TITLE PAGE

Protocol Title: A Phase I First Time in Human Open Label Study of GSK3745417 administered with and without Anticancer Agents in Participants with Advanced Solid Tumors

Protocol Number: 208850/07

Short Title: Phase 1 First Time in Human, open label study of GSK3745417 administered to participants with advanced solid tumors

Compound Number:	GSK3745417

Sponsor Name and Legal Registered Address:

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

Regulatory Agency Identifying Number(s):

Investigational New Drug Number: 139899

European Drug Regulatory Authorities Clinical Trials Number: 2018-001924-20

Approval Date: 04 Aug 2023

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 7	04 Aug 2023
Amendment 6/JPN-1	07-Apr-2022
Amendment 6	19-Jan-2022
Amendment 5/NET-1 (country amendment)	19-JUL-2021
Amendment 4	21-APR-2021
Amendment 3	16-OCT-2020
Amendment 2	27-AUG-2020
Amendment 1	12-DEC-2018
Original Protocol	12-SEP-2018

Amendment 7: 04 Aug 2023

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

CCI [redacted]

In line with GSK's decision, this protocol has been amended to provide updated instructions for study conduct of participants currently on study who are continuing to receive study GSK3745417 monotherapy or GSK3745417 in combination with dostarlimab, those in survival follow-up for any participants receiving treatment under post analysis continued treatment (PACT) phase.

CCI [redacted]

The correction of errors in Protocol Amendment 6.

A table of key changes from Protocol Amendment 6 to Amendment 7 is shown below:

Section Number and Name	Description of Change	Brief Rationale
1 Protocol Summary	CCI [redacted]	
1.1 Synopsis	• Removed Objectives & Endpoints CCI [redacted]. • CCI [redacted]. • Updated safety follow up period to 90 days after last dose or until start of subsequent anticancer treatment, whichever is earlier. • CCI [redacted]	CCI [redacted] • A 90-day safety follow-up after last dose of study drug is appropriate based on the half-life of GSK3741417 and dostarlimab (for dostarlimab consistent with other protocols). • CCI [redacted]
1.1.1 Schema	CCI [redacted]	
1.2 Schedule of Activities	• The updated and revised SoA for further conduct of the study, is provided under Section 1.2.1 Revised Schedule of Activities; and and CCI [redacted]. • CCI [redacted]	• For easy readability and conduct of study in participants receiving study treatment. • CCI [redacted]

Section Number and Name	Description of Change	Brief Rationale
	CCI [redacted]	
2. Introduction		
3. Objectives and Endpoints	• Removed Objectives & Endpoints CCI [redacted]	• CCI [redacted]
4.1 Overall Design	• Updated to reflect no enrollment in the planned dose expansion phase (Parts 1B and 2B). • Addition of 90-day safety follow up period • CCI [redacted] • Added language on the possibility of post-assessment continued treatment (PACT) phase	• CCI [redacted] • A 90-day safety follow-up after last dose of study drug is appropriate considering the half-life of GSK3741417 and dostarlimab.A 90-day safety follow-up after last dose of study drug is appropriate based on the half-life of GSK3741417 and dostarlimab. • PACT language added to enable the continued treatment with study drugs for any participants who may continue to benefit from continued treatment beyond 2 years.
4.1.1 Dose Escalation	CCI [redacted]	
4.1.2 Dose Limiting Toxicity		

Section Number and Name	Description of Change	Brief Rationale
	• CCI [redacted]	
4.1.6 Study Duration	• Updated study duration language in view of PACT language addition	• PACT - Updated based on the recent program level wording
4.2 Number of Participants	• Updated to reflect the actual number of enrolled participants	• Further enrollment ceased in this study
4.3 Participant and Study Completion	• Language updated on definition of study completion and safety follow up of 90 days after last dose	• For more clarity following addition fo PACT language
4.6 End of Study Definition	• Added language on PACT and End of Study	• Added for more clarity
6.6 Dose Modification	• CCI [redacted] • Table 15 on guidelines for immune-related AEs, updated with CCI [redacted]	• CCI [redacted] • CCI [redacted]
6.6.1 Management of Infusion Reactions or Severe Cytokine Release Syndrome (sCRS)	• • Added a note above Table 16 Biomarker panel, that samples will no longer be collected at the time of a CRS event • Instruction added pertaining to dose reduction for CRS	• As adequate chemokine/cytokine and PK samples for characterization of CRS have been obtained further sampling not required, and reducing. burden for ongoing participants, • Dose modification for CRS also added to this section for clarity.
6.6.1.1. Cardiac Monitoring and Dose Modification Guidelines	• Updated to reflect preference of local troponin testing over central testing (same frequency); with Troponin I preferred	• Preference for troponin I over troponin T at localf lab, based on emerging evidence that former may be more informative.
6.8. Continued Access to Study Intervention after the End of the Study	• Updated with PACT language • Added a subsection 6.8.1 on Continued Access to Study Intervention After Data Cut-off prior to EOS	• PACT added to enable the continued access to study treatment (s) for participant who may continue to benefit from continued treatment beyond 2 years

Section Number and Name	Description of Change	Brief Rationale
7.1 Discontinuation of Study Intervention	• Deleted redundant information related to End of Study • The following information has been added: "Participants will be followed up for safety until 90 days after last dose, until start of subsequent anticancer therapy or until death, whichever comes first."	• To align with PACT language • In alignment with the current updates
7.2. Participant Discontinuation/ Withdrawal from the Study	• The term "withdrawl of consent" has been added in the first paragraph for better clarity.	• Added for more clarity
8. Study Assessments And Procedures	• Reference added to the Revised SoA in Section 1.2.1 • PK related information on blood volume collection deleted	• In alignment with the current updates
8.1. Efficacy Assessments	CCI [redacted]	
8.2.8. Chest Imaging (Japan cohort Only)	• Added reference to revised SoA tables in Section 1.2.1 • CCI [redacted]	• Added for more clarity
8.3.1. Time Period and Frequency for Collecting AE and SAE Information	• Updated to reflect the revised SoA • Added PACT language	• Added for more clarity on PACT phase
8.5. Pharmacokinetics – Blood and Urine	CCI [redacted]	

Section Number and Name	Description of Change	Brief Rationale
8.7. Pharmacodynamics/ Biomarkers	CCI [redacted]	
9.1. Statistical Hypotheses		
9.2. Sample Size Determination 9.2.3 Dose Escalation CCI [redacted]		
9.3. Populations for Analyses		
9.4.1. Efficacy Analyses		
9.4.2.2 Adverse Events	• Summaries of AEs to focus on TEAEs as defined in RAP	• Updated according to RAP
9.5. Interim Analyses	• Updated language on potential additional interim analysis requirements	• Any review of aggregate unblinded data is counted as an interim analysis (even if the study is open-label). • Wording added to cover potential future analyses
11.2. Appendix 2: Clinical Laboratory Tests	• In this amendment, any tests conducted in a clinical laboratory will no longer be performed; instead, it will be performed by the local laboratory	• In alignment with the current updates
11.3.5. Reporting of SAE to GSK	• A note added that during the PACT phase, all SAEs and pregnancies will be reported via paper CRFs.	• To align with PACT language
11.15. Appendix 15: Imaging Sub-study	CCI [redacted]	

Section Number and Name	Description of Change	Brief Rationale
11.17 Appendix 17: Protocol Amendment History	• Moved the Amendment 6: 19-JAN-2022 Summary of changes to Appendix 17	• Minor formatting edits

Additional changes were made for typos and other minor clarifications throughout the text.

TABLE OF CONTENTS

PAGE

LIST OF TABLES

PAGE

LIST OF FIGURES

PAGE

LIST OF ABBREVIATIONS AND TRADEMARKS

Abbreviations

ADA	Antidrug antibody
AE	Adverse event(s)
AESI	Adverse events of special interest
ALT	Alanine aminotransferase
AraG	Arabinofuranosyl guanine
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
AUC0-t	Area under the concentration-time curve from time zero to time
AUC(0-inf)	Area under the concentration-time curve from time zero to infinity
BLRM	Bayesian Logistic Regression Model
BP_{ND}	Binding Potential
BNP	B-type Natriuretic Peptide
CBC	Complete blood count
cfDNA	Circulating free DNA
cGAS	Cyclic GMP-AMP synthase
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CL	Clearance
CrCl	Calculated creatinine clearance
Cmax	Maximum observed concentration
CNS	Central nervous system
CPMS	Clinical Pharmacology Modeling and Simulation
CR	Complete response
CRF	Case report form
CRP	C-reactive protein
CRS	Cytokine Release Syndrome
CSR	Clinical Study Report
CT	Computed tomography
CTLA-4	Cytotoxic T-lymphocyte-associated antigen 4
CV	Cardiovascular
CYP	Cytochrome p450
DC	Dendritic cell
DEC	Dose Escalation Committee
DILI	Drug-induced liver injury
dL	Deciliter
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid
EC10	Ten percent effect concentration
ECG	Electrocardiogram(s)
ECOG	Eastern Cooperative Oncology Group
EORTC-QLQ	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire

eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
F-18	Fluorine-18
FACT GP5	Functional Assessment of Cancer Therapy – General Physical Well Being Form Item 5
FACTS	Fixed and Adaptive Clinical Trial Simulator
FDA	Food and Drug Administration
FDG-PET	Fluorodeoxyglucose-positron-emission tomography
FOV	Field of View
FSH	Follicle stimulating hormone
FTIH	First time in human
GCP	Good Clinical Practice
G-CSF	Granulocyte colony-stimulating factor
GFR	Glomerular filtration rate
GMP	Good Manufacturing Practice
GSK	GlaxoSmithKline
h	Hour(s)
HPLC	High performance liquid chromatography
HRT	Hormone replacement therapy
IB	Investigator's Brochure
ICE	Immune Effector Cell-associated Encephalopathy (ICE)
ICH	International Council on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICF	Informed consent form
iCPD	Immune-confirmed progressive disease
IEC	Independent Ethics Committee
IFN	Interferon
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IHC	Immunohistochemistry
IL-6	Interleukin 6
IL-10	Interleukin 10
ILD	Interstitial lung disease
INR	International normalized ratio
irAE	Immune-related adverse event(s)
IRB	Institutional Review Board(s)
iRECIST	Immune-related RECIST
IRR	Infusion related reaction
IV	Intravenous
IVIVE	In vitro to in vivo extrapolation
kg	Kilogram(s)
L	Liter
μg	Microgram
MABEL	Minimally anticipated biologic effect level
MBq	Megabecquerel

mCi	Millicurie
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram(s)
min	Minute(s)
mL	Milliliter(s)
MRI	Magnetic resonance imaging
MSS CRC	Microsatellite stable colorectal cancer
mSv	Millisievert
MTD	Maximum tolerated dose
mTPI	Modified Toxicity Probability Interval
NCI-CTCAE	National Cancer Institute – Common Terminology Criteria for Adverse Events
N-CRM	Neuenschwander-Continuous Reassessment Method
NOAEL	No-observed-adverse-effect level
NTproBNP	N-terminal-pro hormone BNP
NYHA	New York Heart Association
ORR	Objective response rate
OS	Overall survival
PACT	Post-Analysis Continued Treatment
PBMC	Peripheral blood mononuclear cell
PD-1	Programmed death receptor-1
PD	Progressive disease
PET	Positron Emission Tomography
PFS	Progression-free survival
PK	Pharmacokinetic(s)
PR	Partial response
PS	Performance status
CCI	[redacted]
QLQ	Quality of life questionnaire
QTc	Corrected QT interval duration
QTcF	QT duration corrected for heart rate by Fridericia's formula
RAP	Reporting and Analysis Plan
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic acid
RP2D	Recommended phase 2 dose
SAE	Serious adverse event(s)
SC	Subcutaneous
SD	Stable disease
SRM	Study Reference Manual

STING	STimulator of INterferon Genes
SUV	Standardized Uptake Value
TCR	T-cell receptor
t½	Apparent terminal phase half-life
TDV	Treatment discontinuation visit
TGI	Tumor growth inhibition
TLC	Thin layer chromatography
TNF	Tumor necrosis factor
ULN	Upper limit of normal
VT	Volume of Distribution
WOCBP	Women of childbearing potential

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1. PROTOCOL SUMMARY

With this Amendment, the study sponsor GSK CCI [redacted]

In line with GSK's decision, this protocol has been amended to provide updated instructions for study conduct of participants currently on study who are continuing to receive study GSK3745417 monotherapy or GSK3745417 in combination with dostarlimab.

CCI [redacted]

Following the DCO (data cut-off) date for the final analysis, study 208850 may move into a post analysis continued treatment (PACT) phase where the study remains open only to provide continued access to treatment for study participants who are continuing to derive clinical benefit in the opinion of the treating physician. During PACT only SAEs, AEs leading to treatment discontinuation, overdose and pregnancy cases will be reported directly to GSK. The end of study is defined as the date of the last visit of the last participant in the study (e.g. last dose plus 90 days safety reporting period) or last scheduled procedure shown in the SoA for the last participant in the study.

1.1. Synopsis

Protocol Title: A Phase I Open Label Study of GSK3745417 in Combination with Anticancer Agents in Participants with Advanced Solid Tumors.

Short Title: PH1 FTIH, OL study of GSK3745417 administered to participants with advanced solid tumors.

Rationale: The concept of cancer immune surveillance has been well established. The key tenet of this concept is that the immune system plays a critical role in protecting the body from neoplastic disease. Consistent with this concept, the immune checkpoint inhibitors anti-PD(L)-1 and anti-CTLA-4 have demonstrated therapeutic benefit across multiple tumor types, yielding durable responses in some patients. However, a majority of patients do not respond to monotherapy with checkpoint inhibitors, at least in part due to the non-inflamed nature of the tumor. Therefore, strategies to increase the tumor immunogenicity are being actively explored.

STimulator of INterferon Genes (STING) is the key adaptor molecule in the cGAS--STING-TBK1 pathway that mediates the sensing of cytosolic DNA. Activation of STING generates a distinctive set of type I interferons (IFNα and β) and

pro-inflammatory cytokines that instigate T-cell dependent tumor immunity and tumor-vascular collapse. The pre-clinical data strongly suggest that the STING pathway is the intrinsic tumor sensing pathway of the immune system. Therefore, activation of the STING pathway has the potential to boost tumor antigen presentation and the tumor immunogenicity. Potent and durable anti-tumor response has been demonstrated in the syngeneic murine tumor models with STING agonist treatment.

In addition, the effect of STING activation in boosting tumor antigen presentation suggests potential combination benefit with immune check point modulators. Given their non-overlapping mechanisms of action, the combination of the two could simultaneously accelerate separate steps in the cancer-immunity cycle, i.e., the tumor antigen presentation process and the T-cell activation process, therefore generating synergistic anti-tumor effect.

GSK3745417 is a synthetic STING agonist that is being developed by GlaxoSmithKline as an immune stimulatory agent for the treatment of cancer. This study will be the first time in human (FTIH) study of GSK3745417 to assess the safety, pharmacokinetic (PK), CCI [redacted] of GSK3745417 administered alone and in combination with other immunotherapies to participants with advanced solid tumors. The initial combination partner is dostarlimab, based on mechanisms of action targeting complementary modes of the cancer-immunity cycle and compelling antitumor activity observed in preclinical models. Subsequent combination partners and/or additional routes of administration may be evaluated (following protocol amendment/s) based on biologic rationale, nonclinical data, and/or emerging clinical data.

This open label, dose escalation study will assess the safety, PK, CCI [redacted]

With this Amendment, the study sponsor GSK CCI [redacted]

In line with GSK's decision, this protocol has been amended to provide updated instructions for study conduct of participants current on study who are continuing to receive study GSK3745417 monotherapy or GSK3745417 in combination with dostarlimab.

CCI [redacted]

Following the DCO (data cut-off) date for the final analysis, study 208850 may move into a post analysis continued treatment (PACT) phase where the study remains open only to provide continued access to treatment for study participants who are continuing to derive clinical benefit in the opinion of the treating physician. During PACT only SAEs, AEs leading to treatment discontinuation, overdose and pregnancy cases will be reported directly to GSK. The end of study is defined as the date of the last visit of the last participant in the study (e.g. last dose plus 90 days safety reporting period) or last scheduled procedure shown in the SoA for the last participant in the study.

Objectives and Endpoints (Dose Escalation, Part 1A and Part 2A):

Objective	Endpoint
Primary	
• To determine the safety, tolerability, and the recommended phase 2 dose (RP2D) of GSK3745417 alone or in combination with dostarlimab administered intravenously to participants with selected advanced/recurrent solid tumors.	• Incidence of DLT • Incidence and severity of adverse events
Secondary	
• To characterize the PK properties of GSK3745417 alone or in combination with dostarlimab	• GSK3745417 concentrations in plasma and PK parameters
Exploratory	
CCI [redacted]	

Objective	Endpoint
CCI [redacted]	[redacted]
CCI [redacted]	[redacted]

Overall Design: This is a Phase I, FTIH, open-label, repeat-dose, non-randomized, multicenter, multi-country study to evaluate the safety, tolerability, and CCI [redacted] and establish a recommended dose of GSK3745417 administered CCI [redacted] or in combination with dostarlimab (Part 2A) in participants with refractory/relapsed solid tumors. Both Part 1A and Part 2A consist of a dose escalation phase only.

CCI [redacted]

CCI [redacted]

Disclosure Statement: This is an open label interventional study.

CCI [redacted]

Intervention Groups and Duration: Participants will initially receive GSK3745417 as monotherapy during dose escalation in Part 1A. Escalating doses of GSK3745417 will be evaluated as guided by the Bayesian Logistic Regression Model (BLRM) approach. In Part 2A, escalating doses of GSK3745417 in combination with dostarlimab CCI [redacted] will be evaluated as guided by the BLRM approach. CCI [redacted].

