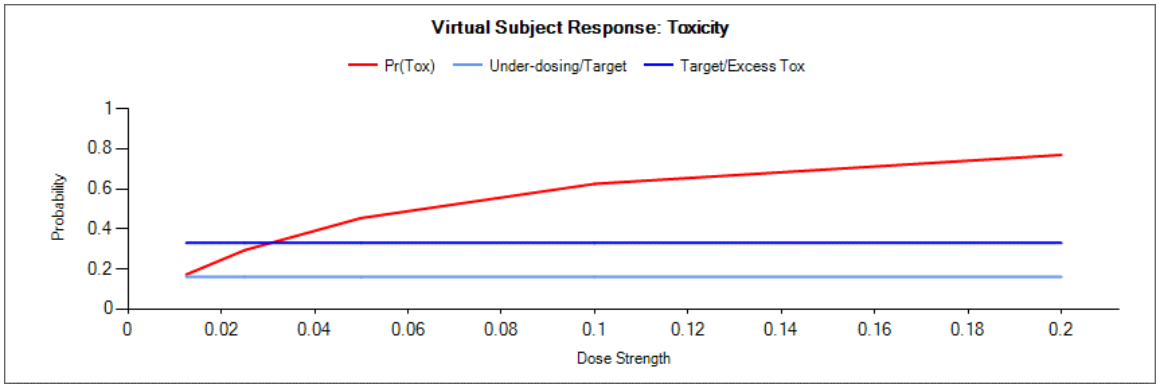
The following dose levels were used in statistical simulations: 12.5, 25, 50, 100, 200 µg. The proposed doses of GSK3745417 may be adjusted, as appropriate, based on the safety, tolerability, and PK data obtained in preceding cohorts.

The N-CRM uses a Bayesian framework where the parameters α and β are assumed to have a bivariate normal prior distribution. Using Fixed and Adaptive Clinical Trial Simulator (FACTS) software (version 6.1; Berry Consultants [Austin, TX]), the parameters (mean [standard deviation {SD}]) of the bivariate normal prior for (α, ln(β)) were derived. The parameters (SD) of the explicit distribution are α = -1.7907 (1.6787), ln(β) = 0.1961 (0.1706), and ρ = -0.7729 where α and ln(β) are distributed as bivariate normal with correlation ρ.

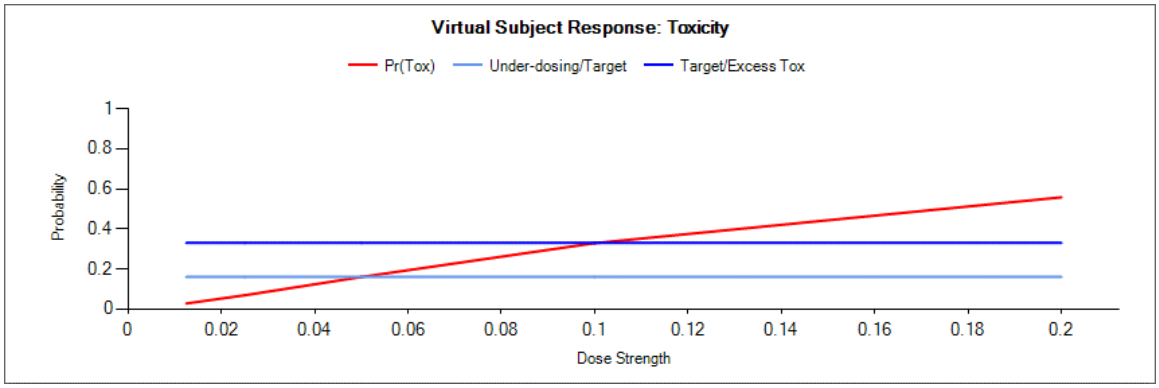
Simulations were conducted to determine the average sample size and percentage of times each dose would be selected under three different scenarios, assuming the projected dose levels and N-CRM dose recommendations are followed. Simulations assumed cohorts of three participants would be enrolled starting with dose level 1. Three scenarios were considered for this simulation: scenario 1 (low-dose DLT) representing target toxicity at relatively low dose(s); scenario 2 (mid-dose DLT) representing target toxicity at intermediate dose(s); scenario 3 (high-dose DLT) representing target toxicity at relatively high dose(s). The toxicity curves for these three scenarios are shown in Figure 7.

Figure 7 Dose Toxicity Scenarios (with dose strength shown in units of mg)

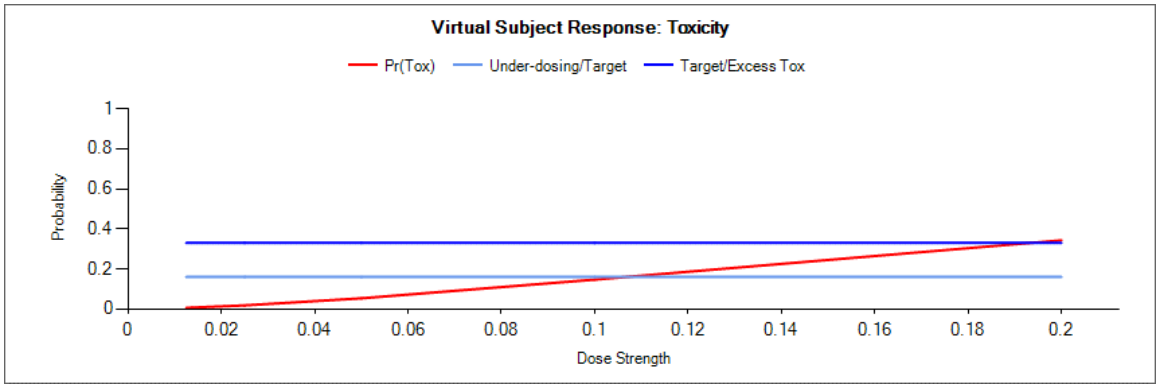
Low-dose DLT



Mid-dose DLT



High-dose DLT



For each scenario, 10000 clinical trials were simulated. The average sample sizes over the 10000 clinical trials simulated under the three scenarios were 14, 20, 22, respectively.