The study includes a screening period, a treatment period, and a follow-up period. Participants will be screened for eligibility beginning 4 weeks before the start of treatment. The duration of study intervention is expected to be up to 2 years. Ongoing participants will be followed up for safety until 90 days after the last dose or until start of subsequent anticancer treatment, whichever is earlier. Participants who have already progressed will no longer be followed for survival.

Data Monitoring Committee: No.

CCI

[redacted]

1.2. Schedule of Activities (SoA)

Note: In this protocol amendment, participants receiving study treatments should follow Schedule of Assessment according to their cohort assignment as outlined in Section 1.2.1, and in the Imaging Sub-study (Appendix 15, Section 11.15, Table 30-1).

The timing and number of planned study assessments, including safety, laboratory, CCI [redacted], pharmacokinetic (PK), and CCI [redacted] assessments included in the tables below may be altered during the course of the study based on newly available data (e.g., to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.

CCI [redacted]

For the PACT Phase: Participants who continue to receive study treatment during the PACT phase will be monitored and will receive follow-up care in accordance with standard local clinical practice. Assessments will revert to the standard of care at a participant's particular study site and only SAEs, AEs leading to discontinuation of study treatment, overdoses, and pregnancy cases, will be reported directly to the Sponsor via

paper forms (see Section 11.3.5). For participants discontinuing treatment under PACT, a +90days Safety Follow-up visit is required.

Any changes in the timing or addition of time points for any planned study assessments must be documented and approved by the sponsor and then archived in the sponsor and site study files but will not constitute a protocol amendment. The Institutional Review Board (IRB)/ Independent Ethics Committees (IEC) will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the informed consent form (ICF). The changes will be approved by the IEC/IRB before implementation.

NOTE: For Study participants receiving study treatment and in post-treatment survival follow-up, follow the Schedule of Assessment tables as outlined in Section 1.2.1

Table 1 Schedule of Assessments (Part 1A, Arm A1: GSK3745417 Monotherapy CCI [redacted]

	Screening[a]	Study Intervention Period				
Study Procedure		CCI [redacted]				**Notes**
Week						
Day	≤28					
Informed consent	X					
Inclusion and exclusion criteria	X					
Demographics, Medical History, Prior Medications, Disease Characteristics	X					Include use of antibiotics and probiotics taken up to 60 days prior to study intervention.
Anticancer Therapy	X					
Participant Registration	X					Source document only.
Safety Assessments						
24 Hour In-House Monitoring		Day 1 only				During the first study intervention participants should be monitored in a medically qualified unit/clinic/hospital for at least 24 hours following the administration of GSK3745417. This requirement may be eliminated as safety data emerge. At all other visits, participants should stay for an 8-hour observation following dosing with GSK3745417. Participants may be released after a 6-hour observation period if, in the opinion of the investigator, it is safe to do so, **and there is no protocol mandated**

	Screening[a]	Study Intervention Period				
Study Procedure		CCI [redacted]				**Notes**
Week						
Day	≤28					
						assessment after this time. However, on Weeks 2 and 3, sites encouraged to observe for CCI 8h to allow for collection of CCI 8h PK and biomarker samples. Additional in-house monitoring should be considered for 8-24 hrs post-dose as clinically indicated.
Physical Exam	X	CCI [redacted]		X		Refer to Section 8.2.1 for physical examination details. At screening, a complete physical exam including height and weight is required, at subsequent visits, brief or targeted physical exams are acceptable.
ECOG PS[d]	X			X		
Vital Signs	X			X		On CCI (i.e. during 24-hour in-house monitoring), vital signs should be collected pre-dose CCI On all other visits that do not require 24-hour in-house monitoring, vital signs must be collected pre-dose CCI
Weight	X			X		
Echocardiogram	X		CCI (or when clinically indicated)	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 or ECHO is not available, MUGA scans may be used. The modality used at baseline should be

	Screening[a]	Study Intervention Period				
Study Procedure		CCI [redacted]				**Notes**
Week						
Day	**≤28**					
						repeated throughout the study to ensure comparison to baseline. ECHO/MUGA obtained within a -4-day window pre-dose, and at TDV (unless performed in the previous 4 weeks).
12-lead ECG	X	CCI [redacted]		X		Triplicate ECGs will be obtained at screening. Single ECGs should be obtained prior to GSK3745417 dosing, CCI [redacted], and within 2 hours prior to completion of clinic visit. Post Week 6, next ECG should be on Week 9, then CCI [redacted] thereafter. Patients with new onset symptoms consistent with immune-mediated pericarditis or myocarditis should have additional ECGs as clinically indicated.
Holter Monitoring		Day 1				12-lead Holter monitoring will be conducted on Day 1 and must start at least -2h (pre-dose), followed by normal activity (ambulatory) until -30 min predose, when participant will be lying supine until time 0. Holter monitoring will end at 24h for all participants 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. If heart rate is increased or based on emerging data, hospitalization time might be extended. The requirement for Holter monitoring may be waived by study sponsor based on emerging data.

	Screening[a]	Study Intervention Period				
Study Procedure		CCI [redacted]				**Notes**
Week						
Day	**≤28**					
Neurological Assessment including ICE scoring	X	Conduct if clinically indicated				Refer to Section 8.2.5. for neurological assessment details.
AE/SAE Review		Continuous: Assess AEs at each visit from first dose until the TDV. AESIs and SAEs to be collected until 90 days after the last dose or until start of subsequent anticancer treatment. SAEs related to study participation are collected from time of informed consent.				
Concomitant Medication Review		Continuous: Assess at each visit from first dose of study intervention				
Follow Up Phone Call		CCI [redacted]				After each of the first 6 doses of study intervention, 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						
Hepatitis B and C screening	X					
Pregnancy Test	X (urine)	Week 4 (pre-dose urine)	CCI [redacted] (pre-dose urine)	X	X	Negative serum pregnancy test required within 72 hours prior to date of first dose of study treatment on Day 1 for WOCBP; predose urine pregnancy test conducted every 3 weeks for duration of study, on last day of treatment (if possible), at TDV, and at the Follow-Up visits.
	≤72 hours (serum) of first dose					
CBC with differential[d]	X	CCI [redacted]		X		Sample collection times: Predose, EOI+4h and CCI [redacted]. If a participant experiences cytokine release syndrome, perform CBC with differential at CCI [redacted] 8h too. The CCI [redacted] sample is only

Study Procedure	Screening[a]	Study Intervention Period CCI [redacted]			Notes
Week					
Day	≤28				
					required if participant remains in the clinic for either 24-hour monitoring, or other purposes.
Clinical Chemistry[d]	X[e]	CCI [redacted]		X	Sample collection time: Predose. See Section 11.2 for complete list of required laboratory assessments. Additional clinical chemistry samples should be collected in the event of CRS (see Section 6.6.1)
C-Reactive Protein	X			X	Sample collection times: Predose, CCI [redacted] sample collections are only required if participant remains in the clinic for either 8 - 24-hour monitoring, or other purposes. Additional C-Reactive Protein samples should be collected in the event of CRS (see Section 6.6.1)
Thyroid function[d]	X			X	After Screening, first assessment should be done at CCI [redacted]
Troponin I, T	X			X	See Section 6.6.1.1 for details. Samples for Troponin T for central lab, and T or I for local lab, to be collected pre-dose and result available before dosing. Samples will be collected every CCI [redacted] weeks. On weeks where ECHO is required, pre-dose Troponin can also be obtained during the 4 days leading up to dose day.
BNP (or NTproBNP)	X	Repeat as clinically indicated			Repeat test as outlined in management of cardiac events (Section 6.6.1.1)
eGFR	X				

	Screening[a]	Study Intervention Period			
Study Procedure		CCI			**Notes**
Week					
Day	**≤28**				
Urinalysis[d]	X	CCI	X		If urinalysis is abnormal, a microscopy should be performed.
Coagulation[d]	X				Coagulation test required at screening and starting at CCI . Additional coagulation samples should be collected in the event of CRS (see Section 6.6.1)
Laboratory Assessments for HBV/HCV Populations					
HBV DNA[d]	X	Week 4	CCI	X		Sample collection time: Predose starting on CCI This test to be performed in participants diagnosed with hepatocellular carcinoma (HCC) and positive for HBV on screening.
Quantitative HBsAg[d]	X			X		This test to be performed in participants diagnosed with HCC and positive for HBV on screening.
HCV antibody, HCV RNA	X					This test to be performed in participants diagnosed with HCC and positive for HCV on screening.
CCI						

	Screening[a]	Study Intervention Period				
Study Procedure		CCI				**Notes**
Week						
Day	≤28					
						CCI
Efficacy Assessments						
CCI						

	Screening[a]	Study Intervention Period				
Study Procedure		CCI				**Notes**
Week						
Day	≤28					
CCI						CCI
Archival tumor tissue	X					
Fresh tumor biopsy	X	Week 5 (required) (preferred within 48h window post dose)	Week 13 (optional)	X (at disease progression, optional)		

	Screening[a]	Study Intervention Period			
Study Procedure		CCI			**Notes**
Week					
Day	**≤28**				

CCI

[redacted]

	Screening[a]	Study Intervention Period			
Study Procedure		CCI			**Notes**
Week					
Day	**≤28**				

CCI

	Screening[a]	Study Intervention Period			
Study Procedure		CCI			**Notes**
Week					
Day	**≤28**				
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 infusion; h=hour; ICF=informed consent form; m=min;
CCI

Timepoint Definitions for assessments:
X = Anytime during visit (sampling date/time should be recorded)
CCI

CCI [redacted]

a. All assessments performed at Screening must be performed within 28 days prior to first dose unless otherwise specified.
b. Procedures should be performed at all 6 weekly study interventions, unless otherwise specified
c. 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 CCI [redacted]
d. Procedures scheduled pre-dose on study treatment administration days can be performed within 3 days prior to dosing day, unless otherwise specified.
e. Baseline ALT in Participants with HCC and positive for HBV or positive for HCV should be determined by taking the mean value of the screening ALT and the pre-dose Day 1 ALT.
f. CCI [redacted]

Table 2 Schedule of Assessments (Part 1A, Arm A2: CCI [redacted])

	Screening[a]	Study Intervention Period				
Study Procedure		CCI [redacted]				**Notes**
Week						
Day	**≤28**					
Informed consent	X					
Inclusion and exclusion criteria	X					
Demographics, Medical History, Prior Medications, Disease Characteristics	X					Include use of antibiotics and probiotics taken 60 days prior to study intervention.
Anticancer Therapy	X					
Participant Registration	X					Source document only.
Safety Assessments						
24 Hour In-House Monitoring		Day 1 only				During the first study intervention, participants should be monitored in a medically qualified unit/clinic/hospital for at least 24 hours following the administration of GSK3745417. This requirement may be eliminated as safety data emerge. At all other visits, participants should stay for an 8-hour observation following dosing with GSK3745417. Participants may be released after a 6-hour observation period if, in the opinion of the investigator, it is safe to do so, **and there is no protocol mandated assessment after this time**. However, on Weeks 4 and 7, sites encouraged to observe for EOI+8h to allow for collection of EOI+8h PK and biomarker samples. In-house monitoring

Study Procedure	Screening[a]	Study Intervention Period CCI [redacted]		Notes
Week				
Day	**≤28**			
				should be considered for 8-24 h post-dose as clinically indicated.
Physical Exam	X	CCI [redacted]	X	Refer to Section 8.2.1 for physical examination details. At screening, a complete physical exam including height and weight is required, at subsequent visits, brief or targeted physical exams are acceptable.
ECOG PS[d]	X		X	
Vital Signs	X		X	On Weeks 1 through 16 (i.e., during 24 hour in-house monitoring), vital signs should be collected pre-dose GSK3745417 and at the following times after the end of infusion CCI [redacted]. On all other visits that do not require 24-hour in-house monitoring, vital signs must be collected pre-dose GSK3745417 and 2 hours following the infusion.
Weight	X		X	
Echocardiogram	X		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 or ECHO is not available, MUGA scans may be used. The modality used at baseline should be repeated throughout the study to ensure comparison to baseline. ECHO/MUGA obtained within a -4-day window pre-dose, and at TDV (unless performed in the previous 4 weeks).

	Screening[a]	Study Intervention Period			
Study Procedure		CCI [redacted]			**Notes**
Week					
Day	≤28				
12-lead ECG	X	CCI [redacted]		X	Triplicate ECGs will be obtained at screening Single ECGs should be obtained prior to GSK3745417 dosing, CCI [redacted] prior to completion of clinic visit. Patients with new onset symptoms consistent with immune-mediated pericarditis or myocarditis should have additional ECGs as clinically indicated.
Holter Monitoring		Day 1			12-lead Holter monitoring will be conducted on Day 1 and must start at least -2h (pre-dose), followed by normal activity (ambulatory) until CCI [redacted], when participant will be lying supine until time 0. Holter monitoring will end at 24h for all participants 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. If heart rate is increased or based on emerging data, hospitalization time might be extended. The requirement for Holter monitoring may be waived for individual participants upon approval from GSK.
Neurological Assessment including ICE scoring	X	Conduct if clinically indicated			Refer to Section 8.2.5. for neurological assessment details.
AE/SAE Review		Continuous: Assess AEs at each visit from first dose until the TDV. AESIs and SAEs collected to be collected until 90 days after the last dose or until start of subsequent anticancer treatment. SAEs related to study participation are collected from time of informed consent.			

	Screening[a]	Study Intervention Period				
Study Procedure		CCI				**Notes**
Week						
Day	**≤28**					
Concomitant Medication Review		Continuous: Assess at each visit from first dose of study intervention				
Follow Up Phone Call		CCI				After the first 6 doses of study intervention, 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						
Hepatitis B and C screening	X					
Pregnancy Test	X (urine)	CCI	CCI	X	X	Negative serum pregnancy test required within 72 hours prior to date of first dose of study treatment on Day 1 for females of childbearing potential; predose urine pregnancy test conducted every 3 weeks for duration of study, on last day of treatment (if possible), at TDV, and at the Follow-Up visits
	≤72 hours (serum) of first dose					
CBC with differential[d]	X	CCI		X		Sample collection times: Predose, CCI and CCI If a participant experiences cytokine release syndrome, perform CBC with differential at CCI too. The CCI sample is only required if participant remains in the clinic for either 24-hour monitoring, or other purposes.
Clinical Chemistry[d]	X[e]			X		Additional clinical chemistry samples should be collected in the event of CRS (see Section 6.6.1) Sample collection time: Predose. See Section 11.2 for complete list of required laboratory assessments.

	Screening[a]	Study Intervention Period			
Study Procedure		CCI [redacted]			**Notes**
Week					
Day	**≤28**				
C-Reactive Protein	X	CCI [redacted]	X		Sample collection times: Predose, CCI [redacted] sample collections are only required if participant remains in the clinic for either 8 - 24-hour monitoring, or other purposes. Additional C-Reactive Protein samples should be collected in the event of CRS (see Section 6.6.1)
Thyroid function[d]	X		X		After Screening, first assessment should be done at CCI [redacted]
Troponin I, T	X		X		See Section 6.6.1.1 for details. Samples for Troponin T for central lab, and T or I for local lab, to be collected pre-dose and result available before dosing. Samples will be collected every 3 weeks. On weeks when ECHO is required, pre-dose Troponin can also be obtained during the 4 days leading up to dose day.
BNP (or NTproBNP)	X	Repeat as clinically indicated			Repeat test as outlined in management of cardiac events (Section 6.6.1.1)
eGFR	X				
Urinalysis[d]	X	CCI [redacted]	X		If urinalysis is abnormal, a microscopy should be performed.
Coagulation[d]	X				Coagulation test required at screening starting at CCI [redacted] thereafter. Additional coagulation samples should be collected in the event of CRS (see Section 6.6.1)

	Screening[a]	Study Intervention Period			
Study Procedure		CCI			**Notes**
Week					
Day	≤28				
Laboratory Assessments for HBV/HCV Populations					
Liver Function Test[d]	X	CCI	X		After CCI, etc. unless ALT is ≥8x ULN, or ≥5x ULN and increasing, in which case continue weekly LFTs This test to be performed in participants testing positive for HBV or HCV[f] at Screening. Note: On visit days where pre-dose Clinical Chemistry is performed, LFTs do not have to be performed as a separate test.
HBV DNA[d]	X		X		CCI These tests to be performed in participants diagnosed with HCC and positive for HBV on screening.
Quantitative HBsAg[d]	X		X		Tests to be performed in participants diagnosed with Hepatocellular carcinoma (HCC) and positive for HBV on screening.
HCV antibody, HCV RNA	X				These tests to be performed in participants diagnosed with HCC and positive for HCV on screening.
CCI					

	Screening[a]	Study Intervention Period			
Study Procedure		CCI			**Notes**
Week					
Day	≤28				
					CCI
Efficacy Assessments					
CCI					

	Screening[a]	Study Intervention Period			
Study Procedure		CCI			**Notes**
Week					
Day	**≤28**				
CCI					

	Screening[a]	Study Intervention Period			
Study Procedure		CCI			**Notes**
Week					
Day	**≤28**				

CCI

	Screening[a]	Study Intervention Period			
Study Procedure		CCI			**Notes**
Week					
Day	≤28				

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 infusion; h=hour; ICF=informed consent form; m=min;
CCI [redacted]

Timepoint Definitions for assessments:
X = Anytime during visit (sampling date/time should be recorded)
CCI [redacted]

a. All assessments performed at Screening must be performed within 28 days prior to first dose unless otherwise specified.
b. Procedures should be performed at all 6 study interventions, unless otherwise specified
c. 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 CCI [redacted].
d. Procedures scheduled pre-dose on study treatment administration days can be performed within 3 days prior to dosing day, unless otherwise specified.
e. Baseline ALT in Participants with HCC and positive for HBV or positive for HCV should be determined by taking the mean value of the screening ALT and the pre-dose day 1 ALT.
f. When LFT and clinical chemistry collection time points coincide, samples for clinical chemistry only will be collected as the clinical chemistry panel includes LFT.
g. CCI [redacted]

Table 3 Schedule of Assessments CCI [redacted]

	Screening[a]	Study Intervention Period			Follow-Up	
Study Procedure		CCI [redacted]				**Notes**
Week	**≤4**					
Day	**≤28**					
Informed consent	X					
Inclusion and exclusion criteria	X					
Demographics, Medical History, Prior Medications, Disease Characteristics	X					Include use of antibiotics and probiotics taken 60 days prior to study intervention.
Anticancer Therapy	X					
Participant Registration	X					Source document only.
Safety Assessments						
24-Hour In-House Monitoring		CCI [redacted]				24-hour In-house monitoring is required on CCI [redacted] The requirement for the 24-hour stays may be eliminated as safety data emerge. At all visits, participants should be monitored in a medically qualified unit/clinic/hospital for minimum of 30 min pre-dose and for an 8-hour observation following dosing with GSK3745417 or GSK3745417 and dostarlimab. Participants may be released after a 6-hour observation period if, in the opinion of the investigator, it is safe to do so. Additional in-house monitoring should be considered for 8-24 h post-dose as clinically indicated.
Physical Exam	X			X		Refer to Section 8.2.1 for physical examination details. At screening, a complete physical exam is required, at subsequent visits, brief or

	Screening[a]	Study Intervention Period		Follow-Up	
Study Procedure		CCI [redacted]			**Notes**
Week	**≤4**				
Day	**≤28**				
					targeted physical exams are acceptable.
ECOG PS[d]	X	CCI [redacted]	X		
Vital Signs	X		X		On Weeks CCI [redacted] and CCI vital signs should be collected predose GSK3745417 and at the following times after the end of infusion CCI [redacted] measurement is collected if subject is in the clinic at this time for observation or other reason. On all other visits, vital signs will be collected predose CCI [redacted]
Weight	X		X		
Echocardiogram	X		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 or ECHO is not available, MUGA scans may be used. The modality used at baseline should be repeated throughout the study to ensure comparison to baseline. ECHO/MUGA obtained within a -4-day window pre-dose, and at TDV (unless performed in the previous 4 weeks).