Details of the simulation results are provided in Table 14. For the simulations, the selected reference dose was the median (0.05 mg).

Table 14 Summary of Simulation Results

Scenario	% of Trials Selecting Correct Dose(s) as MTD	% of Trials Selecting Underestimating MTD	% of Trials Selecting Overestimating MTD	Average Sample Size
Low-dose DLT	92.69%	-	2.88%	~14
Mid-dose DLT	85.72%	13.76%	0.52%	~20
High-dose DLT	87.01%	12.99%	-	~22

Maximum Tolerated Dose: The MTD will be defined as the dose that has the highest probability of having a DLT rate within the target toxicity interval, and for which the probability that the DLT rate lies within the excessive toxicity, or the unacceptable toxicity window is less than 25%. The DLT observation period will be 28 days.

Part 2:

Approximately 50 participants will be recruited for Part 2, 25 AML participants and 25 HR-MDS participants. Part 2 cohort expansion is designed based on predictive probability methodology of Lee and Liu (Lee, 2008). A test that the overall response rate [ORR] (p) is less than or equal to the null hypothesis rate versus the response rate is greater than or equal to the alternative rate is being performed separately in each indication using the stopping rules shown in Table 15.

For Part 2 the hypotheses in terms of overall response rate (p) are detailed below.

The null hypothesis is:

H_0: $p \leq 10\%$

The alternative hypothesis is:

H_A: $p \geq 30\%$

The null hypothesis of p=10% was specified given low likelihood of response following failure of standard therapies. The alternative hypothesis of p≥30% was specified to ensure robust evidence for efficacy to support advancement of a novel drug.

GSK3745417 will be evaluated for efficacy in approximately 13 to 25 participants with AML and separately in 13 to 25 HR-MDS participants in the expansion cohorts.

The futility evaluation will occur after 13 participants have completed induction and allow for a maximum number of 25 participants. This design will have a type I error rate (α) of 0.09 and a power of 0.88. A cohort (AML and/or MDS) can be terminated early for futility if the predictive posterior probability of the response rate greater than the null hypothesis of 10% being above 80% is very low, i.e., below 10% (θL) for this design. The type I error rate and power were derived by explicitly stating null and alternative

hypotheses of response rate, the minimum and maximum sample size, boundaries of predictive probability for futility criteria and the selection of the optimizing criterion as the maximization of power under the alternative hypothesis. The Bayesian prior used in determining the design was Beta (0.01, 0.09), a distribution with a mean response rate of 10%. Under the null hypothesis, that is, if the true response rate is less than 10%, the expected sample size of the design is 17.5 participants per cohort and probability of early termination is 62.1%. Under the alternative hypothesis, that is, if the true response rate is at least 30%, the expected sample size of the design is 24.2 participants and probability of early termination is 6.4%.

Table 15 Stopping Rules for Part 2 Cohort Expansion

Number of Evaluable Participants[a]	Stop for Futility if No. of Responders Less Than or Equal to This Number[b]
13	1
25	4

a. Evaluable participants for response assessment are defined by any or all of the following criteria:
   - Participants who have at least one post-baseline disease assessment.
   - Participants who have progressed or have died or have withdrawn from study treatment due to any reason.

b. The specific criteria for stopping an expansion cohort due to futility. For instance, if 13 participants are enrolled, then the cohort may be stopped for futility if number of Responders ≤1.
   Note: These rules will be applied to both AML and HR-MDS cohorts in Part 2.

Enrollment into AML and/or HR-MDS cohorts in Part 2 may be stopped according to the rules in Table 15 once all enrolled participants in the expansion cohort have met criteria for evaluability (as defined in the footnote to Table 15) after induction. The futility stopping rules are intended as a guideline only. Actual decisions will depend on the totality of the data.

Up to 18 of these (AML and HR MDS) participants who respond to induction will continue to maintenance dosing. The maintenance dosing schedule will be determined based on data from the FTIH 208850 study. If enrollment into one of the cohorts (AML or HR MDS) is stopped early, additional participants in the other cohort may be enrolled to have a sufficient number of participants for maintenance dosing evaluation. Fewer doses in maintenance therapy are expected to be studied for dose escalation; therefore, the modified Toxicity Probability Interval (mTPI) procedure (Ji, 2013) (and not N-CRM) will be used to identify the MTD of GSK3745417 during maintenance dosing after 2 to 3 cycles of daily dosing at the induction MTD determined from Part 1. Part 2 will evaluate 3 increasing dose levels starting at the MTD determined from Part 1. The DLT period for Part 2 will be 28 days starting at Day 1 of each cycle. Dose escalation will target 3 participants up to a target maximum of 6 at each dose level. Dose escalation will proceed until the MTD for GSK3745417 in maintenance dosing is determined.

The rules guiding dose escalation based on the mTPI procedure are provided in Figure 8. Columns provide the number of participants treated at the current dose level, and rows provide the corresponding numbers of participants experiencing toxicity. The recommended decision (E = escalate to next higher dose, S = stay at current dose, D = de-escalate, DU = unacceptably toxic dose) is determined by taking the row showing the total number of participants with DLT at the current dose and finding the cell that

corresponds to the column showing total number of participants in the current dose level. For example, when one of three participants experiences a DLT at the current dose, the decision can be located at row indicating 1 and column indicating 3, which is S (to stay at the current dose level). All dose escalation decisions will be assessed by the GSK study team and investigators.

Figure 8 Dose Finding Spreadsheet of the Modified Toxicity Probability Interval (mTPI) Method

Number of dose limiting toxicities (DLT's)	Number of patients treated at current dose														
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
0	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E
1	D	S	S	S	S	E	E	E	E	E	E	E	E	E	E
2		DU	D	S	S	S	S	S	S	S	E	E	E	E	E
3			DU	DU	D	S	S	S	S	S	S	S	S	S	S
4				DU	DU	DU	D	D	S	S	S	S	S	S	S
5					DU	DU	DU	DU	DU	D	S	S	S	S	S
6						DU	DU	DU	DU	DU	DU	D	S	S	S
7							DU	DU	DU	DU	DU	DU	DU	D	S
8								DU	DU	DU	DU	DU	DU	DU	DU
9									DU	DU	DU	DU	DU	DU	DU
10										DU	DU	DU	DU	DU	DU
11											DU	DU	DU	DU	DU
12												DU	DU	DU	DU
13													DU	DU	DU
14														DU	DU
15															DU

E = Escalate to the next higher dose
S = Stay at the current dose
D = De-escalate to the next lower dose
U = The current dose is unacceptably toxic
MTD = 30%
Sample Size = 15
Epsilon1 = 0.05

The spreadsheet was generated based on a beta/binomial model and precalculated before trial initiation. The letters in different colors are computed based on the decision rules under the mTPI method and represent different dose-finding actions. In addition to actions de-escalate the dose (D), stay at the same dose (S), and escalate the dose (E), the table includes action unacceptable toxicity (DU), which is defined as the execution of the dose-exclusion rule in mTPI.

9.3. Analysis Sets

For purposes of analysis, the following populations are defined:

Population	Description	Analyses Evaluated
All screened	All participants who sign the ICF to participate in the clinical study. Participants in this population will be used for the screen failure summary.	Study Population
Safety	All participants who take at least 1 dose of study intervention. Participants will be analyzed 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.	Summary/Listing of Dose-Limiting Toxicities during the Determinative Period
PK population	All participants from the safety population for whom a PK sample is obtained and analyzed.	PK
PD population	All participants who contribute a predose and at least one on-treatment PD/biomarker sample(s).	PD

9.4. Statistical Analyses

The statistical analysis plan (SAP) will be finalized prior to FSFV and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

Data will be listed and summarized according to the GSK reporting standards, where applicable. Complete details will be documented in the SAP. Any deviations from, or additions to, the original analysis plan described in this protocol will be documented in the SAP and clinical study report (CSR).

9.4.1. Efficacy Analyses

The safety population will be used for anticancer activity analyses. Since this is a Phase 1 study, anticancer activity will be evaluated based on clinical evidence and response criteria.

Overall response rate (ORR) for AML is defined as the percentage of participants with a complete remission (CR), CRp, CRi, or a partial remission (PR) as per response criteria for AML (Cheson, 2003) and HR MDS (Cheson, 2006), respectively. Participants with unknown or missing response will be included in the denominator when calculating the percentage.

The estimate of ORR along with 95% exact confidence interval (CI) will be provided.

Duration of response (DOR) for AML is defined as the time from first evidence of response to earlier date of disease progression or death due to any cause, for participants with a complete remission (CR), CRp, CRi, or a partial remission (PR) as per response criteria for acute myeloid leukemia. Participants who have not progressed or died at the data cut-off, will be censored at the date of last adequate disease assessment. In addition, participants with an extended time without adequate assessment or who start a new anticancer therapy prior to a DOR event will be censored at the date of last adequate disease assessment (assessment where visit level response is CR, CRp, CRi, or PR) prior to the extended time without adequate assessment or initiation of new anti-cancer therapy, respectively. Further details on rules for censoring will be provided in the Statistical Analysis Plan. DOR will be summarized using Kaplan-Meier quantile estimates along with 95% CIs.

Event-free survival (EFS) is defined as the time from first dose of study intervention to disease progression, failure to achieve CR, or relapse from CR, or death resulting from any cause, whichever occurs earliest. Participants who achieve induction treatment success and are alive and in remission at the data cut-off, will be censored at the date of last adequate disease assessment. In addition, participants with an extended time without adequate assessment or who start a new anticancer therapy prior to an EFS event will be censored at the date of last adequate disease assessment (assessment where visit level response is CR, CRp, CRi, PR, or SD) prior to the extended time without adequate assessment or initiation of new anti-cancer therapy, respectively. Further details on rules for censoring will be provided in the SAP. The milestone EFS at 6 months will be summarized using Kaplan-Meier quantile estimates along with 95% CIs.

9.4.2. Safety Analyses

The safety population will be used for the analysis of safety data. All serially collected safety endpoints (e.g., laboratory tests, vital signs, ECGs) will be summarized according to the scheduled, nominal visit at which they were collected and across all on-treatment time points using a “worst-case” analysis. Complete details of the safety analyses will be provided in the SAP.

9.4.2.1. Extent of Exposure

The number of participants administered study intervention will be summarized according to the duration of therapy.

9.4.2.2. Adverse Events

AEs will be coded using the standard MedDRA and grouped by system organ class. AEs will be graded by the investigator according to the NCI-CTCAE (version 5.0). Events will be summarized with frequency and percentage by preferred term. Separate summaries will be provided for all AEs regardless of grade, treatment-related AEs, treatment-related AEs by maximum grade, serious adverse events (SAEs), treatment-related SAEs, AEs leading to discontinuation of study intervention, AEs leading to dose reductions and AEs leading to dose interruptions/delays. Details will be provided in the statistical analysis plan (SAP). Dose-limiting toxicities (DLTs) will be listed and summarized by dose cohort based on the DLT Evaluable Population. Any AEs

of special interest will be summarized as detailed in the SAP. The incidence of deaths and the primary cause of death will be summarized.