	Screening[a]	Study Intervention Period		Follow-Up	
Study Procedure		CCI [redacted]			**Notes**
Week	**≤4**				
Day	**≤28**				
12-lead ECG	X	CCI [redacted]	X		Triplicate ECGs will be obtained at screening. Single ECGs should be obtained prior to GSK3745417 dosing, CCI [redacted] to completion of clinic visit. Post Week 6, next ECG should be on Week9 and then CCI [redacted] thereafter. Patients with new onset symptoms consistent with immune-mediated pericarditis or myocarditis should have additional ECGs as clinically indicated.
Neurological Assessment including ICE scoring	X	Conduct if clinically indicated			Refer to Section 8.2.5. for neurological assessment details.
AE/SAE Review		Continuous: Assess AEs at each visit from first dose until the TDV. AESIs and SAEs collected to be collected until 90 days after the last dose or until start of subsequent anticancer treatment. SAEs related to study participation are collected from time of informed consent.			
Concomitant Medication Review		Continuous: Assess at each visit from first dose of study intervention			
Follow-Up Phone Call		CCI [redacted]			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					
Hepatitis B and C screening	X				

	Screening[a]	Study Intervention Period		Follow-Up	
Study Procedure		CCI			**Notes**
Week	**≤4**				
Day	**≤28**				
Pregnancy Test	X (urine) ≤72 hours (serum) of first dose	CCI	CCI	X	X	Negative serum pregnancy test required at screening and within 72 hours prior to date of first dose of study treatments on Day 1 for females of childbearing potential; predose urine pregnancy test conducted every 3 weeks for duration of study, on last day of treatment (if possible), at TDV, and at the Follow-Up visits.
CBC with differential[d]	X	CCI		X		Sample collection times: CCI and CCI. If a participant experiences cytokine release syndrome, perform CBC with differential at CCI too. The CCI sample is only required if participant remains in the clinic for either 24-hour monitoring, or other purposes. CCI administered.
Clinical Chemistry[d]	X[e]			X		Sample collection time: Predose. See Section 11.2 for complete list of required laboratory assessments. Additional clinical chemistry samples should be collected in the event of CRS (see Section 6.6.1)
C-Reactive Protein	X			X		Sample collection times: Predose, CCI and CCI. When both study drugs are given, CCI sample

	Screening[a]	Study Intervention Period		Follow-Up	
Study Procedure		CCI [redacted]			**Notes**
Week	**≤4**				
Day	**≤28**				
					collections are only required if participant remains in the clinic for 8 - 24 hours of monitoring, or other purposes. Additional C-Reactive Protein samples should be collected in the event of CRS (see Section 6.6.1)
Thyroid function[d]	X	CCI [redacted]	X		After Screening, first assessment should be done at CCI [redacted]
Troponin I, T	X		X		See Section 6.6.1.1 for details. Samples for Troponin T for central lab, and T or I for local lab, to be collected pre-dose and result available before dosing. Samples will be collected CCI [redacted] On weeks when ECHO is required, pre-dose Troponin can also be obtained during the 4 days leading up to dose day.
BNP (or NTproBNP)	X	Repeat as clinically indicated			Repeat test as outlined in Cardiac Effects (Section 2.3.1) and management of cardiac events (Section 6.6.1.1)
eGFR	X				See Section 6.6.2 for management of renal events (if needed).
Urinalysis[d]	X	CCI [redacted]	X		If urinalysis is abnormal, a microscopy should be performed.
Coagulation[d]	X				Coagulation test required at screening starting at CCI [redacted] thereafter. Additional

	Screening[a]	Study Intervention Period			Follow-Up	
Study Procedure		CCI [redacted]				**Notes**
Week	**≤4**					
Day	**≤28**					
						coagulation samples should be collected in the event of CRS (see Section 6.6.1)
Laboratory Assessments for HBV/HCV Populations						
HBV DNA[d]	X	CCI [redacted]		X		Sample collection time: Predose. This test to be performed in participants diagnosed with HCC and positive for HBV on screening.
Quantitative HBsAg[d]	X			X		This test to be performed in participants diagnosed with HCC and positive for HBV on screening.
HCV antibody, HCV RNA	X					This test to be performed in participants diagnosed with HCC and positive for HCV on screening.
Study Intervention						
CCI [redacted]						Study Intervention must be administered within ±1 day of scheduled visit unless otherwise indicated. Subsequent doses should be administered at least 5 days apart. Infuse GSK3745417 over 2 minutes. When overnight stays are not required, participants should be observed for 8 hours, but can released at CCI [redacted] hours if in the opinion of the investigator it is safe to do so. See Section 4.1.6 for maximum duration of study intervention.[f]
						Dostarlimab will be started on Week 1, CCI [redacted]

	Screening[a]	Study Intervention Period			Follow-Up	
Study Procedure		CCI				**Notes**
Week	**≤4**					
Day	**≤28**					
			Note: For participants in Japan, dostarlimab dosing will be dosed at 500 mg CCI throughout the treatment period.			Dostarlimab should be administered via an IV infusion over 30 minutes (-5 minute and +15 minute) with a post-dostarlimab infusion observation period of 2 hours. See Section 6.1
Efficacy Assessments						
CCI						

	Screening[a]	Study Intervention Period			Follow-Up	
Study Procedure		CCI				**Notes**
Week	**≤4**					
Day	**≤28**					
						CCI
Pharmacokinetics (PK),						
CCI						

	Screening[a]	Study Intervention Period		Follow-Up	
Study Procedure		CCI			**Notes**
Week	**≤4**				
Day	**≤28**				
CCI					

	Screening[a]	Study Intervention Period			Follow-Up	
Study Procedure		CCI				**Notes**
Week	**≤4**					
Day	**≤28**					
CCI						
Dostarlimab Serum PK		Week 1 and 4	Weeks 13, 19, and then Q18W	X	W12	Dostarlimab PK Sampling Schedule: Predose-dose (within 1h prior to the start of the dostarlimab infusion) and 1 hour following the EOI of dostarlimab. One sample should be obtained 12 weeks after the last dose.
Dostarlimab Serum ADA		Week 1 and 4	Weeks 13, 19, and then Q18W	X	W12	Dostarlimab antidrug antibody (ADA) samples should be collected within 1h prior to the start of the dostarlimab infusion. One sample should be obtained 12 weeks after the last dose.

	Screening[a]	Study Intervention Period		Follow-Up	
Study Procedure		CCI			**Notes**
Week	**≤4**				
Day	**≤28**				
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 infusion; h=hour; ICF=informed consent form; m=min;

CCI

Timepoint Definitions for assessments:
X = Anytime during visit (sampling date/time should be recorded)

CCI

CCI [redacted]

a. All assessments performed at Screening must be performed within 28 days prior to first dose unless otherwise specified.
b. Procedures should be performed at all 12 weekly study interventions, unless otherwise specified
c. 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 CCI [redacted]
d. Procedures scheduled on study treatment administration days can be performed within 3 days prior to dosing day, unless otherwise specified.
e. Baseline ALT in Participants with HCC and positive for HBV or positive for HCV should be determined by taking the mean value of the screening ALT and the pre-dose Day 1 ALT.
f. CCI [redacted]

Table 4 Schedule of Assessments CCI [redacted]

	Screening[a]	Study Intervention Period			Follow-Up	
Study Procedure		CCI [redacted]				**Notes**
Week	**≤4**					
Day	**≤28**					
Informed consent	X					
Inclusion and exclusion criteria	X					
Demographics, Medical History, Prior Medications, Disease Characteristics	X					Include use of antibiotics and probiotics taken 60 days prior to study intervention.
Anticancer Therapy	X					
Participant Registration	X					Source document only.
Safety Assessments						
24-Hour In-House Monitoring		CCI [redacted]				24-Hour In-House monitoring are required on CCI [redacted]. The requirement for the 24-hour stays may be eliminated as safety data emerge. At all visits, participants should be monitored in a medically qualified unit/clinic/hospital for 30 minutes pre-dose and stay for an 8 h observation following dosing with GSK3745417 and dostarlimab. Participants may be released after a 6-hour observation period if, in the opinion of the investigator, it is safe to do so. Additional in-house monitoring should be considered for 8-24 h post-dose as clinically indicated.
Physical Exam	X	CCI [redacted]		X		Refer to Section 8.2.1 for physical examination details. At screening, a complete

	Screening[a]	Study Intervention Period		Follow-Up	
Study Procedure		CCI [redacted]			**Notes**
Week	**≤4**				
Day	**≤28**				
					physical exam is required, at subsequent visits, brief or targeted physical exams are acceptable.
ECOG PS[d]	X	CCI [redacted]	X		
Vital Signs	X		X		On Weeks CCI [redacted] vital signs should be collected predose GSK3745417 and at the following times after the CCI [redacted] measurement is collected if subject is in the clinic at this time for observation or other reason. On all other visits, vital signs will be collected CCI [redacted]
Weight	X		X		
Echocardiogram	X		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 or ECHO is not available, MUGA scans may be used. The modality used at baseline should be repeated throughout the study to ensure comparison to baseline. ECHO/MUGA obtained within a -4-day window pre-dose, and at TDV (unless performed in the previous 4 weeks).

	Screening[a]	Study Intervention Period		Follow-Up	
Study Procedure		CCI [redacted]			**Notes**
Week	**≤4**				
Day	**≤28**				
12-lead ECG	X	CCI [redacted]	X		Triplicate ECGs will be obtained at screening. Single ECGs should be obtained prior to GSK3745417 dosing, within CCI [redacted] and within 2 hours prior to completion of clinic visit. Patients with new onset symptoms consistent with immune-mediated pericarditis or myocarditis should have additional ECGs as clinically indicated.
Neurological Assessment including ICE scoring	X	Conduct if clinically indicated			Refer to Section 8.2.5. for neurological assessment details.
AE/SAE Review		Continuous: Assess AEs at each visit from first dose until the TDV. AESIs and SAEs to be collected until 90 days after the last dose or until start of subsequent anticancer treatment. SAEs related to study participation are collected from time of informed consent.			
Concomitant Medication Review		Continuous: Assess at each visit from first dose of study intervention			
Follow-Up Phone Call		CCI [redacted]			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					
Hepatitis B and C screening	X				

	Screening[a]	Study Intervention Period			Follow-Up	
Study Procedure		CCI				**Notes**
Week	**≤4**					
Day	**≤28**					
Pregnancy Test	X (urine)	CCI (pre-dose urine)	CCI (pre-dose urine)	X (urine)	X (urine)	Negative serum pregnancy test required at screening and within 72 hours prior to date of first dose of combination treatment on Day 1 for females of childbearing potential; predose urine pregnancy test conducted CCI for duration of study, on last day of treatment (if possible), at TDV, and at the Follow-Up visits.
	≤72 hours (serum) of first dose					
CBC with differential[d]	X	CCI		X		Sample collection times: Predose, CCI If a participant experiences cytokine release syndrome, perform CBC with differential at CCI sample is only required if participant remains in the clinic for either 24-hour monitoring, or other purposes. Note that CCI of dostarlimab on days when both study drugs are administered.
Clinical Chemistry[d]	X[e]			X		Sample collection time: Predose; see Section 11.2 for complete list of required laboratory assessments. Additional clinical chemistry samples should be collected in the event of CRS (see Section 6.6.1)
C-Reactive Protein	X			X		Sample collection times: Predose, CCI

	Screening[a]	Study Intervention Period		Follow-Up	
Study Procedure		CCI			**Notes**
Week	**≤4**				
Day	**≤28**				
					sample collections are only required if participant remains in the clinic for 8 - 24 hours of monitoring, or other purposes Additional C-Reactive Protein samples should be collected in the event of CRS (see Section 6.6.1)
Thyroid function[d]	X	CCI	X		After Screening, first assessment should be done at CCI .
Troponin I, T	X		X		See Section 6.6.1.1 for details. Samples for Troponin T for central lab, and T or I for local lab, to be collected pre-dose and result available before dosing Samples will be collected every 3 weeks. On weeks when ECHO is required, pre-dose Troponin can also be obtained during the 4 days leading up to dose day.
BNP (or NTproBNP)	X	Repeat as clinically indicated			Repeat test as outlined in management of cardiac events (Section 6.6.1.1)
eGFR	X				See Section 6.6.2 for management of renal events (if needed).
Urinalysis[d]	X	CCI	X		If urinalysis is abnormal, a microscopy should be performed.
Coagulation[d]	X				Coagulation test required at screening, and starting at CCI and CCI thereafter. Additional coagulation

Study Procedure	Screening[a]	Study Intervention Period			Follow-Up	Notes
Week	**≤4**	CCI				
Day	**≤28**					
						samples should be collected in the event of CRS (see Section 6.6.1)
Laboratory Assessments for HBV/HCV Populations						
Liver Function Test[d]	X[e]	CCI		X		After Week 13, LFTs will be evaluated CCI the next LFT evaluation will be at Week 13, 16, etc., unless ALT is ≥8xULN, or ≥5x ULN and increasing, in which case continue weekly LFTs. This test to be performed in participants testing positive for HBV or HCV[f] at Screening. Note: On visit days where pre-dose Clinical Chemistry is performed, LFTs do not have to be collected as a separate test since they will be part of clinical chemistry.
HBV DNA[d]	X			X		Sample collection time: Predose. CCI This test to be performed in participants diagnosed with HCC and positive for HBV on screening.
Quantitative HBsAg[d]	X			X		This test to be performed in participants diagnosed with HCC and positive for HBV on screening.
HCV antibody, HCV RNA	X					This test to be performed in participants diagnosed with HCC and positive for HCV on screening.

	Screening[a]	Study Intervention Period		Follow-Up	
Study Procedure		CCI			**Notes**
Week	**≤4**				
Day	**≤28**				
Study Intervention					
CCI					Study Intervention CCI CCI CCI. When overnight stays are not required, participants should be observed CCI if in the opinion of the investigator it is safe to do so.
					Dostarlimab will be started on Week 1, one hour after completion of the CCI Dostarlimab should be administered via an IV infusion over 30 minutes (a -5/+15 minute window is permitted). Patients will be observed for 2 hours post-dostarlimab infusion. See Section 6.1

	Screening[a]	Study Intervention Period		Follow-	
Study Procedure		CCI			**Notes**
Week	**≤4**				
Day	**≤28**				
Efficacy Assessments					
CCI					

	Screening[a]	Study Intervention Period		Follow-Up	
Study Procedure		CCI			**Notes**
Week	**≤4**				
Day	**≤28**				
Pharmacokinetics (PK), CCI					
CCI					

	Screening[a]	Study Intervention Period		Follow-Up	
Study Procedure		CCI			**Notes**
Week	**≤4**				
Day	**≤28**				
CCI					

	Screening[a]	Study Intervention Period		Follow-Up	
Study Procedure		CCI			**Notes**
Week	**≤4**				
Day	**≤28**				
Plasma CCI		CCI			
CCI					
Dostarlimab Serum PK		Week 1 and 4	CCI	X	W12	Dostarlimab PK Sampling Schedule: Predose (within 1h prior to the start of the dostarlimab infusion), and 1 hour following the EOI of dostarlimab. One sample should be obtained 12 weeks from the last dose.
Dostarlimab Serum ADA		CCI				Dostarlimab antidrug antibody (ADA) samples should be collected within 1h prior to the start of the dostarlimab infusion. One sample should be obtained 12 weeks from the last dose.
CCI					

	Screening[a]	Study Intervention Period		Follow-Up	
Study Procedure		CCI			**Notes**
Week	**≤4**				
Day	**≤28**				
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 infusion; h=hour; ICF=informed consent form; m=min; CCI ; SAE=serious adverse event; W=week; TDV=treatment discontinuation visit

Timepoint Definitions for assessments:
X = Anytime during visit (sampling date/time should be recorded)
CCI

CCI [redacted]

a. All assessments performed at Screening must be performed within 28 days prior to first dose unless otherwise specified.
b. Procedures should be performed at all study interventions, unless otherwise specified.
c. 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 CCI [redacted]
d. Procedures scheduled pre-dose on study treatment administration days can be performed within 3 days prior to dosing day, unless otherwise specified.
e. Baseline ALT in participants with HCC and positive for HBV or positive for HCV should be determined by taking the mean value of the screening ALT and the pre-dose Day 1 ALT.
f. When LFT and clinical chemistry collection time points coincide, samples for clinical chemistry only will be collected as the clinical chemistry panel includes LFT.
g. CCI [redacted].