9.4.2.3. Clinical Laboratory Evaluations

Hematology and clinical chemistry data will be summarized using frequencies and proportions according to NCI-CTCAE v5. Laboratory test results outside the reference ranges that do not have associated NCI-CTCAE v5 criteria will be summarized using proportions. Further details will be provided in the SAP.

9.4.2.4. Other Safety Analyses

Data for vital signs and ECGs will be summarized based on predetermined criteria identified to be of potential clinical concern. Further details will be provided in the SAP.

9.4.3. Other Analyses

PK, PD, , and biomarker exploratory analyses will be described in the SAP. The population PK, PD, analyses may be presented separately from the main CSR.

9.4.3.1. Pharmacokinetic Analyses

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. The following PK parameters will be determined if data permit:
  - C_{max}
  - area under the plasma concentration-time curve ($AUC_{(0-t)}$, $AUC_{(0-\tau)}$, [repeat dosing] and/or $AUC_{(0-\infty)}$ [single dose])
  - apparent terminal phase elimination rate constant (λ_z)
  - apparent terminal phase half-life ($t_{1/2}$) (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.

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

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

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.

9.4.3.2. Pharmacokinetic/Pharmacodynamic Analyses

Data obtained from the pharmacodynamic samples may be descriptively and/or graphically summarized, CCI [redacted]. Results may be reported separately.

9.4.3.3. Exploratory Biomarker Analyses

CCI [redacted]

9.5. Interim Analysis

The primary driver for the dose-escalation decision(s) will be safety and tolerability of each dose cohort. For Part 1 induction and Part 2 maintenance, dose escalation and de-escalation decisions will be guided by an N-CRM model and mTPI, respectively. Predicted DLT rates will be provided with the aim of escalating to doses with small probability of excessive or unacceptable toxicity. Preliminary safety and available PK/PD data will be reviewed by the GSK study team and investigators after completion of each dose cohort. This review will support the decision on the dose level in the next dose cohort.

After the last cohort of participants completes the DLT observation period for induction in Part 1, a formal interim analysis will be performed to support the initiation of Part 2 and the recommended dose level for induction. Data considered to support these decisions will include, but are not limited to, safety, PK profile, PD, and observed signs of clinical activity. Details of the interim analysis will be provided in the SAP.

For Part 2, assessment of efficacy and safety will be performed after the first futility assessment based upon a minimum of 13 participants with available unconfirmed overall response data, separately for the AML and HR-MDS cohorts. If the stopping criteria for futility are met in either the AML or MDS cohort, further enrollment in that cohort may be stopped.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, IB, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IEC/IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC
  - Notifying the IRB/IEC of SAE or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations

10.1.2. Financial Disclosure

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

10.1.3. Informed Consent Process

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

The ICF contains a separate section that addresses the use of participant data and remaining samples for optional further research. The investigator or authorized designee will inform each participant of the possibility of further research not related to the study/disease. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a participant's agreement to allow any participant data and/or remaining specimens to be used for further research. Participants who decline further research will tick the corresponding “No” box in the ICF.

10.1.4. Data Protection

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

10.1.5. Committees Structure

Not applicable.

10.1.6. Dissemination of Clinical Study Data

- Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually agreeable location.
- GSK will also provide all investigators who participated in the study with a summary of the study results and will tell the investigators what treatment their participants received. The investigator(s) is/are encouraged to share the summary results with the study subjects, as appropriate.
- Under the framework of the SHARE initiative, GSK intends to make anonymized participant-level data from this trial available to external researchers for scientific analyses or to conduct further research that can help advance medical science or improve patient care. This helps ensure the data provided by trial participants are used to maximum effect in the creation of knowledge and understanding. Requests for access may be made through www.clinicalstudydatarequest.com.

10.1.7. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- Guidance on completion of CRFs will be provided in the eCRF Completion Guidelines.
- Quality tolerance limits (QTLs) will be pre-defined in the Data Quality Plan to identify systematic issues that can impact participant safety and/or reliability of study results. These pre-defined parameters will be monitored during and at the end of the study and all deviations from the QTLs and remedial actions taken will be summarized in the clinical study report.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy including definition of study critical data items and processes (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the study specific Monitoring Plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (e.g., Contract Research Organizations).

- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 25 years from the issue of the final Clinical Study Report (CSR)/ equivalent summary unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.1.8. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data, and its origin can be found in [Source Data Acknowledgment].
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.9. Study and Site Start and Closure

First Act of Recruitment

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the first site open and will be the study start date.

Study/Site Termination

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

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

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

For study termination:

- Discontinuation of further study intervention development

For site termination:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate or no recruitment of participants (evaluated after a reasonable amount of time) by the investigator
- If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the subject and should assure appropriate participant therapy and/or follow-up.