Table 5 Schedule of Assessments CCI [redacted]

Study Procedure	Pre CCI [redacted]	Study Intervention CCI [redacted]	Notes
Week (in combination)	≤1 (unless indicated)		
Day (in combination)	≤7 day (unless indicated)		
Informed consent	X		Participant signs informed consent for Part 2A
Inclusion/Exclusion	X		
Participant Registration	X		Source document only
Safety Assessments			
24-Hour In-House Monitoring		Follow SoA for A3 (Table 3) or A4 (Table 4) at crossover, as assigned	
Physical Exam	X		Refer to Section 8.2.1 for physical examination details. At pre-crossover baseline, a complete physical exam is required, at subsequent visits, brief or targeted physical exams are acceptable.
ECOG PS	X		
Vital Signs	X		
Weight	X		
Oxygen saturation	CCI [redacted]		
CCI [redacted]			Applies only to participants in Japan cohort. Chest CT scan (preferred) or chest x-ray. If tumor imaging for a given participant is conducted via chest CT scan or chest x-ray, the same imaging may be used for ILD assessment (Section 8.2.8)

Study Procedure	Pre-CCI [redacted] [a]	Study Intervention CCI [redacted]	Notes
Week (in combination)	**≤1 (unless indicated)**		
Day (in combination)	**≤7 day (unless indicated)**		
Echocardiogram	ECHO/MUGA performed if not conducted within 4 weeks prior to start of combination treatment	Follow SoA for A3 (Table 3) or A4 (Table 4) at crossover, as assigned	If available, a 3D ECHO is preferred, otherwise a 2D ECHO may be performed. Where the quality of the ECHO examination is sub-optimal or ECHO is not available, MUGA scans may be used. The modality used at baseline should be repeated throughout the study to ensure comparison to baseline.
12-lead ECG	X	Follow SoA for A3 (Table 3) or A4 (Table 4) at crossover, as assigned	Triplicate ECGs will be obtained at pre-combination baseline.
Neurological Assessment including ICE scoring	X		Refer to Section 8.2.5. for neurological assessment details.
AE/SAE Review			Continuous: Assess AEs at each visit from first monotherapy dose until the combination TDV. For AESI and SAEs collected until 90 days after the last combination dose or until start of subsequent anticancer treatment. SAEs related to study participation are collected from informed consent for monotherapy.
Concomitant Medication Review	Continuous: Assess at each visit from first dose of study intervention		
Safety Laboratory Assessments			
Pregnancy Test	≤72 hours (serum) of first combination dose	Follow SoA for A3 (Table 3) or A4 (Table 4) at crossover, as assigned	See Section 6.6.1
CBC with differential	X		
Clinical Chemistry	X		
C-Reactive Protein	X		See Section 6.6.1

Study Procedure	Pre-CCI [redacted] [a]	Study Intervention CCI [redacted]	Notes
Week (in combination)	**≤1 (unless indicated)**		
Day (in combination)	**≤7 day (unless indicated)**		
Thyroid function	If not performed within 7 days prior to first combination dose		
Troponin I, T	Samples for Troponin T for central lab, and T or I for local lab, collected pre-dose and result available before first combination dose		See Section 6.6.1.1
BNP (or NTproBNP)	X		
eGFR	X		See Section 6.6.2 for management of renal events (if needed).
Urinalysis	X		If urinalysis is abnormal, a microscopy should be performed.
Coagulation	X		Coagulation test required at pre-combination baseline
Laboratory Assessments for HBV/HCV Populations			
HBV DNA	Repeat If not performed within prior 3 weeks of Day 1 of combination	Follow SoA for A3 (Table 3) or A4 (Table 4) at crossover, as assigned	This test to be performed in participants diagnosed with HCC and positive for HBV on initial screening in monotherapy.
Quantitative HBsAg	X		This test to be performed in participants diagnosed with HCC and positive for HBV on initial screening in monotherapy.
Study Intervention			
Administer GSK3745417		Follow SoA for A3 (Table 3) or A4 (Table 4) at crossover, as assigned	
Administer Dostarlimab			

CCI [redacted]

Study Procedure	Pre CCI	Study Intervention CCI	Notes
Week (in combination)	≤1 (unless indicated)		
Day (in combination)	≤7 day (unless indicated)		
Pharmacokinetics (PK), CCI			
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 infusion; h=hour; ICF=informed consent form; m=min;
CCI

X = Anytime during visit (sampling date/time should be recorded)

a. Assessments to be repeated at pre-combination baseline if assessment has not been performed within 7 days prior to first combination dose unless otherwise specified.

1.2.1. Revised Schedule of Assessments

Table 1-1 Schedule of Assessments CCI [redacted]

	Screening[a]	Study Intervention Period			
Study Procedure		CCI [redacted]			**Notes**
Week					
Day	≤28				
Safety Assessments					
Physical Exam	X	CCI [redacted]	X		Refer to Section 8.2.1 for physical examination details. At screening, a complete physical exam including height and weight is required, at subsequent visits, brief or targeted physical exams are acceptable.
ECOG PS[d]	X		X		
Vital Signs	X		X		Vital signs must be collected pre-dose GSK3745417 and +2h CCI [redacted] CCI [redacted]: pulse oximetry will be part of vitals.
Weight	X		X		
CCI [redacted]					
Oxygen saturation	X	CCI [redacted]	X		Applies only to participants in CCI [redacted] only. (Section 8.2.2)
Echocardiogram	X				If available, a 3D ECHO is preferred, otherwise a 2D ECHO may be performed.

	Screening[a]	Study Intervention Period			
Study Procedure		CCI [redacted]			**Notes**
Week					
Day	**≤28**				
		CCI [redacted]			Where the quality of the ECHO examination is sub-optimal or ECHO is not available, MUGA scans may be used. The modality used at baseline should be repeated throughout the study to ensure comparison to baseline. ECHO/MUGA obtained within a -4-day window pre-dose
12-lead ECG	X	CCI [redacted]	X		Triple ECGs will be obtained at Screening. Single ECGs should be obtained prior to GSK3745417 dosing, CCI [redacted]. Post Week 4, ECGs should be on Week 7, then CCI [redacted] thereafter. Patients with new onset symptoms consistent with immune-mediated pericarditis or myocarditis should have additional ECGs as clinically indicated.
Neurological Assessment including ICE scoring	X	Conduct if clinically indicated			Refer to Section 8.2.5. for neurological assessment details.
Follow Up Phone Call				X	Participant contacted at +90 days from end of treatment for Safety Follow-up assessment of AESIs and SAEs (below)

	Screening[a]	Study Intervention Period			
Study Procedure		CCI [redacted]			**Notes**
Week					
Day	**≤28**				
AE/SAE Review		Continuous: Assess AEs at each visit from first dose until the TDV. AESIs and SAEs to be collected until 90 days after the last dose or until start of subsequent anticancer treatment. SAEs related to study participation are collected from time of informed consent.			
Concomitant Medication Review		Continuous: Assess at each visit from first dose of study intervention			
Safety Laboratory Assessments					
Pregnancy Test	X (urine)	CCI [redacted] (pre-dose urine)	CCI [redacted] (pre-dose urine)	X	Negative serum pregnancy test required within 72 hours prior to date of first dose of study treatment on Day 1 for WOCBP; predose urine pregnancy test conducted every 3 weeks for duration of study, on last day of treatment (if possible), at TDV, and at the Follow-Up visits.
	≤72 hours (serum) of first dose				
CBC with differential[d]	X	CCI [redacted]		X	Sample collection times: CCI [redacted] and CCI [redacted]. If a participant experiences cytokine release syndrome, perform CBC with differential at CCI [redacted] too. The CCI [redacted] sample is only required if participant remains in the clinic for either 24-hour monitoring, or other purposes.
Clinical Chemistry[d]	X			X	Sample collection time: Predose. See Section 11.2 for complete list of required laboratory assessments. Additional clinical chemistry samples should be collected in the event of CRS (see Section 6.6.1)
C-Reactive Protein	X			X	Sample collection times: Predose, EOI+ 4h, EOI+8h and EOI+24h. The EOI+8h and EOI+24h sample collections are only

	Screening[a]	Study Intervention Period				
Study Procedure		CCI [redacted]				**Notes**
Week						
Day	**≤28**					
						required if participant remains in the clinic for either 8 - 24-hour monitoring, or other purposes. Additional C-Reactive Protein samples should be collected in the event of CRS (see Section 6.6.1)
Troponin I, T	X	CCI [redacted]		X		See Section 6.6.1.1 for details. Samples for Troponin at local lab (for local lab Troponin I is preferred), to be collected pre-dose and result available before dosing. Samples will be collected CCI [redacted]. On weeks where ECHO is required, pre-dose troponin can also be obtained during the 4 days leading up to dose day. The same local laboratory test (troponin I or troponin T) should be used consistently for an individual subject throughout the study. **Note: Samples for troponin at central lab no longer required.**
Thyroid function[d]	X			X		After Screening, first assessment should be done at CCI [redacted].
Urinalysis[d]	X			X		If urinalysis is abnormal, a microscopy should be performed.
Coagulation[d]	X					Coagulation test required at screening and starting at CCI [redacted]. Additional coagulation samples should be collected in the event of CRS (see Section 6.6.1)

	Screening[a]	Study Intervention Period			
Study Procedure		CCI			**Notes**
Week					
Day	≤28				
Laboratory Assessments for HBV/HCV Populations					
HBV DNA[d]	X	CCI	X		Sample collection time: Predose starting on CCI and continue CCI. This test to be performed in participants diagnosed with hepatocellular carcinoma (HCC) and positive for HBV on screening.
Quantitative HBsAg[d]	X		X		This test to be performed in participants diagnosed with HCC and positive for HBV on screening.
CCI					

	Screening[a]	Study Intervention Period			
Study Procedure		CCI			**Notes**
Week					
Day	**≤28**				
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 infusion; h=hour; ICF=informed consent form; m=min;
CCI

Timepoint Definitions for assessments:
X = Anytime during visit (sampling date/time should be recorded)
CCI

CCI [redacted]

a. All assessments performed at Screening must be performed within 28 days prior to first dose unless otherwise specified.
b. Procedures should be performed at all 6 weekly study interventions, unless otherwise specified
c. 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.
d. Procedures scheduled pre-dose on study treatment administration days can be performed within 3 days prior to dosing day, unless otherwise specified.
e. +90 day Safety Follow-up assessment must be completed within 90 days from the date study treatment was discontinued. The window for this visit is +/-10 days

Table 2-1 Schedule of Assessments (Part 1A, Arm A2: GSK3745417 Monotherapy Every 3 Weeks Dosing Schedule)

	Screening[a]	Study Intervention Period			
Study Procedure		CCI [redacted]			**Notes**
Week					
Day	**≤28**				
Safety Assessments					
Physical Exam	X	CCI [redacted]	X		Refer to Section 8.2.1 for physical examination details. At screening, a complete physical exam including height and weight is required, at subsequent visits, brief or targeted physical exams are acceptable.
ECOG PS[d]	X		X		
Vital Signs	X		X		Vital signs must be collected pre-dose GSK3745417 and 2 hours CCI [redacted] pulse oximetry will be part of vitals.
Weight	X		X		
Echocardiogram	X				If available, a 3D ECHO is preferred, otherwise a 2D ECHO may be performed. Where the quality of the

	Screening[a]	Study Intervention Period			
Study Procedure		CCI [redacted]			**Notes**
Week					
Day	**≤28**				
		(and when clinically indicated for elevated biomarkers or cardiovascular symptoms)			ECHO examination is sub-optimal or ECHO is not available, MUGA scans may be used. The modality used at baseline should be repeated throughout the study to ensure comparison to baseline. ECHO/MUGA obtained within a -4-day window pre-dose.
12-lead ECG	X	CCI [redacted]	X		Triplicate ECGs will be obtained at screening Single ECGs should be obtained prior to GSK3745417 dosing, CCI [redacted] Patients with new onset symptoms consistent with immune-mediated pericarditis or myocarditis should have additional ECGs as clinically indicated.
Neurological Assessment including ICE scoring	X	Conduct if clinically indicated			Refer to Section 8.2.5. for neurological assessment details.
Follow Up Phone Call				X	Participant contacted at +90 days from end of treatment for Safety Follow-up assessment of AESIs and SAEs (below)
AE/SAE Review		Continuous: Assess AEs at each visit from first dose until the TDV. AESIs and SAEs to be collected until 90 days after the last dose or until start of subsequent anticancer treatment. SAEs related to study participation are collected from time of informed consent.			
Concomitant Medication Review		Continuous: Assess at each visit from first dose of study intervention			

	Screening[a]	Study Intervention Period			
Study Procedure		CCI [redacted]			**Notes**
Week					
Day	**≤28**				
Safety Laboratory Assessments					
Pregnancy Test	X (urine) ≤72 hours (serum) of first dose	CCI [redacted]	X		Negative serum pregnancy test required within 72 hours prior to date of first dose of study treatment on Day 1 for females of childbearing potential; predose urine pregnancy test conducted every CCI [redacted] for duration of study, on last day of treatment (if possible), at TDV, and at the Follow-Up visits
CBC with differential[d]	X	CCI [redacted]	X		Sample collection times: CCI [redacted] If a participant experiences cytokine release syndrome, perform CBC with differential at CCI [redacted] too. CCI [redacted]
Clinical Chemistry[d]	X[e]		X		Additional clinical chemistry samples should be collected in the event of CRS (see Section 6.6.1) Sample collection time: Predose. See Section 11.2 for complete list of required laboratory assessments.
C-Reactive Protein	X		X		Sample collection times: CCI [redacted] sample collections are only required if participant remains in the clinic for either 8 - 24-hour monitoring, or other purposes. Additional C-Reactive Protein samples should be collected in the event of CRS (see Section 6.6.1)
Thyroid function[d]	X		X		After Screening, first assessment should be done at CCI [redacted]

	Screening[a]	Study Intervention Period			
Study Procedure		CCI [redacted]			**Notes**
Week					
Day	**≤28**				
Troponin I, T	X	CCI [redacted]	X		See Section 6.6.1.1 for details. Samples for Troponin T or I at local lab (for local lab Troponin I is preferred), to be collected pre-dose and result available before dosing. Samples will be collected CCI [redacted]. On weeks when ECHO is required, pre-dose Troponin can also be obtained during the 4 days leading up to dose day. **Note: Samples for Troponin at central lab no longer required.**
Urinalysis[d]	X		X		If urinalysis is abnormal, a microscopy should be performed.
Coagulation[d]	X				Coagulation test required at screening starting at CCI [redacted] thereafter. Additional coagulation samples should be collected in the event of CRS (see Section 6.6.1)
Laboratory Assessments for HBV/HCV Populations					
Liver Function Test[d]	X	CCI [redacted]	X		After CCI [redacted], etc. unless ALT is ≥8x ULN, or ≥5x ULN and increasing, in which case continue weekly LFTs This test to be performed in participants testing positive for HBV or HCV[f] at Screening. Note: On visit days where pre-dose Clinical Chemistry is performed, LFTs do not have to be performed as a separate test.
HBV DNA[d]	X		X		Sample collection time: Predose starting on CCI [redacted]

	Screening[a]	Study Intervention Period				
Study Procedure		CCI				**Notes**
Week						
Day	**≤28**					
						These tests to be performed in participants diagnosed with HCC and positive for HBV on screening.
Quantitative HBsAg[d]	X	CCI		X		Tests to be performed in participants diagnosed with Hepatocellular carcinoma (HCC) and positive for HBV on screening.
Study Intervention						
Administer GSK3745417		CCI				CCI When overnight stays are not required, participants should be observed for 8 hours, but can released at CCI hours if in the opinion of the investigator it is safe to do so.
CCI						

	Screening[a]	Study Intervention Period			
Study Procedure		CCI			**Notes**
Week					
Day	≤28				

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 infusion; h=hour; ICF=informed consent form; m=min; CCI ; PBMC = peripheral blood mononuclear cells RECIST=response evaluation criteria in solid tumors; CCI ; SAE=serious adverse event; W=week; TDV=treatment discontinuation visit

Timepoint Definitions for assessments:
X = Anytime during visit (sampling date/time should be recorded)
CCI

a. All assessments performed at Screening must be performed within 28 days prior to first dose unless otherwise specified.
b. Procedures should be performed at all 6 study interventions, unless otherwise specified

c. 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 CCI [redacted]

d. Procedures scheduled pre-dose on study treatment administration days can be performed within 3 days prior to dosing day, unless otherwise specified.

e. +90 day Safety Follow-up assessment must be completed within 90 days from the date study treatment was discontinued. The window for this visit is +/-10 days

Table 3-1 Schedule of Assessments CCI [redacted]

	Screening[a]	Study Intervention Period			
Study Procedure		CCI [redacted]			**Notes**
Week	**≤4**				
Day	**≤28**				
Safety Assessments					
Physical Exam	X	CCI [redacted]	X		Refer to Section 8.2.1 for physical examination details. At screening, a complete physical exam is required, at subsequent visits, brief or targeted physical exams are acceptable.
ECOG PS[d]	X		X		
Vital Signs	X		X		On Weeks CCI [redacted] and CCI [redacted] vital signs should be collected predose GSK3745417 and at the following times after the CCI [redacted] measurement is collected if subject is in the clinic at this time for observation or other reason. On all other visits, vital signs will be collected predose GSK3745417 and 2 hours CCI [redacted]
Weight	X		X		

	Screening[a]	Study Intervention Period			
Study Procedure		CCI [redacted]			**Notes**
Week	**≤4**				
Day	**≤28**				
Echocardiogram	X		CCI [redacted] (and when clinically indicated for elevated biomarkers or cardiovascular symptoms)		If available, a 3D ECHO is preferred, otherwise a 2D ECHO may be performed. Where the quality of the ECHO examination is sub-optimal or ECHO is not available, MUGA scans may be used. The modality used at baseline should be repeated throughout the study to ensure comparison to baseline. ECHO/MUGA obtained within a -4-day window pre-dose.
12-lead ECG	X	CCI [redacted]		X	Triplicate ECGs will be obtained at screening. Single ECGs should be obtained prior to GSK3745417 dosing, CCI [redacted], and CCI [redacted] prior to completion of clinic visit. Post Week 6, next ECG should be on Week9 and then CCI [redacted] thereafter. Patients with new onset symptoms consistent with immune-mediated pericarditis or myocarditis should have additional ECGs as clinically indicated.
Neurological Assessment including ICE scoring	X	Conduct if clinically indicated			Refer to Section 8.2.5. for neurological assessment details.
Follow Up Phone Call				X	Participant contacted at +90 days from end of treatment for Safety Follow-up assessment of AESIs and SAEs (below)

	Screening[a]	Study Intervention Period			
Study Procedure		CCI [redacted]			**Notes**
Week	**≤4**				
Day	**≤28**				
AE/SAE Review		Continuous: Assess AEs at each visit from first dose until the TDV. AESIs and SAEs collected to be collected until 90 days after the last dose or until start of subsequent anticancer treatment. SAEs related to study participation are collected from time of informed consent.			
Concomitant Medication Review		Continuous: Assess at each visit from first dose of study intervention			
Safety Laboratory Assessments					
Pregnancy Test	X (urine)	CCI [redacted]	X		Negative serum pregnancy test required at screening and within 72 hours prior to date of first dose of study treatments on Day 1 for females of childbearing potential; predose urine pregnancy test conducted every 3 weeks for duration of study, on last day of treatment (if possible), at TDV, and at the Follow-Up visits.
	≤72 hours (serum) of first dose				
CBC with differential[d]	X	CCI [redacted]	X		Sample collection times: CCI [redacted] If a participant experiences cytokine release syndrome, perform CBC with differential CCI [redacted] too. The EOI+24h sample is only required if participant remains in the clinic for either 24-hour monitoring, or other purposes. Note that CCI [redacted] of dostarlimab on days when both study drugs are administered.
Clinical Chemistry[d]	X[e]	[redacted]	X		Sample collection time: Predose. See Section 11.2 for complete list of required laboratory assessments. Additional clinical chemistry

	Screening[a]	Study Intervention Period			
Study Procedure		CCI [redacted]			**Notes**
Week	**≤4**				
Day	**≤28**				
					samples should be collected in the event of CRS (see Section 6.6.1)
C-Reactive Protein	X	CCI [redacted]	X		Sample collection times: CCI [redacted]. When both study drugs are given, CCI [redacted] collections are only required if participant remains in the clinic for 8 - 24 hours of monitoring, or other purposes. Additional C-Reactive Protein samples should be collected in the event of CRS (see Section 6.6.1)
Thyroid function[d]	X		X		After Screening, first assessment should be done at CCI [redacted].
Troponin I, T	X		X		See Section 6.6.1.1 for details. Samples for troponin T or I at local lab (for local lab, troponin I is preferred), to be collected pre-dose and result available before dosing. Samples will be collected CCI [redacted]. On weeks when ECHO is required, pre-dose troponin can also be obtained during the 4 days leading up to dose day. **Note: Samples for troponin for central lab no longer required.**
Urinalysis[d]	X		X		If urinalysis is abnormal, a microscopy should be performed.
Coagulation[d]	X				Coagulation test required at screening starting at CCI [redacted] thereafter. Additional

	Screening[a]	Study Intervention Period				
Study Procedure		**GSK3745417 Weekly+ Dostarlimab**		**TDV[c]**	**Safety F-U**	**Notes**
Week	**≤4**	**1-12[b]**	**13-104**	**+4**		
Day	**≤28**	**1 - 78**	**85 - 722**	**+30d**	**+90d[e]**	
						coagulation samples should be collected in the event of CRS (see Section 6.6.1)
CCI						
HBV DNA[d]	X	CCI		X		Sample collection time: Predose. This test to be performed in participants diagnosed with HCC and positive for HBV on screening.
Quantitative HBsAg[d]	X			X		This test to be performed in participants diagnosed with HCC and positive for HBV on screening.
Study Intervention						
Administer GSK3745417		CCI				
Administer Dostarlimab						

	Screening[a]	Study Intervention Period			
Study Procedure		CCI [redacted]			**Notes**
Week	**≤4**				
Day	**≤28**				
Efficacy Assessments					
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 infusion; h=hour; ICF=informed consent form; m=min;

CCI [redacted]; SAE=serious adverse event; W=week; TDV=treatment discontinuation visit

Timepoint Definitions for assessments:
X = Anytime during visit (sampling date/time should be recorded)

CCI [redacted]

CCI [redacted]

a. All assessments performed at Screening must be performed within 28 days prior to first dose unless otherwise specified.
b. Procedures should be performed at all 12 weekly study interventions, unless otherwise specified
c. 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 CCI [redacted]
d. Procedures scheduled on study treatment administration days can be performed within 3 days prior to dosing day, unless otherwise specified.
e. +90 day Safety Follow-up assessment must be completed within 90 days from the date study treatment was discontinued. The window for this visit is +/-10 days

Table 4-1 Schedule of Assessments CCI [redacted]

Study Procedure	Screening[a]	Study Intervention Period			Notes
		CCI [redacted]			
Week	≤4				
Day	≤28				
Safety Assessments					
Physical Exam	X		X		Refer to Section 8.2.1 for physical examination details. At screening, a complete physical exam is required, at subsequent visits, brief or targeted physical exams are acceptable.
ECOG PS[d]	X		X		
Vital Signs	X		X		On CCI [redacted], vital signs should be collected predose GSK3745417 and at the following times after the end of infusion CCI [redacted] measurement is collected if subject is in the clinic at this time for observation or other reason.On all other visits, vital signs will be collected predose GSK3745417 and 2 h CCI [redacted]
Weight	X		X		
Echocardiogram	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 or ECHO is not available, MUGA scans may be used. The modality used at

	Screening[a]	Study Intervention Period			
Study Procedure		CCI [redacted]			**Notes**
Week	**≤4**				
Day	**≤28**				
					baseline should be repeated throughout the study to ensure comparison to baseline. ECHO/MUGA obtained within a -4-day window pre-dose.
12-lead ECG	X	CCI [redacted]	X		Triplicate ECGs will be obtained at screening. Single ECGs should be obtained prior to CCI [redacted] Patients with new onset symptoms consistent with immune-mediated pericarditis or myocarditis should have additional ECGs as clinically indicated.
Neurological Assessment including ICE scoring	X	Conduct if clinically indicated			Refer to Section 8.2.5. for neurological assessment details.
Follow Up Phone Call				X	Participant contacted at +90 days from end of treatment for Safety Follow-up assessment of AESIs and SAEs (below)
AE/SAE Review		Continuous: Assess AEs at each visit from first dose until the TDV. AESIs and SAEs to be collected until 90 days after the last dose or until start of subsequent anticancer treatment. SAEs related to study participation are collected from time of informed consent.			
Concomitant Medication Review		Continuous: Assess at each visit from first dose of study intervention			

	Screening[a]	Study Intervention Period			
Study Procedure		CCI [redacted]			**Notes**
Week	**≤4**				
Day	**≤28**				
Safety Laboratory Assessments					
Pregnancy Test	X (urine)	CCI [redacted]			Negative serum pregnancy test required at screening and within 72 hours prior to date of first dose of combination treatment on Day 1 for females of childbearing potential; predose urine pregnancy test conducted every 3 weeks for duration of study, on last day of treatment (if possible), at TDV, and at the Follow-Up visits.
	≤72 hours (serum) of first dose				
CBC with differential[d]	X	CCI [redacted]	X		Sample collection times: CCI [redacted] If a participant experiences cytokine release syndrome, perform CBC with differential at CCI [redacted] sample is only required if participant CCI [redacted] for either 24-hour monitoring, or other purposes. Note that EOI here refers to EOI of dostarlimab on days when both study drugs are administered.
Clinical Chemistry[d]	X[e]		X		Sample collection time: Predose; see Section 11.2 for complete list of required laboratory assessments. Additional clinical chemistry samples should be collected in the event of CRS (see Section 6.6.1)
C-Reactive Protein	X		X		Sample collection times: CCI [redacted]

	Screening[a]	Study Intervention Period			
Study Procedure		CCI [redacted]			**Notes**
Week	**≤4**				
Day	**≤28**				
					sample collections are only required if participant CCI [redacted] or other purposes Additional C-Reactive Protein samples should be collected in the event of CRS (see Section 6.6.1)
Thyroid function[d]	X	CCI [redacted]		X	After Screening, first assessment should be done at CCI [redacted].
Troponin I, T	X			X	See Section 6.6.1.1 for details. Samples for troponin T or I at local lab (for local lab troponin I is preferred), to be collected pre-dose and result available before dosing Samples will be collected CCI [redacted]. On weeks when ECHO is required, pre-dose troponin can also be obtained during the 4 days leading up to dose day. **Note: Samples for troponin for central lab no longer required.**
Urinalysis[d]	X			X	If urinalysis is abnormal, a microscopy should be performed.
Coagulation[d]	X				Coagulation test required at screening, and starting at CCI [redacted]. Additional coagulation samples should be collected in the event of CRS (see Section 6.6.1)

	Screening[a]	Study Intervention Period			
Study Procedure		CCI [redacted]			**Notes**
Week	**≤4**				
Day	**≤28**				
Laboratory Assessments for HBV/HCV Populations					
Liver Function Test[d]	X[e]	CCI [redacted]	X		After Week 13, LFTs will be evaluated CCI [redacted] the next LFT evaluation will be at Week 13, 16, etc., unless ALT is ≥8xULN, or ≥5x ULN and increasing, in which case continue weekly LFTs. This test to be performed in participants testing positive for HBV or HCV[f] at Screening. Note: On visit days where pre-dose Clinical Chemistry is performed, LFTs do not have to be collected as a separate test since they will be part of clinical chemistry.
HBV DNA[d]	X		X		Sample collection time: Predose. CCI [redacted] This test to be performed in participants diagnosed with HCC and positive for HBV on screening.
Quantitative HBsAg[d]	X		X		This test to be performed in participants diagnosed with HCC and positive for HBV on screening.
Study Intervention					
Administer GSK3745417		CCI [redacted]			CCI [redacted]

	Screening[a]	Study Intervention Period				
Study Procedure		**GSK3745417 Every 3 Weeks + Dostarlimab**		**TDV[c]**	**Safety F-U**	**Notes**
Week	**≤4**	**1, 4, 7, and 10 [b]**	**13-104**	**+4**		
Day	**≤28**	**1, 22, 43, and 64**	**85 - 722**	**+30d**	**+90d[e]**	
						CCI [redacted]
Administer Dostarlimab		CCI [redacted]				
Efficacy Assessments						
CCI [redacted]						

	Screening[a]	Study Intervention Period			
Study Procedure		CCI			**Notes**
Week	**≤4**				
Day	**≤28**				
					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 infusion; h=hour; ICF=informed consent form; m=min; CCI ; SAE=serious adverse event; W=week; TDV=treatment discontinuation visit

Timepoint Definitions for assessments:
X = Anytime during visit (sampling date/time should be recorded)
CCI

a. All assessments performed at Screening must be performed within 28 days prior to first dose unless otherwise specified.
b. Procedures should be performed at all study interventions, unless otherwise specified.
c. 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 CCI
d. Procedures scheduled pre-dose on study treatment administration days can be performed within 3 days prior to dosing day, unless otherwise specified.
e. +90 day Safety Follow-up assessment must be completed within 90 days from the date study treatment was discontinued. The window for this visit is +/-10 day

Table 5-1 Schedule of Assessments CCI [redacted]

Study Procedure	Pre-Crossover Baseline [a]	Study Intervention CCI [redacted]	Notes
Week (in combination)	≤1 (unless indicated)		
Day (in combination)	≤7 day (unless indicated)		
Informed consent	X		Participant signs informed consent for Part 2A
Inclusion/Exclusion	X		
Participant Registration	X		Source document only
Safety Assessments			
24-Hour In-House Monitoring		Follow SoA for A3 (Table 3) or A4 (Table 4) at crossover, as assigned	
Physical Exam	X		Refer to Section 8.2.1 for physical examination details. At pre-crossover baseline, a complete physical exam is required, at subsequent visits, brief or targeted physical exams are acceptable.
ECOG PS	X		
Vital Signs	X		CCI [redacted]
Weight	X		
CCI [redacted]			

Study Procedure	Pre-Crossover Baseline [a]	Study Intervention CCI [redacted]	Notes
Week (in combination)	**≤1 (unless indicated)**		
Day (in combination)	**≤7 day (unless indicated)**		
Echocardiogram	ECHO/MUGA performed if not conducted within 4 weeks prior to start of combination treatment	Follow SoA for A3 (Table 3-1) or A4 (Table 4-1) at crossover, as assigned	If available, a 3D ECHO is preferred, otherwise a 2D ECHO may be performed. Where the quality of the ECHO examination is sub-optimal or ECHO is not available, MUGA scans may be used. The modality used at baseline should be repeated throughout the study to ensure comparison to baseline.
12-lead ECG	X	Follow SoA for A3 (Table 3-1) or A4 (Table 4-1) at crossover, as assigned	Triplicate ECGs will be obtained at pre-combination baseline.
Neurological Assessment including ICE scoring	X		
Follow-up phone call			Participant contacted at +90 days from end of treatment for Safety Follow-up assessment of AESIs and SAEs (below)
AE/SAE Review			Continuous: Assess AEs at each visit from first monotherapy dose until the combination TDV. For AESI and SAEs collected until 90 days after the last combination dose or until start of subsequent anticancer treatment. SAEs related to study participation are collected from informed consent for monotherapy.
Concomitant Medication Review	Continuous: Assess at each visit from first dose of study intervention		
Safety Laboratory Assessments			
Pregnancy Test	≤72 hours (serum) of first combination dose	Follow SoA for A3 (Table 3-1) or A4 (Table 4-1) at crossover, as assigned	See Section 6.6.1
CBC with differential	X		
Clinical Chemistry	X		

	Pre-Crossover Baseline [a]	Study Intervention	Notes
Study Procedure		CCI [redacted]	
Week (in combination)	**≤1 (unless indicated)**		
Day (in combination)	**≤7 day (unless indicated)**		
C-Reactive Protein	X	Follow SoA for A3 (Table 3-1) or A4 (Table 4-1) at crossover, as assigned	See Section 6.6.1
Thyroid function	If not performed within 7 days prior to first combination dose		
Troponin I, T	Samples for Troponin I for central lab, and T or I for local lab (Troponin I at local lab is preferred), collected pre-dose and result available before first combination dose		See Section 6.6.1.1
BNP (or NTproBNP)	X		
eGFR	X		See Section 6.6.2 for management of renal events (if needed).
Urinalysis	X		If urinalysis is abnormal, a microscopy should be performed.
Coagulation	X		Coagulation test required at pre-combination baseline
Laboratory Assessments for HBV/HCV Populations			
HBV DNA	Repeat If not performed within prior 3 weeks of Day 1 of combination	Follow SoA for A3 (Table 3-1) or A4 (Table 4-1) at crossover, as assigned	This test to be performed in participants diagnosed with HCC and positive for HBV on initial screening in monotherapy.
Quantitative HBsAg	X		This test to be performed in participants diagnosed with HCC and positive for HBV on initial screening in monotherapy.
Study Intervention			
Administer GSK3745417		CCI [redacted]	
Administer Dostarlimab			

Study Procedure	Pre-Crossover Baseline [a]	Study Intervention GSK3745417 Weekly or 3 Weekly + Dostarlimab	Notes
Week (in combination)	≤1 (unless indicated)	1-104	
Day (in combination)	≤7 day (unless indicated)	1-722	
Efficacy Assessments			
CCI [redacted]		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 infusion; h=hour; ICF=informed consent form; m=min; CCI [redacted]; SAE=serious adverse event; W=week; TDV=treatment discontinuation visit Timepoint Definitions for assessments:

X = Anytime during visit (sampling date/time should be recorded)

a. Assessments to be repeated at pre-combination baseline if assessment has not been performed within 7 days prior to first combination dose unless otherwise specified.