10.1.10. Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2. Appendix 2: Clinical Laboratory Tests

- All safety laboratory assessments, as defined in Section 1.3, will be performed by local laboratory unless otherwise noted.
- Additionally, if the local laboratory results are used to make either a study intervention decision or response evaluation, the results must be recorded.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 16 Protocol-Required Safety Laboratory Tests

Local Safety Laboratory Assessments			
Laboratory Assessments	**Parameters**		
Clinical Chemistry[1]	BUN[a] Creatinine Fasting Glucose eGFR	Potassium Sodium Calcium Total Protein Albumin	AST (SGOT) ALT (SGPT) Alkaline Phosphatase Total and direct bilirubin Lactate dehydrogenase (LDH) Phosphate, uric acid,
Thyroid Function	Thyroid Stimulating Hormone, free T4		
Cardiac Function	Troponin I or T		
Routine Urinalysis	Specific gravity pH, glucose, protein, blood, ketones by dipstick Microscopic examination (if blood or protein is abnormal)		
Other Screening Tests	Hepatitis B (HBsAg) Quantitative HBsAg Hepatitis C (Hep C antibody) Serum Pregnancy test (as needed for WOCBP)		
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit	RBC Indices: MCV MCH %Reticulocytes	WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils Myeloblasts (if present)
Central Safety Laboratory Assessments			
Coagulation	PTT, PT/NR, fibrinogen		
Cardiac Function	Troponin T		
Other	C-Reactive Protein		

a Required if local lab testing does not include BUN standards.

NOTES :

1. Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 7.1.1 and Appendix 7. All events of ALT ≥3 × upper limit of normal (ULN) and bilirubin ≥2 × ULN (>35% direct bilirubin) or ALT ≥3 × ULN and international normalized ratio (INR) >1.5, if INR measured, which may indicate severe liver injury (possible Hy's Law), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis).
2. If the local laboratory is unable to perform any assessment, the central laboratory may be utilized.

10.3. Appendix 3: AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

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

Definition of Unsolicited and Solicited AE
• An unsolicited adverse event is an adverse event that was not solicited using a Participant Diary and that is communicated by a participant who has signed the informed consent. Unsolicited AEs include serious and non-serious AEs. • Potential unsolicited AEs may be medically attended (i.e., symptoms or illnesses requiring a hospitalization, or emergency room visit, or visit to/by a health care provider). The participant will be instructed to contact the site as soon as possible to report medically attended event(s), as well as any events that, though not medically attended, are of participant's concern. Detailed information about reported unsolicited AEs will be collected by qualified site personnel and documented in the participant's records. • Unsolicited AEs that are not medically attended nor perceived as a concern by participant will be collected during interview with the participants and by review of available medical records at the next visit. • Solicited AEs are predefined local at the injection site and systemic events for which the participant is specifically questioned, and which are noted by the participant in their diary.

Events <u>Meeting</u> the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.

- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected intervention- intervention interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.
- "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

Events NOT Meeting the AE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed:
a. Results in death
b. Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization • In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AE. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. • Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
d. Results in persistent or significant disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
f. Is a suspected transmission of any infectious agent via an authorized medicinal product
g. Other situations: • Possible Hy's Law case: ALT≥3×ULN AND total bilirubin ≥2×ULN (>35% direct bilirubin) or international normalized ratio (INR) >1.5 must be reported as SAE • Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardize the participant or may require

medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

- Examples of such events include invasive or malignant cancers, intensive treatment for allergic bronchospasm, blood dyscrasias, convulsions, or development of intervention dependency or intervention abuse.

10.3.3. Definition of Cardiovascular Events

Cardiovascular Events (CV) Definition:

Investigators will be required to fill out the specific CV event page of the CRF for the following AEs and SAEs:

- Myocardial infarction/unstable angina
- Congestive heart failure
- Arrhythmias
- Valvulopathy
- Pulmonary hypertension
- Cerebrovascular events/stroke and transient ischemic attack
- Peripheral arterial thromboembolism
- Deep venous thrombosis/pulmonary embolism
- Revascularization

10.3.4. Recording and Follow-Up of AE and SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to GSK in lieu of completion of the GSK required form.
- There may be instances when copies of medical records for certain cases are requested by GSK. In this case, all participant identifiers, except for the participant number, will be redacted on the copies of the medical records before submission to GSK.

- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will assess severity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort, and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AE and SAE can be assessed as severe.
- An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report to GSK. However, **it is very important that the investigator always assess causality for every event before the initial transmission of the SAE data to** GSK**.**
- The investigator may change his/her opinion of causality considering follow-up information and send an SAE follow-up report with the updated causality assessment.

- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by GSK to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator may be requested to provide GSK with a copy of any postmortem findings including histopathology.
- New or updated information will be recorded in the originally submitted documents.
- The investigator will submit any updated SAE data to GSK within 24 hours of postmortem receipt of the information.

10.3.5. Reporting of SAE to GSK

SAE Reporting to GSK via Electronic Data Collection Tool

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

SAE Reporting to GSK via Paper Data Collection Tool

- Facsimile transmission of the SAE paper data collection tool is the preferred method to transmit this information to the **SAE coordinator**.

- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE data collection tool within the designated reporting time frames.
- Contacts for SAE reporting can be found in the Study Reference Manual.

10.4. Appendix 4: Adverse Events of Special Interest

The list of terms and reporting requirements for AESI are provided below. These are selected non-serious AEs and SAEs that **must be reported to the GSK medical monitor within 24 hours** regardless of relationship to study treatment. Any event that meets the criteria described below must be reported regardless of investigator-determined relationship to study treatment or if considered immune-related (unless otherwise specified). Investigators/study coordinators/designated site personnel are required to record these experiences in the eCRF (as described in the eCRF completion guidance document) and to provide supplemental information (such as medical history, concomitant medications, investigations, etc.) about the event.

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.

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		
Any grade of hemophagocytic lymphohistiocytosis		

10.5. Appendix 5: Contraceptive and Barrier Guidance

10.5.1. Definitions:

Woman of Childbearing Potential (WOCBP)

Women in the following categories are considered WOCBP (fertile):

1. Following menarche
2. From the time of menarche until becoming post-menopausal unless permanently sterile (see below)

Notes:

- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement >40 IU/L or mIU/mL is required.
    - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrolment.
- Permanent sterilization methods (for the purpose of this study) include:
    - Documented hysterectomy
    - Documented bilateral salpingectomy
    - Documented bilateral oophorectomy
- For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), investigator discretion should be applied to determining study entry.
- **Note:** Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

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

10.5.2. Contraception Guidance:

Participants are required to agree to abide by the gender specific contraceptive requirements below:

- Female participants are eligible to participate if they are not either pregnant or breastfeeding, and at least one of the following conditions applies:
- Is not a woman of childbearing potential (WOCBP), or
- Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), with low user dependency during the study treatment period and for at least 7 days after the last dose of study treatment and agrees not to donate eggs (ova, oocytes) for the purpose of reproduction during this period. The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study treatment.
- A WOCBP must have a negative highly sensitive pregnancy test (urine or serum) as required by local regulations) within 7 days before the first dose of study intervention. If a urine test cannot be confirmed as negative (e.g., an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.
- Additional requirements for pregnancy testing during and after study treatment will be described in the protocol.
- The investigator is responsible for a review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.
- Male participants and WOCBP taking hydroxyurea during the study must follow contraceptive guidance in the hydroxyurea prescribing information.

• **CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:**
• **Highly Effective Methods[b] That Have Low User Dependency** *Failure rate of <1% per year when used consistently and correctly.*
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)[c]
• Bilateral tubal occlusion
• Vasectomized partner   • *Note: Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.*

• **Highly Effective Methods [b] That Are User Dependent** *Failure rate of <1% per year when used consistently and correctly.*

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

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

• Sexual abstinence   • *Note: Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant*
a. Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies. b. Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly. c. If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action. Note: Periodic abstinence (calendar, sympto-thermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception. Male condom and female condom should not be used together (due to risk of failure with friction)

10.6. Appendix 6: Genetics

CCI

[redacted]

10.7. Appendix 7: Liver Safety: Required Actions and Follow-up Assessments and Study Intervention Restart/Rechallenge Guidelines

- http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf
- http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdfhttp://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf
  - http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf
  - https://doi.org/10.1016/j.jhep.2019.02.014

Phase 1 oncology liver chemistry stopping criteria have been designed to assure participant safety and to evaluate liver event etiology.

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

Required Actions and Follow up Assessments following ANY Liver Stopping Event	
Actions	**Follow Up Assessments**
• **Immediately** discontinue study treatment • Report the event to GSK **within 24 hours** • Complete the liver event CRF and complete SAE data collection tool if the event also meets the criteria for an SAE[2] • Perform liver event follow up assessments • Monitor the participant until liver chemistries resolve, stabilize, or return to within baseline (see **MONITORING** below) • **Do not restart/rechallenge** participant with study treatment unless allowed per protocol and GSK Medical Governance approval **is granted** (refer to Appendix 7) • If restart/rechallenge **not allowed per protocol or not granted**, permanently discontinue study treatment and may continue participant in the study for any protocol specified follow up assessments **MONITORING:** **For bilirubin or INR criteria:** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin, and INR) and	• Viral hepatitis serology[4] • Obtain INR and recheck with each liver chemistry assessment until the transaminases values show downward trend • Blood sample for pharmacokinetic (PK) analysis, obtained within 48h of the last dose[6] • Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH). • Fractionate bilirubin, if total bilirubin≥2xULN • Obtain complete blood count with differential to assess eosinophilia • Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form • Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications • Record alcohol use on the liver event alcohol intake case report form

perform liver event follow up assessments within 24 **hr** • Monitor participants twice weekly until liver chemistries resolve, stabilize, or return to within baseline • A specialist or hepatology consultation is recommended **For All other criteria:** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin and INR) and perform liver event follow up assessments within **24-72 hr** • Monitor participants weekly until liver chemistries resolve, stabilize, or return to within baseline	**For bilirubin or INR criteria:** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG or gamma globulins) • Serum acetaminophen adduct HPLC assay (quantifies potential acetaminophen contribution to liver injury in participants with definite or likely acetaminophen use in the preceding week [James, 2009]). **NOTE: not required in China** • Liver imaging (ultrasound, magnetic resonance, or computerized tomography) and /or liver biopsy to evaluate liver disease: complete Liver Imaging and/or Liver Biopsy CRF forms

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that participant if ALT ≥ 3xULN and bilirubin ≥ 2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, record presence of detectable urinary bilirubin on dipstick, indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT ≥ 3xULN and bilirubin ≥ 2xULN (>35% direct bilirubin) or ALT ≥ 3xULN and INR>1.5, which may indicate severe liver injury (possible 'Hy's Law'), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis); the threshold value stated will not apply to participants receiving anticoagulants
3. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash, or eosinophilia)
4. Includes: Hepatitis A IgM antibody; Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM); Hepatitis C RNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody
5. If hepatitis delta antibody assay cannot be performed, it can be replaced with a PCR of hepatitis D RNA virus (where needed) [Le Gal , 2005].
6. PK sample may not be required for participants known to be receiving placebo or non-GSK comparator treatments.) Record the date/time of the PK blood sample draw and the date/time of the last dose of study treatment prior to blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the participant's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SRM. Not required for single-dose studies

10.7.1. Study Treatment Restart or Rechallenge

If participant meets liver chemistry stopping criteria do not restart participant with study treatment unless:

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

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

10.7.2. Restart Following Transient Resolving Liver Stopping Events Not Related to Study Treatment

Restart refers to resuming study treatment following liver stopping events in which there is a clear underlying cause (other than DILI) of the liver event (e.g., biliary obstruction, pancreatic events, hypotension, acute viral hepatitis). Furthermore, restart is not permitted following liver stopping event when the underlying cause was alcoholic hepatitis.