2. INTRODUCTION

2.1. Study Rationale

The concept of cancer immune surveillance has been well established. The key tenet of this concept is that the immune system plays a critical role in protecting the body from neoplastic disease. Consistent with this concept, the immune checkpoint inhibitors anti-PD(L)-1 and anti-CTLA-4 have demonstrated therapeutic benefit across multiple tumor types, yielding durable responses in some patients. However, a majority of patients do not respond to monotherapy with checkpoint inhibitors, at least in part due to the non-inflamed nature of the tumor. Therefore, strategies to increase the tumor immunogenicity are being actively explored.

STimulator of INterferon Genes (STING) is the key adaptor molecule in the cGAS--STING-TBK1 pathway that mediates the sensing of cytosolic DNA [Chen, 2016; Sun, 2013]. Activation of STING generates a distinctive set of type I interferons (IFNα and β) and pro-inflammatory cytokines that instigate T-cell dependent tumor immunity and tumor-vascular collapse [Ishikawa, 2009; Woo, 2014; Mahadevan, 1990]. Innate immune sensing of the cytosolic DNA, and the subsequent type I interferon production, has been demonstrated to be crucial for tumor antigen-specific CD8 cytotoxic T-cell priming mediated via the activation of dendritic cell (DC) subsets. Given the prominent role of STING in cytosolic DNA sensing and type I IFN production, it is believed that STING is a central player in triggering body's spontaneous sensing of tumor by activating dendritic cells. The pre-clinical data strongly suggest that the STING pathway is the intrinsic tumor sensing pathway of the immune system. Therefore, activation of the STING pathway has the potential to boost tumor antigen presentation and the tumor immunogenicity. Potent and durable anti-tumor response has been demonstrated in the syngeneic murine tumor models with STING agonist treatment [Corrales, 2015; Sivick, 2018; Woo, 2014].

In addition, the effect of STING activation in boosting tumor antigen presentation suggests potential combination benefit with immune check point modulators. Given their non-overlapping mechanisms of action, the combination of the two could simultaneously accelerate separate steps in the cancer-immunity cycle, i.e., the tumor antigen presentation process and the T-cell activation process, therefore generating synergistic anti-tumor effect. The enhanced anti-tumor activity with the combination of STING activation and PD(L)1 blockade in preclinical murine models has been demonstrated [Moore, 2016; Wang, 2017]. In addition, checkpoint inhibitors (anti-PD-L1/anti-CTLA4) have diminished efficacy in STING deficient mice [Woo, 2014].

GSK3745417 is a synthetic STING agonist that is being developed by GlaxoSmithKline as an immune stimulatory agent for the treatment of cancer. This study will be the first time in human study (FTIH) of GSK3745417 to assess the safety, pharmacokinetic (PK), pharmacodynamics, and preliminary clinical activity of GSK3745417 administered alone and in combination with other immunotherapies to participants with advanced solid tumors. The planned initial combination partner is dostarlimab, a PD-1 antagonist that abrogates the PD-1/PD-L1 signalling pathway to regain an anti-tumor immune response.

Dostarlimab is marketed for dMMR, endometrial and solid tumors and is being evaluated clinically as an immunotherapy for advanced malignancies.

Subsequent combination partners and/or additional routes of administration may be evaluated (following protocol amendment/s) based on biologic rationale, nonclinical data, and/or emerging clinical data.

This FTIH, open label, dose escalation study will assess the safety, PK, CCI [redacted] in participants with advanced or recurrent solid tumors as monotherapy (Part 1A), in combination with dostarlimab (Part 2A), and potentially in combination with additional therapies. However, the study sponsor decided CCI [redacted]. Subsequently, the planned monotherapy cohort expansion (Part 1B) and the combination with dostarlimab cohort expansion (Part 2B) arms CCI [redacted]

2.2. Background

2.2.1. GSK3745417

An overview of GSK3745417 is provided below. Detailed information concerning the biology, pharmacology, PK, and safety characteristics can be found in the Investigators' Brochure (IB) for GSK3745417.

GSK3745417 is a novel, first-in-class, non-CDN (cyclic dinucleotide, natural ligand of STING) STING agonist belonging to a dimeric 2-amidobenzimidazole (ABZI) scaffold that is active against all known haplotypes of human STING. CCI [redacted]

2.2.1.1. GSK3745417 Nonclinical Studies

2.2.1.1.1. Pharmacology

CCI [redacted]

CCI

[redacted]

2.2.1.1.2. Toxicology

CCI

[redacted]

CCI [redacted]

2.2.2. Clinical Safety of GSK3745417

The first clinical study evaluating GSK3745417 is this first time in human study 208850. In this study, CCI [redacted].

A summary of adverse events (AEs) and dose limiting toxicities (DLTs) is included in the GSK3745417 Investigator's Brochure.

For this ongoing study of GSK3745417 advanced solid tumors, data are summarized for CCI [redacted] that have been dosed with GSK3745417 monotherapy as of the cut-off date of CCI [redacted]

Upon review of the clinical safety data received during the period of this report CCI [redacted].

2.2.3. Dostarlimab

Detailed information concerning the biology, pharmacology, PK, and safety characteristics can be found in the IB for dostarlimab.

2.2.4. GSK3745417 and Dostarlimab Combination Background

The rationale for combining a STING agonist with an anti-PD-1 agent such as dostarlimab is because these two agents target different steps in the cancer-immunity cycle and may result in synergistic anti-tumor activity. Administration of GSK3745417 in advance of dostarlimab is expected to increase the priming/activation of antitumor T-cells while the anti-PD-1 agent dostarlimab prevents the inhibitory effect of the PD-1/PD-L1 pathway on effector T-cells in the tumor.

Administration of GSK3745417 in combination with an anti-PD1 antibody CCI [redacted]

2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of GSK3745417 in the form of summaries of findings from nonclinical studies conducted may be found in the IB.

Detailed information about the known and expected benefits and risks and reasonably expected AEs of dostarlimab in the form of summaries of findings from nonclinical studies conducted may be found in the IB for dostarlimab.

The following section outlines the risk assessment and mitigation strategy for this protocol.

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP) GSK3745417 (GSK417) and dostarlimab (where noted)		
Infusion related reactions (IRR) including cytokine release syndrome (CRS)	CCI [redacted]	**General Measures:** • Sites selected based on 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 24hr hospital observation post- dosing. **Mitigation:** • CCI [redacted] • Dose staggering of participants for previously uncleared dose levels to allow assessment initial safety data before enrolling next participant. • Guidelines on the management of CRS symptoms is provided in Table 17 and dose modifications in Section 6.6. •
Anemia		**Monitoring** • Frequent monitoring of complete blood count and differential **Mitigation**

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	CCI	• Anemia has been included as an expected event in the reference safety information of the IBs both GSK417 and dostarlimab. • Inclusion of patients with hemoglobin ≥9 g/dL • All grade 4 anemias are reported as AESIs[1] within 24 hours to medical monitor • Grade 3 anemia requiring transfusion or Grade 4 anemia reports are DLTs with discontinuation of study treatment.
Reproductive toxicity		**Mitigation:** • Contraception guidelines will be included as inclusion criteria for females. • Exclusion of lactating and pregnant women (See Section 5.1). • Patients who are women of childbearing potential (WOCBP) will be informed that taking dostarlimab or GSK417 may involve unknown risks to the fetus if pregnancy occurs during the study. To participate in the study, women of child bearing potential in heterosexual relationships must adhere to the contraception guideline (defined in Section 11.4.2) during the study and through 150 days after the last dose of dostarlimab or 7 days after last dose of GSK417 in monotherapy patients.
Immune-related AEs		**General** • 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

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	CCI	Guidelines on the management of potential immune-related AEs is provided in Section 6.6 and Table 15.
Renal toxicity		**Monitoring** • Frequent monitoring of clinical chemistry including serum creatinine and eGFR as per schedule of activities (SOA), Section 1.2.1. **Mitigation** • Inclusion criteria for eGFR ≥ 60 mL/min/1.73 m^2 • Specific renal stopping criteria and management guidelines are defined in the protocol (See Section 6.6.2). • Manage immune-mediated events with dostarlimab treatment modifications and corticosteroids, as outlined in Section 11.11.
Cardiac effects		**Monitoring** • Frequent study cardiac monitoring with ECG, ECHO, and troponin (see SOA and Section 6.6.1.1. cardiac monitoring). • Holter monitoring per SOA. **Mitigation** • Inclusion of those with adequate LF function (Section 5.1)

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	CCI [redacted]	• 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 7.1.2
Hepatic toxicity		• Inclusion criteria for ALT≤2.5x ULN and bilirubin≤1.5x ULN **Mitigation Strategy** • Inclusion criteria for ALT ≤2.5x ULN and bilirubin ≤1.5x ULN. • Standard phase 1 oncology Liver Chemistry Stopping Criteria. (See Section 7.1.1). • Guidelines on the management of potential immune-related hepatic AEs is provided in Section 6.6 and Table 15.

[1]AESI: Adverse event of special interest

2.3.2. Overall Benefit: Risk Conclusion

In this FTIH study, only participants with advanced stage solid tumors will be enrolled. All participants in this study will have exhausted all approved and effective therapies prior to receiving GSK3745417. The study protocol has been specifically designed to carefully monitor all participants and thereby, minimize the clinical risk of intervention related toxicities.

Consistent with other Phase 1 trials for the treatment of cancer, a target DLT rate has been set as 16-33%, and a Bayesian adaptive dose escalation design is employed to efficiently determine the dose(s) associated with this DLT rate. Overall, the benefit:risk is typical of a Phase I study of participants with advanced cancer.

Considering the novel and very relevant mode-of-action, the anti-tumor activity observed in pre-clinical tumor models, and the clinical monitoring measures incorporated into this study protocol, the sponsor believes that the potential clinical benefit associated with GSK3745417 study intervention outweighs the risk of severe, intervention-emergent toxicities.

3. OBJECTIVES AND ENDPOINTS

Dose Escalation (Part 1A GSK3745417 Monotherapy and Part 2A Combination GSK3745417 and Dostarlimab)	
Objective	**Endpoint**
Primary	
• To determine the safety, tolerability, and the recommended phase 2 dose (RP2D) of GSK3745417 alone or in combination with dostarlimab administered intravenously to participants with advanced/recurrent solid tumors.	• Incidence of DLT • Incidence and severity of adverse events
Secondary	
• To characterize the PK properties of GSK3745417 alone or in combination with dostarlimab	• GSK3745417 concentrations in plasma and PK parameters
Exploratory[b]	
CCI [redacted]	

Dose Escalation (Part 1A GSK3745417 Monotherapy and Part 2A Combination GSK3745417 and Dostarlimab)	
Objective	**Endpoint**
CCI [redacted]	

a) CCI

b) [redacted]

Objectives and endpoints for the Imaging Sub-study are described in Appendix 15.

4. STUDY DESIGN

4.1. Overall Design

This is a Phase I, FTIH, open-label, repeat-dose, non-randomized, multicenter, multicountry study to evaluate the safety, tolerability, and preliminary clinical activity and establish a recommended dose of GSK3745417 administered intravenously (IV) alone (Part 1A) or in combination with dostarlimab (Part 2A) in participants with refractory/relapsed solid tumors. Both Part 1A and Part 2A consist of a dose escalation phase only; dose expansion phases (Part 1B and 2B) will not be conducted following sponsor's decision to cease further enrolment into the study.

CCI

CCI [redacted]

- **Part 1A:** The safety and tolerability of escalating doses of GSK3745417 CCI [redacted] will be evaluated according to a Bayesian Logistic Regression Model (BLRM) design [Neuenschwander, 2014] (see Section 4.1.1).

CCI [redacted]

CCI [redacted]

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. The duration of study treatment will be up to 2 years. Ongoing participants will be followed up for safety until 90 days after the last dose or until start of subsequent anticancer treatment, whichever is earlier. CCI [redacted]

CCI [redacted]. The decision whether a participant will receive additional treatment will be discussed and agreed upon by the treating investigator and the Sponsor/Medical Monitor on a case-by-case basis.

CCI [redacted]

Participants receiving study treatment at the time of the final analysis data cut-off date may continue to receive it, if in the opinion of their treating physician, they are benefiting from continued treatment, and they do not meet any protocol-defined treatment discontinuation criteria (see Section 7.1). Study treatment will continue until a study treatment discontinuation criterion (see Protocol Section 7.1), as assessed by the investigator, has been met.

Participants who continue study treatment in the PACT phase will be cared for in accordance with local standard clinical practice. Participants will continue to be monitored for all SAEs, AEs leading to treatment discontinuation, overdoses, pregnancy cases while receiving study treatment. Information relating to participant care will be recorded on participant medical records, except for SAEs, AEs leading to treatment discontinuation, overdoses, pregnancy cases that must continue to be reported to GSK. Investigators must report all SAEs, AEs leading to treatment discontinuation, overdose and pregnancy cases until 90 days after the participant's last dose of study treatment in accordance with Section 11.3.5 (Reporting of Serious Adverse Events).

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4.1.1. CCI [redacted]

Part 1A Starting Dose: Dose escalation for GSK3745417 monotherapy will begin with a starting dose of CCI [redacted]

Dose escalation for GSK3745417 monotherapy subjects will be conducted in Arm A1 CCI [redacted]. Alternative dosing schedules may be explored based on emerging data.

CCI [redacted]: Once a dose of GSK3745417 has been identified that is both tolerable and demonstrates CCI [redacted], enrolment in Part 2A may begin. Dose escalation for GSK3745417 in combination with dostarlimab will begin with a starting dose of CCI [redacted]

CCI [redacted]

Dose Schedule:

- **Part 1A:** CCI [redacted]
  CCI [redacted]

  Following discussion with the sponsor Medical Monitor, and if in the best interest of and in agreement with the study participant, the dosing frequency may be changed from CCI [redacted] to reduce the burden to the participant.

- CCI [redacted] There will be two arms in Part 2A: combination of CCI [redacted]. Dostarlimab will be added to this regimen starting at CCI [redacted] This dostarlimab regimen may be extended to participants receiving combination therapy outside of CCI [redacted] The first

3 participants in each dose level will begin treatment ≥48 hours apart to allow assessment of initial safety data in each participant before beginning the next participant's treatment. All evaluable participants in the dose level cohort must complete the CCI observation period and the available safety data must be reviewed before a decision is made on whether to proceed to the next dose level. Once a CCI observation period has been completed, BLRM analysis will be performed to guide the dose level to which the next 3 participants will be assigned based on the posterior probability of the DLT rate (Section 9.2). If a participant withdraws from the study before completion of the 29-day DLT period for reasons other than DLT, the participant will not be counted as DLT evaluable and will be replaced.

- Following discussion with the sponsor Medical Monitor, and if in the best interest of and in agreement with the study participant, the dosing frequency may be changed from CCI

CCI

Dose Escalation (Part 1A and Part 2A): After each dose cohort, BLRM will be used to guide dose escalation decisions for monotherapy and combination therapy. At the time of each dose escalation decision, BLRM will be used to obtain, for each potential dose, an updated estimate of the toxicity curve and the posterior probabilities that the DLT rate for that dose lies in each of four toxicity intervals (underdosing, target toxicity range, excessive toxicity, and unacceptable toxicity). The four DLT toxicity intervals are defined as follows:

- (0%, 16%] =Underdosing range;
- (16%, 33%] =Target toxicity range;

- (33%, 50%] =Excessive toxicity range;
- (50%, 100%] =Unacceptable toxicity range.

The dose with the highest posterior probability of lying in the Target Toxicity range will be the model-recommended dose for the next cohort. 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%.
- The recommended dose is no more than two-fold (100%) of the previous dose.

Note that de-escalation as well as escalation is possible using this method. Statistical properties of BLRM design are described in Section 9.

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 maximum administered dose 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 two DLTs have been observed.

All available data, including safety, PK and CCI [redacted] data from current and prior cohorts will be reviewed at the dose escalation meeting. Although the BLRM design will be used to recommend the next dosing level, clinical judgment by the Medical Monitor, recommendation from GSK clinical pharmacologist, GSK scientist and GSK

statistician, and in consultation with the investigators can halt 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 with the highest posterior probability of lying in the target toxicity range with the additional requirement that the sum of the posterior probabilities of the DLT rate lying in the excessive toxicity range or unacceptable toxicity range is less than 25%.

CCI [redacted]

Table 8 3+3 Dose-Escalation Guidelines

Number of Participants with DLT at a Given Dose Level	Action
0 of 3	Escalate to the next dose level
1 of 3	Accrue 3 additional participants at current dose level for a total of 6 evaluable participants • If 0 of the additional 3 participants experience a DLT, escalate to next dose level • If ≥1 of the additional 3 participants experiences a DLT, stop dose escalation
1 of 6	Escalate to the next dose level
≥2 of up to 6	Stop dose escalation

All dose escalation/de-escalation decisions will be made by the DEC. Although the 3+3 dose escalation procedure will be used to recommend the next dosing decision, clinical judgment by the Medical Monitor with input from the sponsor study team, and in consultation with the investigators, can halt dose escalation or reduce the recommended dose as deemed appropriate at any time during the trial.

CCI [redacted] dose escalation cohort will be analyzed separately from the monotherapy dose escalation study conducted outside CCI [redacted]

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

Exploration of lower or intermediate dose levels than the BLRM recommended dose (or expansion of a previously tested dose level) will be allowed if agreed upon by the Medical Monitor and treating investigators. The progression from one dose level to another will be made based on the assessment of all the available data (even outside of

DLT criteria) from previous dose levels, including the BLRM recommended dose as described in Section 9.2. All dose escalation decisions will be assessed by the Dose Escalation Committee.

CCI [redacted]

Cohorts permitted IRR/CRS prophylaxis: At the discretion of the DEC, cohorts may be opened which explore the effects of IRR/CRS prophylaxis in designated dose levels.