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

- Investigator requests consideration for study treatment restart if liver chemistries have a clear underlying cause (e.g., biliary obstruction, hypotension and liver chemistries have improved to normal or are within 1.5 × baseline and ALT <3×ULN).

- Possible study treatment-induced liver injury has been excluded by the investigator and the study team. This includes the absence of markers of hypersensitivity (otherwise unexplained fever, rash, eosinophilia). Where a study treatment has an identified genetic marker associated with liver injury (e.g., lapatinib, abacavir, amoxicillin/clavulanate), the presence of the marker should be excluded. If study treatment-related liver injury cannot be excluded, the guidance on rechallenge in Section 10.7.2 will apply.

- There is no evidence of alcoholic hepatitis.

- Ethics Committee or Institutional Review Board approval of study treatment restart must be obtained, as required.

- If restart of study treatment is approved by GSK Medical Governance in writing, the participant must be provided with a clear description of the possible benefits and risks of study treatment administration, including the possibility of recurrent, more severe liver injury or death.

- The participant must also provide signed informed consent specifically for the study treatment restart. Documentation of informed consent must be recorded in the study chart.

- Study treatment must be administered at the dose specified by GSK.

- Participants approved by GSK Medical Governance for restarting study treatment must return to the clinic once a week for liver chemistry tests until stable liver chemistries have been demonstrated and then laboratory monitoring may resume as per protocol.

- If after study treatment re-start, participant meets protocol-defined liver chemistry stopping criteria, follow usual stopping criteria instructions.

- GSK Medical Monitor, and the Ethics Committee or Institutional Review Board as required, must be informed of the participant's outcome following study treatment restart.

- GSK to be notified of any adverse events, as per Section 10.3.

10.8. Appendix 8: IWG Criteria for Response for Participants with MDS

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

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

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

e. Modification to IWG response criteria for MDS [Cheson, 2006].

10.9. Appendix 9: Response Criteria for Participants with AML

[Modified Cheson, 2003]

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

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

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

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

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

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

References

Cheson BD, Bennett JM, Kopecky KJ, Buchner T, Willman CL, Estey EH. Revised recommendations of the International Working Group for diagnosis, standardisation of response criteria, treatment outcomes, and Reporting Standards for therapeutic trials in Acute Myeloid Leukemia. Journal of Clinical Oncology 2003 Dec 15; 21 (24):4642-9.

10.10. Appendix 10: ECOG Performance Status[a]

Grade	Descriptions
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

a. Oken, 1982.

10.11. Appendix 11: Cairo-Bishop Clinical Tumor Lysis Syndrome Definition and Grading

Cairo-Bishop clinical tumor lysis syndrome definition* and grading

Complication	Grade					
	0	1	2	3	4	5
Creatinine¶Δ	≤1.5 x ULN	1.5 x ULN	>1.5-3.0 x ULN	>3.0-6.0 x ULN	>6.0 x ULN	Death
Cardiac arrhythmia¶	None	Intervention not indicated	Nonurgent medical intervention indicated	Symptomatic and incompletely controlled medically or controlled with device (eg, defibrillator)	Life-threatening (eg, arrhythmia associated with HF, hypotension, syncope, shock)	Death
Seizure¶	None	-	One brief, generalized seizure; seizure (s) well controlled by anticonvulsants or infrequent focal motor seizures not interfering with ADL	Seizure in which consciousness is altered; poorly controlled seizure disorder; with breakthrough generalized seizures despite medical intervention	Seizure of any kind which are prolonged, repetitive or difficult to control (eg, status epilepticus, intractable epilepsy)	Death

ULN: upper limit of normal; HF: heart failure; ADL: activities of daily living.
* Clinical tumor lysis syndrome defined as laboratory tumor lysis syndrome plus at least one clinical complication.
¶ Not directly or probably attributable to therapeutic agent.
Δ If no institutional ULN is specified, age/sex ULN creatinine may be defined as follows: >1 to <12 years of age, both male and female, 61.6 mmol/L; ≥12 to <16 years, both male and female, 88 mmol/L; ≥16 years, female 105.6 mmol/L, male 114.4 mmol/L.

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10.12. Appendix 12: Abbreviations and Definitions and Trademarks

ADR	Adverse drug reaction
AE	Adverse event
ALT	Alanine aminotransferase
AML	Acute myeloid leukemia
AST	Aspartate aminotransferase
CNS	Central nervous system
CRP	C-reactive protein
CRS	Cytokine Release Syndrome
CV	Cardiovascular
CYP	Cytochrome P450
DMPK	Drug Metabolism and Pharmacokinetics
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
EU	European Union
FTIH	First Time in Humans
GSK	GlaxoSmithKline
HPLC/MS/MS	High performance liquid chromatography with tandem mass spectrometry
IB	Investigator's Brochure
ICH	International Conference on Harmonization
IFN	Interferon
IL	Interleukin
IV	Intravenous
MABEL	Minimum anticipated biological effect level
MC	Multicenter
ND	Not determined
OATP	Organic anion transporter polypeptide
OL	Open label
PD	Pharmacodynamic
PD-1	Programmed death receptor 1
PEG	Polyethylene glycol
P-gp	P-glycoprotein
PK	Pharmacokinetic
RP2D	Recommended Phase 2 Dose
SAE	Serious adverse event
SD	Standard deviation
SOC	System organ class
STING	STimulator of InterferoN Genes
TBK1	TANK binding kinase-1
TK	Toxicokinetic
TNF	Tumor necrosis factor
Treg	T-regulatory
WBC	White blood cell

11. REFERENCES

Arber DA, Orazi A, Hasserjian R, Jurgen T, Borowitz M, Le Beau M, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood. 2016;127(20):2391-2405.