4.1.2. Dose-Limiting Toxicity

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 Table 9. If an AE is considered related to the underlying disease, it is not a DLT.

CCI [redacted]

Table 9 Dose-Limiting Toxicity Criteria

DLT Criteria for Non-hematologic Toxicity[a, c]	
Cytokine Release Syndrome[b]	• Grade 3 or Grade 4 (See Appendix 12)
Liver Toxicity[d]	• ALT ≥3x upper limit of normal (ULN), plus bilirubin ≥2x ULN (>35% direct) or plus international normalized ration (INR)>1.5 (Possible Hy's law) OR • Both ALT ≥5x ULN and ≥2x baseline value (in participants with liver metastases/tumor infiltration or HCC at baseline)
Any 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

DLT Criteria for Non-hematologic Toxicity[a, c]	
	○ Individual parameters of cytokine release syndrome (CRS) which collectively constitute < Grade 3 CRS ○ Diarrhea adequately controlled with supportive care within 48 hours ○ Nausea and vomiting resolving to Grade ≤1 within 48 hours ○ Alopecia of any grade ○ Grade 3 fatigue with duration <7 days ○ Grade 3 headache which resolves with supportive treatment to ≤ Grade 2 within 24 hours • Grade ≥3 immune-related toxicity that does not resolve to ≤ Gr1 or baseline within 8 days despite adequate immune suppressive therapy • Grade ≥3 infusion-related reactions • Any treatment-related non-hematologic toxicity specifically defined as: ○ Grade ≥2 uveitis, eye pain, or blurred vision that does not resolve with topical therapy within 2 weeks ○ Grade ≥2 immune-related endocrine toxicity that requires hormone replacement (except Grade 2 thyroiditis or thyroid dysfunction) ○ Grade ≥2 colitis or diarrhea that persists without resolution to Grade ≤1 for ≥7 days despite adequate steroid therapy • Grade ≥2 Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS) • Any other event which in the judgment of the investigator and GSK Medical Monitor is considered to be a DLT
DLT Criteria for Hematologic Toxicity[a, c]	
Neutropenia	• Grade 4 neutropenia of ≥7 days duration or Grade 3 or 4 associated with infection or febrile neutropenia
Thrombocytopenia	• Grade 4 thrombocytopenia or Grade 3 thrombocytopenia with bleeding or requiring platelet transfusion
Anemia	• Grade 4 anemia or Grade 3 requiring blood transfusion
Hematologic Events	• Any other hematologic event which, in the judgment of the investigator and GSK Medical Monitor, is considered to be a DLT

ALT=alanine aminotransferase; AST=aspartate aminotransferase; BSC=best supportive care; DLT=dose limiting toxicity; NCI CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events; ULN=upper limit of normal
[a]Toxicity graded according to the NCI-CTCAE, Version 5.0 [NCI, 2017]
[b]Grading according to Lee, 2019
[c]The following event is not considered as a DLT: Changes in leukocyte parameters within 48 hours of GSK3745417 administration

Participants unable to receive at least 80% of scheduled doses for reasons other than toxicity (e.g., acute illness, disease progression) will be replaced in the cohort, however any low-grade toxicity not constituting a DLT will be taken into consideration for dose escalation decisions. If an AE is considered related to the underlying disease, it is not 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 tumor regression, 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 6.6.

4.1.3. Dose Escalation Committee

The Dose Escalation Committee (DEC) will be established by GSK to monitor intervention-emergent data on an ongoing basis throughout study conduct for the purpose of ensuring the continued safety of participants enrolled in this study as described in the Dose Escalation Plan. The DEC will be chaired by the GSK medical monitor and membership will include a GSK scientist, GSK pharmacovigilance physician, GSK statistician, GSK clinical pharmacologist, along with additional GSK staff as appropriate and all participating investigators.

In Part 1A, the DEC will review relevant safety, PK, and PD data generated immediately after all participants treated in the same dose cohort have passed the DLT period. Although the escalation of the GSK3745417 dose will be guided by the BLRM and 3+3 dose escalation procedure for Japan monotherapy participants, the DEC can override this recommendation.

Participants will be enrolled in this study as described in the Dose Escalation Plan.

In addition, throughout the conduct of the study the DEC may decide to:

1. Modify the dose escalation of GSK3745417 proposed by the BLRM/3+3 dose escalation procedure based on clinical judgment. *Note:* GSK3745417 dose steps which will not exceed two-fold (100%) increments

2. Investigate alternative dosing regimens

3. Modify the timing, frequency, and/or type of safety assessments performed during study conduct

4. Approve continuation of GSK3745417 study therapy in participants who have experienced DLT provided the toxicity did not meet study discontinuation criteria and has resolved at the time of re-start.

5. Request intervention of additional participants at previously completed dose levels for the purpose of obtaining additional safety, PK, PD, metabolite, or biomarker data.

6. Recommend intra-participant dose escalation allowing participants to be moved from a lower to a higher GSK3745417 dose not exceeding the MTD if the DEC has declared the next dose cohort as acceptable safety profile.

7. Decide on intervention beyond initial evidence of disease progression in participants who receive clinical benefit (i.e., stable Eastern Cooperative Oncology Group or ECOG performance status and no clinical symptoms indicative of rapid disease progression)

8. Halt enrollment into any cohorts as deemed appropriate based on emerging clinical data at any time during the trial.

During Part 1A and Part 2A of the study, the DEC will meet at least after each dose cohort is fully recruited and all participants have completed the DLT evaluation period. The schedule of dose escalation meetings will depend on the frequency of DLT and when an RP2D is determined.

Documentation of DEC meeting outcomes will be maintained by GSK. Decisions with potential impact on the safety of study participants (i.e., unfavorable change in risk/benefit assessment) will be promptly communicated to regulatory authorities and study sites as appropriate.

4.1.4. Tumor Types Enrolled During Parts 1A and 2A

Participants with advanced solid tumors will be enrolled.

4.1.5. Participant Re-Treatment

Upon initiation of Part 2A combination therapy with dostarlimab, participants in Part 1A monotherapy may be considered on a case-to-case basis and when required criteria are met (below) to transition to a cleared combination dose/frequency regimen as tested in Part 2A.

Participants must have completed at least 1 treatment period of GSK3745417 monotherapy without the occurrence of drug-related Grade ≥3 AEs or serious adverse events (SAEs) of any severity Grade in the first 21 days (for those in Arm A1, Q1W regimen) or 29 days (for those in Arm A2, Q3W regimen) of treatment and meet disease progression criteria (i.e., only confirmed radiologic progression as defined by iRECIST) at the current dose.

A participant who upon disease progression is permitted to re-start treatment and receive GSK3745417 in combination with dostarlimab will be reconsented, and follow the Schedule of Assessments as outlined in Table 5-1.
Additionally, the GSK medical monitor must be consulted and approve the decision before re-treatment is permitted.

For participants who CCI [redacted] the data prior to crossover will be considered for analysis in the monotherapy arm and data after crossover will be analyzed in a different treatment group (i.e. Crossover GSK3745417 + dostarlimab). Additional safety assessments or PK sampling may be specified at the time of dose escalation or schedule modification based on the safety profile in previous participants at the higher dose level.

4.1.6. Study Duration

In this study, participants will receive GSK3745417 monotherapy or combination therapy with GSK3745417 and dostarlimab. Participants will be screened for eligibility beginning

approximately 4 weeks before the start of treatment. Following the screening phase, participants will initiate the treatment phase of the study. The duration of treatment with GSK3745417 monotherapy or in combination with dostarlimab is expected to be 2 years. Participants will continue study therapy until one of the following events occurs: disease progression, death, unacceptable toxicity including meeting stopping criteria for liver chemistry or withdrawal of consent.

The decision whether a participant will receive additional treatment beyond two years will be discussed and agreed upon by the treating investigator and the Sponsor/Medical Monitor on a case-by-case basis.

Following discontinuation of the treatment phase, participants will enter the follow-up phase of the study. During the follow-up phase, participants will complete clinic visits for assessments of safety and for AESI and SAEs until 90 days after the last dose of study treatment or until the start of subsequent anti-cancer treatment.

4.2. Number of Participants

It is estimated that approximately [redacted] will be enrolled in the escalation arms of this study. In addition, [redacted] will be enrolled into a [redacted]

4.3. Participant and Study Completion

Participants will be considered to have completed the DLT portion of the study if they complete screening assessments and receive at least 1 study treatment and experience a DLT during the 21- or 29-day DLT observation period or complete the DLT observation period.

Under this amendment, participants will be considered to have completed the study if they complete the safety follow-up until 90 days after last dose, start subsequent therapy or die. Participants who are in follow-up at the time of this amendment and have been followed for at least 90 days are considered as having completed the study. The end of study visit will be used to capture study completion.

A participant will be considered to have withdrawn from the study if the participant has not died and is lost to follow-up, has withdrawn consent, at the investigator's discretion is no longer being followed or if the study is closed/terminated. Disease progression, discontinuation of study treatment, and AEs, are not by themselves reasons for withdrawal from the study.

4.4. Scientific Rationale for Study Design

Given the high unmet medical need of relapsed/refractory advanced solid tumors, this two-part Phase I study is proposed. This study evaluates the safety, tolerability, pharmacology, and CCI of GSK3745417 alone or co--administered with dostarlimab. The study comprises a dose escalation phase to identify the MTD/ RP2D [GSK Document Number 2020N357563_04].

Blood, urine, CCI

CCI

Eligibility criteria require that participants have progressed after standard therapies or are otherwise unsuitable for standard therapies, and the criteria are intended to minimize the risk of adverse reactions to treatment with immunotherapies.

Dose escalation of GSK3745417 alone or in combination with dostarlimab will be performed using a BLRM approach used to optimize the allocation of participants to dose levels with a CCI. The DLT criteria are based on typical oncology rules with additional modifications for toxicities expected for the study treatments.

CCI

4.5. Justification for Dose

4.5.1. Human PK Prediction

Two methods were used to predict the PK of GSK3745417 in humans using data from in vitro studies conducted with liver microsomes and hepatocytes and from concentration-time data following IV administration of GSK3745417 to various species (mouse, rat, and cynomolgus monkey).

4.5.1.1. In-vitro-to-in-vivo Extrapolation

There was good in vitro-in vivo correlation between clearance (CL) estimates from mouse, rat, monkey, liver microsomes and fresh hepatocytes and CL estimates from in vivo IV plasma PK profiles in mouse, rat, monkey. The hepatic blood clearance of GSK3745417 was predicted to be 13 mL/min/kg or 6 mL/min/kg by in vitro to in vivo extrapolation (IVIVE) using human microsomes or hepatocytes, respectively, assuming a well stirred model. The plasma CL of GSK3745417 was calculated using the scaled up hepatic blood CL values and experimental blood to plasma ratio of 0.59 to be 8 mL/min/kg or 3 mL/min/kg, respectively, from human microsomes or hepatocytes. The predicted CL values for mouse, rat and monkey were within 2.5-fold of the observed in vivo mean plasma clearance values using IVIVE from microsomes or hepatocytes suggesting a good in vitro to in vivo correlation.

4.5.1.2. Allometry

Clearance and Vd values obtained from mouse, rat, and monkey administered GSK3745417 IV were used for allometric scaling. The allometric exponent for the log-log CL to body weight relationship was >0.75; hence, maximum lifespan potential (MLP) correction factor was used to predict human CL; the predicted human CL value using this method was 7.2 mL/min/kg. The geometric mean of these human predicted plasma clearance values (5.6 mL/min/kg = 23372 ml/h for a 70 kg human) was used for human dose and exposure predictions. A low human volume of distribution of 0.17 L/kg was predicted, suggesting distribution in the extracellular fluid. The rat Vd of 0.1 L/kg was used for the most conservative estimate.

Linear PK of GSK3745417 is assumed for human dose predictions as well as for animal PK.

4.5.2. Justification of Starting Dose

CCI [redacted] The minimally anticipated biologic effect level (MABEL) approach was used as the basis for this starting dose for use in cancer patients with advanced tumors to provide the most conservative estimate of starting dose for this STING agonist. In addition, 1/10 STD10 (Severely Toxic Dose in 10% rodent species) and 1/6 HNSTD (highest non-severely toxic dose in a non-rodent species) were considered for starting dose estimates. The approaches used are in consideration of the International Council on

Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) S9 guidance on selection of starting dose for a molecule with immune agonistic properties. The starting dose for the study was determined after consideration of relevant *in vitro* and *in vivo* preclinical data as described below.

CCI [redacted]

In order to provide the most conservative systemic exposure estimate, the lowest predicted CL value of 3 mL/min/kg (12600 mL/h, for a 70 kg human) and lowest Vd estimate of 0.1 L/kg (7000 mL, for a 70 kg human) were used to calculate exposures following a CCI [redacted]

4.5.2.1. Calculation of MABEL (Minimally Anticipated Biological Effect Level)

A panel of cytokines (IFNγ, IL-1β, IL-6, TNFα, IP-10, MIP-1α, MIP-1β, IL-8) from human and monkey ex vivo assays and monkey in vivo studies was evaluated. Of these, the response of cytokines IL-6 and IP-10 in relation to GSK3745417 concentration were considered the most sensitive and were used as the basis for MABEL dose estimation. This relationship was investigated in both ex vivo assays in monkey and human whole blood and in the in vivo monkey GLP toxicology study.

MABEL based on ex vivo cytokine response in whole blood assays, cynomolgus monkey and human

Monkey whole blood and human whole blood was spiked with GSK3745417 ranging in concentration from 0.04 to 30 μM (n=8 donors per concentration level) and cytokine concentrations were measured 4 hours later.

An E_{max} model was fit to concentration-response curves for IL-6 and IP-10. The ten percent effect concentration (EC_{10}) corrected to plasma (human blood-to-plasma ratio of 0.59) was calculated and related to the predicted plasma human C_{max} using the predicted human Vd of 11900 mL (based on 70 kg human and predicted Vd of 0.17 L/kg).

A summary of the range of predicted human starting dose for IL-6 and IP-10 based on the ex vivo whole blood assay in monkey and human is shown in Table 11.

Table 11 Predicted human starting dose based on ex vivo cytokine response in monkey and human whole blood, corrected to plasma

Cytokine	Species	Plasma EC_{10} (ng/mL)	Predicted human starting dose range (mg)
IL-6	Monkey	349	CCI [redacted]
	Human	1409	
IP-10	Monkey	114	
	Human	338	

MABEL based on in vivo cytokine response, cynomolgus monkey

Activation of the STING pathway in the cytosol drives a downstream signal transduction cascade leading to transcriptional changes and production of type I IFNs and proinflammatory cytokines. To approximate this indirect relationship, the relationship between each cytokine and PK was examined using the following parameters: 1) cytokine AUC vs. GSK3745417 AUC, 2) cytokine C_{max} vs. GSK3745417 AUC, and 3) cytokine C_{max} vs. GSK3745417 C_{max}. An E_{max} model was fit for each IL-6 and IP-10 to GSK3745417 relationship. The ten percent effect AUC ($E(AUC)_{10}$) or maximal concentration ($E(C_{max})_{10}$) was calculated. The dose of GSK3745417 estimated to achieve a AUC or C_{max} approximating $E(AUC)_{10}$ or $E(C_{max})_{10}$, respectively, was calculated using the predicted human PK parameters described in Section 4.5.2.

For IL-6, the estimated starting dose range is CCI [redacted]. For IP-10, the estimated starting dose range is CCI [redacted]. A summary of the range of predicted human starting dose for IL-6 and IP-10 is shown in Table 12.

Table 12 Predicted human starting dose based on in vivo cytokine response in cynomolgus monkey

Cytokine	Cytokine to PK relationship	Target exposure parameter and estimate	Relate to human parameter	CCI [redacted]
IL-6	AUC vs. AUC	$E(AUC)_{10}$ = 125 ng.h/mL	AUC[1]	
	C_{max} vs. AUC	$E(AUC)_{10}$ = 157 ng.h/mL	AUC[1]	
	C_{max} vs. C_{max}	$E(C_{max})_{10}$= 967 ng/mL	C_{max}[2]	
IP-10	AUC vs. AUC	$E(AUC)_{10}$ = 64 ng.h/mL	AUC[1]	
	C_{max} vs. AUC	$E(AUC)_{10}$ = 48 ng.h/mL	AUC[1]	
	C_{max} vs. C_{max}	$E(C_{max})_{10}$= 457 ng/mL	C_{max}[2]	

[1]Using human predicted CL = 5.6 ml/min/kg ~ 23372 mL/h (based on 70 kg human)
[2]Using human predicted V = 0.17 L/kg ~ 11900 mL (based on 70 kg human)

As a good correlation between monkey ex vivo and in vivo cytokine response is observed for IL-6 and IP-10, a similar correlation is anticipated in human. Therefore, ex vivo human EC_{10} values for IL-6 and IP-10 were considered appropriate to use to estimate the MABEL. A dose of CCI [redacted] was considered as the most conservative estimate per the MABEL approach.

4.5.2.2. Starting dose based on ICH S9 guidance

Data from the GLP toxicology studies, allowed calculation of starting dose based on 1/10 STD10 (Severely Toxic Dose in 10% rodent species) and 1/6 HNSTD (highest non-severely toxic dose in a non-rodent species) per the ICH S9 guidance.

The STD10 in mouse was 3 mg/kg administered IV once weekly for 4 weeks. A starting dose based on this STD10, assuming a 60 kg human with BSA of 1.62 m^2, and taking 1/10 of this value, translates to a dose of CCI .

The HNSTD in cynomolgus monkey was 0.03 mg/kg IV once weekly for 4 weeks, a human equivalent dose of 1/6 HNSTD of 100 mcg IV given once weekly. Monkey is the more sensitive nonclinical species.