Baba T, Yoshida T, Tanabe Y, Nishimura T, Morishita S, Gotoh N, et al. Cytoplasmic DNA accumulation preferentially triggers cell death of myeloid leukemia cells by interacting with intracellular DNA sensing pathway. Cell Death Dis. 2021;12(4):322. Published 2021 Mar 26.

Brahmer JR, Lacchetti C, Schneider BJ, Atkins M, Brassil K, Caterino J, et al. Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol. 2018;36(17):1714-1768.

Cairo MS, Bishop M. Tumour lysis syndrome: new therapeutic strategies and classification. Br J Haematol. 2004 Oct;127(1):3-11.

Chen DS and Mellman I. Elements of cancer immunity and the cancer-immune set point. *Nature,* 2017;541:321-30.

Cheson BD, Bennett JM, Kopecky KJ, Buchner T, Willman CL, Estey EH. Revised recommendations of the International Working Group for diagnosis, standardisation of response criteria, treatment outcomes, and Reporting Standards for therapeutic trials in Acute Myeloid Leukemia. Journal of Clinical Oncology 2003 Dec 15; 21 (24):4642-9.

Cheson BD, Greenberg PL, Bennett JM, Lowenberg R, Wijermans PW, Nimer SD, et al. Clinical application and proposal for modification of the International Working Group (IWG) response criteria in myelodysplasia. Blood. 2006 July 15;108, Number 2: 419-425.

Curran E, Chen X, Corrales L, Kline DE, Dubensky TW Jr, Duttagupta P, et al. STING Pathway Activation Stimulates Potent Immunity against Acute Myeloid Leukemia. Cell Rep. 2016 Jun 14;15(11):2357-66.

Gaidt MM, Ebert TS, Chauhan D, Ramshorn K, Pinci F, Zuber S, et al. The DNA inflammasome in human myeloid cells is initiated by a STING-cell death program upstream of NLRP3. Cell. 2017;171(5):1110-1124.e18.

GSK Document Number 2018N357563_03, Investigator's Brochure for GSK3745417. Version 03. 2020.

Gulen MF, Koch U, Haag SM, Schuler F, Apetoh F, Villunger A, et al. Signalling strength determines proapoptotic functions of STING. Nat Commun. 2017;8(1):427. Published 2017 Sep 5.

Ishikawa H, Ma Z, Barber GN. STING regulates intracellular DNA-mediated, type I interferon-dependent innate immunity. Nature. 2009;461(7265):788-792.

James LP, Letzig L, Simpson PM, Capparelli E, Roberts D, Hinson J, et al. Pharmacokinetics of acetaminophen-protein adducts in adults with acetaminophen overdose and acute liver failure. Drug Metab Dispos. 2009 Aug;37(8):1779-84.

Ji Y, Wang SJ. Modified toxicity probability interval design: a safer and more reliable method than the 3 + 3 design for practical phase I trials. J Clin Oncol. 2013 May 10;31(14):1785-91.

Le Gal F, Gordien E, Affolabi D, Hanslik T, Alloui C, Deny P, et al. Quantification of hepatitis delta virus RNA in serum by consensus real-time PCR indicates different patterns of virological response to interferon therapy in chronically infected patients. J Clin Microbiol. 2005 May;43(5):2363-9.

Lee DW, Santomasso BD, Locke FL, Ghobadi A, Turtle CJ, Brudno JN, et al. ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells. Biol Blood Marrow Transplant. 2019;25:625-638.

Lee, J. J., & Liu, D. D. A predictive probability design for phase II cancer clinical trials. *Clinical Trials*, (2008). *5*(2), 93-106.

Mahadevan V, Malik ST, Meager A, Fiers W, Lewis GP, Hart I. Role of tumor necrosis factor in flavone acetic acid-induced tumor vasculature shutdown. R. Cancer Res. 1990 Sep 1;50(17):5537-42.

Maus MV, Alexander S, Bishop MR, Brudno J, Callahan C, Davila M, et al. Society for Immunotherapy of Cancer (SITC) clinical practice guideline on immune effector cell-related adverse events. J Immunother Cancer. 2020 Dec;8(2):e001511.

NCI (2017) Common Terminology Criteria for Adverse Events (CTCAE), version 5.0. Nov, 2017. https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf

NYHA: The Criteria Committee of the New York Heart Association (NYHA). Nomenclature and criteria for diagnosis of diseases of the heart and great vessels. 9th Ed. Boston, Mass: Little, Brown & Co.; 1994:253-256.

Oken, MM, Creech, RH, Tormey, DC, Horton, J, Davis, TE, McFadden, ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982; 5:649-655.

Palaskas N, Lopez-Mattei J, Durand JB, Iliescu C, Deswal A. Immune Checkpoint Inhibitor Myocarditis: Pathophysiological Characteristics, Diagnosis, and Treatment. J Am Heart Assoc. 2020;9(2):e013757.

Schwartz LB. Diagnostic Value of Tryptase in Anaphylaxis and Mastocytosis. *Immunol Allergy Clin.* 2006, 26(3):451-463.

Sun L, Wu J, Du F, Chen X, Chen ZJ. Cyclic GMP-AMP synthase is a cytosolic DNA sensor that activates the type I interferon pathway. Science. 2013;339(6121):786-791.

Woo SR, Fuertes MB, Corrales L, Spranger S, Furdyna M, Leung M, et al. STING-dependent cytosolic DNA sensing mediates innate immune recognition of immunogenic tumors [published correction appears in Immunity. 2015 Jan 20;42(1):199]. Immunity. 2014;41(5):830-842.