4.5.2.3. Potential therapeutic dose

Anti-tumor efficacy in BALB/c mice inoculated with CT-26 cells was investigated upon IV administration of GSK3745417 with doses of CCI Treatment with CCI resulted in complete tumor regression in 50% of mice (5/10); treatment with CCI resulted in complete tumor regression in 100% of mice (9/9). The mouse exposure area under the concentration-time curve from time zero to infinity [$AUC_{(0\text{-inf})}$] for a CCI was estimated to be 958 ng.h/mL and 3194 ng.h/mL, using mouse plasma concentration profiles observed in the GLP toxicology study where GSK3745417 IV was administered and assuming linear PK. A predicted human dose range of CCI would deliver a similar exposure range that was shown to be efficacious in 50% to 100% mice based on predicted human PK parameters. However, the actual exposure of GSK3745417 in humans that would translate into efficacy in humans is not known and the CCI

The anticipated IL-6 and IP-10 response in human following a CCI, at which a predicted C_{max} is 1849 ng/mL, are approximately 30 pg/mL and 2110 pg/mL, respectively, based on the PK/pharmacodynamic relationship observed in the ex vivo whole blood assay, when corrected to plasma. Given the adverse event profiles which were consistent with an inflammatory/cytokine response at the explored monotherapy dose levels of CCI weekly, and where there is incomplete and exploratory biomarker data available for a small number of subjects, CCI

4.5.3. Dostarlimab Dose Rationale

The recommended clinical dose and regimen of dostarlimab is 500 mg CCI for 4 doses followed by 1000 mg CCI This regimen was determined from the results of the Phase 1/2 study 4010-01-001, where the PK, efficacy and safety were evaluated over 3 parts:

- CCI
-

- CCI [redacted]

A two-compartment model with no effect of body weight on dostarlimab clearance described the observed PK data well. Full PD1 receptor occupancy in peripheral blood cells was observed with drug concentrations of CCI [redacted] The predicted arithmetic mean (90% CI) trough concentrations at steady state for the CCI [redacted]
The two regimens maintained trough concentrations at least CCI [redacted] concentration of CCI [redacted], considering the lower bounds of the 90% CI's. Further exposure-response analyses determined CCI [redacted]

CCI [redacted]

4.6. End of Study definition

A final data cut-off representing the end of data collection, prior to the end of study (EOS), is defined as the data cut-off date for the primary/final analysis. Following the final data cut-off date, the study may move into the PACT phase and the clinical study database will be closed to new data. Participants who are receiving study treatment may continue to receive study treatment if they are gaining clinical benefit as assessed by the investigator until they meet any protocol-defined treatment discontinuation criteria. Although the clinical study database will be closed at the time of the final data cut-off date, the study remains open until all participants discontinue study treatment (and complete the 90-day safety follow-up) and the EOS definition is reached.The end of study is defined as the date of the last visit of the last participant receiving study treatment in the study (i.e. last dose plus 90 days safety reporting period) or last scheduled procedure shown in the SoA for the last participant in the study.

5. STUDY POPULATION

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

Specific information regarding warnings, precautions, contraindications, AEs, and other pertinent information on the GSK investigational product or other study treatment that

may impact participant eligibility is provided in the IBs/IB supplements. Deviations from inclusion and exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability, or participant safety. Therefore, adherence to the criteria as specified in the protocol is essential.

5.1. Inclusion Criteria

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

Age

1. Participant must be ≥18 years of age at the time of signing the informed consent. Participants in the Republic of Korea must be ≥19 years of age at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2. Participants with advanced/recurrent solid tumors, with disease progression on, intolerance of, or ineligible for, all available therapies for which clinical benefit has been established.
3. Histological or cytological documentation of an advanced solid tumor.
4. CCI [redacted]
5. Participants must provide a fresh biopsy of a tumor lesion not previously irradiated during the screening period.
6. Measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST version 1.1).
   CCI [redacted]
7. Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0-1.
8. CCI [redacted]
9.
10.
11.

CCI

Sex

12. Male or female

a) 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

- CCI

- CCI [redacted]

Informed Consent

13. Capable of giving signed informed consent as described in Appendix 1 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

5.2. Exclusion Criteria

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

Medical Conditions

1. CCI [redacted]
2. [redacted]
3. Active autoimmune disease that has required systemic disease modifying or immunosuppressive treatment within the last 2 years.
   CCI [redacted]
4. Concurrent medical condition requiring the use of systemic immunosuppressive treatment within 28 days before the first dose of study treatment. CCI [redacted]
5. Current unstable liver or biliary disease CCI [redacted]

CCI [redacted]

6. History of vasculitis at any time prior to study treatment.
7. Evidence or history of significant active bleeding or coagulation disorder.
8. Active infection requiring systemic treatment, known human immunodeficiency virus infection, or positive test for hepatitis B surface antigen or hepatitis C.
   CCI [redacted]
9. QTcF >450 msec or QTcF >480 msec for participants with bundle branch block.
   CCI [redacted]
10. Recent history (within the past 6 months) of acute diverticulitis, inflammatory bowel disease, intra-abdominal abscess, or gastrointestinal obstruction.
11. Recent history of allergen desensitization therapy within 4 weeks of starting study treatment.
12. History or evidence of cardiovascular (CV) risk including any of the following:
    - CCI [redacted]
    - Recent (within the past 6 months) history of any grade of CCI [redacted] or pericarditis.
13. History of idiopathic pulmonary fibrosis, interstitial lung disease, or organizing pneumonia, or evidence of active, non-infectious pneumonitis. CCI [redacted]
14. History of (non-infectious) pneumonitis that required steroids or current pneumonitis.
15. Recent history (within 6 months) of uncontrolled symptomatic ascites or pleural effusions.

16. CCI [redacted]

17. CCI [redacted]

Prior/Concomitant Therapy

18. Prior treatment with the following agents:

- STING agonist at any time.
  - **NOTE:** Does not apply to participants treated in Part 1A/monotherapy with GSK3745417 who move to combination with dostarlimab upon radiologically confirmed disease progression following discussion and approval from the GSK Medical Monitor.
- Anticancer therapy or investigational therapy or used an investigational device within 28 days or 5 half-lives of the drug, whichever is shorter.
- Checkpoint inhibitors, including PD-1, PD-L1, PD-L2 and CTLA-4 inhibitors within 28 days.
- Prior radiation therapy: permissible if at least 1 non-irradiated measurable lesion is available for assessment according to RECIST version 1.1 or if a solitary measurable lesion was irradiated, objective progression is documented.
  CCI [redacted]

  CCI [redacted]

19. CCI [redacted].

20. Receipt of any live vaccine within 30 days of the start of study treatment.

21. Prior allogeneic or autologous bone marrow transplantation or other solid organ transplantation.

22. CCI [redacted]

23. CCI [redacted]

24. [redacted]

Other Exclusions

25. Major surgery ≤28 days before the first dose of study treatment. Participants must have also fully recovered from any surgery (major or minor) and/or its complications before initiating study treatment.

26. CCI [redacted]

27. 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

Exclusions Only for participants in Part 2A, participants crossing over to combination therapy, and participants in Imaging Sub-study:

In addition to the criteria listed above, participants are excluded from Part 2A of the study, participants crossing over to combination, and Imaging Sub-study if the following criterion applies:

28. Known hypersensitivity to any of the study interventions or any of their excipients.

5.3. Lifestyle Considerations

5.3.1. Meals and Dietary Restrictions

CCI [redacted]

5.3.2. Caffeine, Alcohol, and Tobacco

CCI [redacted]

CCI [redacted]

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) and be ambulatory when possible.

5.4. Screen Failures

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

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once. This includes retesting specific vital sign measurements, laboratory assessments, etc. that may not have met eligibility criteria.

6. STUDY INTERVENTION

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. The term 'study intervention' is used throughout the protocol to describe any combination of products received by the participant as per the protocol design.

6.1. Study Intervention(s) Administered

Following administration of GSK3745417 monotherapy or GSK3745417 in combination with dostarlimab, assessments should be performed as noted in the SOA, Section 1.2.1. Cytokine-related AEs including changes in vital signs may begin within several hours of administration of GSK3745417. In Arm A1 and Arm A2, participants must be monitored CCI [redacted], however, participants may be released after a 6-hour observation period if in the opinion of the investigator if it is safe to do so; and longer at all visits if clinically indicated. In case of the combination therapy CCI [redacted] On other treatment visits, participants be monitored for 30 minutes CCI [redacted], however, participants may be released

after a 6-hour observation period if in the opinion of the investigator if it is safe to do so, and at least 2 hours after administration of dostarlimab. Guidelines for monitoring cytokine-related AEs are summarized in Section 6.6.1.

GSK3745417 CCI [redacted] alone or in combination with dostarlimab will be administered to participants at each study site under medical supervision of an investigator or designee. When both study interventions are to be administered in Part 2A, the following order of administration should be followed:

CCI [redacted]

Note: Dostarlimab will be administered at the dose of CCI [redacted] for the first 4 doses, followed by 1000 mg CCI [redacted] for subsequent doses. Participants in Japan will receive dostarlimab at a dose and schedule of CCI [redacted] throughout the dosing period.

The date and time of administration will be recorded in the source documents and reported in the eCRF.

In Part 2A, if a participant experiences an CCI [redacted], associated AEs should resolve before dostarlimab is administered. CCI [redacted].

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. Depending on the dosing schedule CCI [redacted] (e.g., scheduling an infusion around a holiday). CCI [redacted] However, such changes from the planned date should not result in changes to consecutive doses of GSK3745417 ± dostarlimab (i.e., participant should return to initial schedule). Subsequent doses should be administered at least 5 days apart in both CCI [redacted]

The Study Reference Manual (SRM) contains specific instructions for the preparation and administration of GSK3745417 and dostarlimab.

Table 14 Investigational Product Dosage/Administration

Intervention Name	GSK3745417	Dostarlimab
Type	Small molecule	Monoclonal antibody IgG4
Dose Formulation	See SRM for details	See SRM for details
Dosage Form	CCI [redacted]	
Unit Dose Strength(s)		
Dosage Level(s)		
Route of Administration		
Reconstitution	See SRM for details	See SRM for details
IMP	GSK3745417	GSK4057190A
Sourcing	Provided centrally by the sponsor	Provided centrally by the sponsor
Packaging and Labelling	Study Intervention will be CCI [redacted] Each vial and carton will be labelled as required per country requirement.	Study intervention will be CCI [redacted]. Each vial and carton will be labelled as required per country requirement.
[Current/Former Name(s) or Alias(es)]	N/A	Dostarlimab

6.2. Preparation/Handling/Storage/Accountability

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.

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 labelled storage conditions with access limited to the investigator and authorized site staff.

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

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

Under normal conditions of handling and administration, study intervention is not expected to pose significant safety risks to site staff.

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.

6.3. Measures to Minimize Bias: Randomization and Blinding

This is an open-label study. All screened participants will be identified by a unique participant number that will remain consistent for the duration of the study. Upon completion of all the required screening assessments, eligible participants will be registered into the study by the investigator or authorized site staff. See SRM for additional information on screening and enrollment procedures.

One to nine participants may be enrolled at a particular dose level in each treatment arm. Each eligible participant entering the study will be allocated into the next available treatment arm, rotating through the list of currently open treatment arms at that time in the order [redacted]

1) Enrollment at a particular dose level of combination therapy will only begin if that dose level DLT period has been cleared in the corresponding monotherapy arm. This rule will not apply to any dose level below the highest dose with an acceptable safety profile in monotherapy.

In case multiple participants are available simultaneously, they will be enrolled in order of their availability for the targeted dosing day.

At a minimum, the first 3 participants in the first 4 dose levels in each arm will receive study treatment ≥48 hours apart to allow assessment of initial safety data in each participant before beginning the next participant's treatment. (e.g., if a participant is dosed on Monday, the earliest the next participant could be dosed is Thursday).

6.4. Study Intervention Compliance

GSK3745417 alone or in combination with dostarlimab CCI [redacted] Administration will be documented in the source documents and reported in the eCRF.

6.5. Concomitant Therapy

Participants will be instructed to inform the investigator before starting any new medications from the time of first dose of study treatment until the end of the study (Final Study Visit). Any concomitant medication(s), including antibiotic and probiotic use within 60 days prior to first dose, non-prescription medication(s), and herbal product(s), taken during the study will be recorded in the eCRF. The minimum requirement is that drug name, dose, and the dates of administration are to be recorded. Additionally, a complete list of all prior anticancer therapies will be recorded in the eCRF.

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

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

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study must be recorded in the eCRF along with:

- reason for use
- dates of administration including start and end dates
- dosage information including dose and frequency

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.5.1. Permitted Medications and Non-Drug Therapies

Supportive Care: Participants should receive full supportive care during the study, including transfusion of blood and blood products, and treatment with antibiotics, antiemetics, antidiarrheals, and analgesics, as appropriate. Seasonal flu vaccine is permitted as an injection only. Intra-nasal flu vaccine is excluded. Elective surgery or

palliative radiation may be permitted on a case-by-case basis in agreement with the Medical Monitor, if these do not include any "target" lesions.

Growth Factors and Bisphosphonates: Bisphosphonates and receptor activator of nuclear factor-kappaB ligand (RANKL) inhibitors (e.g., denosumab): permitted for treatment of bone metastasis or other indicated conditions such as hypercalcemia provided participants have been on a stable dose for at least 4 weeks prior to enrolment date. **Note**: prophylactic use in participants without evidence or history of bone metastasis is not permitted, except for the treatment of osteoporosis. However, the initiation of growth factors and bisphosphonates is not allowed during the first 4 weeks of study treatment, unless used in the management of toxicity and agreed upon by the investigator and Medical Monitor.

Prophylaxis of cytokine-related symptoms: The DEC may authorise the opening of a separate cohort of subjects to determine the effect of prophylaxis with certain medications (including anti-pyretics, antihistamines and steroids) on efficacy and tolerability. For these participants only, the Investigator (in consultation with the Medical Monitor) may consider giving anti-pyretics, anti-histamines and steroids prior to the first, or subsequent doses (see Appendix 13 for suggested CRS prophylaxis regimen).

For subjects in other cohorts, prophylaxis with steroid may be used outside of DLT period for repeated Grade 2 and above CRS at investigator's discretion following consultation with GSK Medical Monitor. Subjects in all cohorts may receive antihistamines and antipyretics prior to dosing with GSK3745417 at the investigator's discretion following consultation with GSK Medical Monitor.

For all cohorts, use of steroids is also permitted for treatment of AEs (as per Section 6.6) while the participant is undergoing treatment on this study.

IL-6/TNFα Inhibitors: Use of IL-6 and TNFα inhibitors is permitted for treatment of AEs while the participant is undergoing treatment on this study.

Participants with conditions pre-existing before study enrollment requiring steroids are permitted to continue taking up to a maximum of 10 mg of prednisone or equivalent provided that the participant has been on a stable dose for at least 4 weeks before enrollment.

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.

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:

- CCI [redacted]

CCI [redacted]

6.6. Dose Modification

AEs associated with treatment with GSK3745417 ± dostarlimab exposure may be immune-mediated. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of GSK3745417 ± dostarlimab treatment, or anywhere in between, and may affect more than one body system simultaneously. Therefore, early recognition of and initiation of treatment for these events is critical to reduce potential complications. For suspected irAEs, ensure adequate evaluation to confirm the etiology or exclude other causes. Additional procedures or tests such as, but not limited to bronchoscopy, endoscopy, or skin biopsy may be included as part of the evaluation. Based on the severity of irAEs, withhold or permanently discontinue GSK3745417 ± dostarlimab and administer corticosteroids.

In study 208850 examining GSK3745417 in participants with advanced solid tumors, CCI [redacted]

CCI [redacted]

Dose modification and toxicity management guidelines for irAEs associated with GSK3745417 or dostarlimab are provided in Table 15. The recent joint American Society of Clinical Oncology and National Comprehensive Cancer Network guidelines for the diagnosis and management of irAEs treated with immune checkpoint inhibitor therapy may be used as a supplement to Table 15 (Schneider, 2021).

In case a dose reduction is necessary, the dose level of GSK3745417 may be changed/stopped as determined by the investigator and sponsor. Participants in combination arms may not discontinue only 1 study treatment. If either study treatment is deemed intolerable and requires discontinuation despite optimal management, as described in Table 15, the participant must be discontinued from both study treatments.

CCI [redacted], if study treatment administration is delayed or withheld due to

non-immune-related adverse event(s) during the DLT-evaluation period, the timing of restart of study treatment should be discussed with GSK Medical Monitor when the adverse events are resolved to Grade 1 or baseline. If Grade 2 symptom(s) persist or worsen to Grade 3 or greater, study investigator should contact GSK Medical Monitor to discuss further treatment, discontinuation, and restart of study treatment.

Table 15 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 (ASCO 2018)	Action taken±	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
Pneumonitis	Grade 2	Restart dosing when toxicity resolves to Grade 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 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 11.6 for additional details on Liver Event Follow-Up Assessments
	Grade 3 or 4	Permanently discontinue[1]	• Administer corticosteroids (initial dose of 1-2 mg/kg methylprednisolone or equivalent) followed by taper	
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	Grade 3 to 4 hyperglycemia or T1DM (associated with metabolic acidosis or ketonuria)β	Restart dosing in appropriately managed, clinically, and metabolically stable patients; insulin replacement therapy is required.	• Initiate insulin replacement therapy for participants with T1DM • Administer anti-hyperglycemic 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 (ASCO 2018)**	**Action taken±**	**irAE management with corticosteroid and/or other therapies**	**Monitor and follow-up**
Hypophysitis	Grade 2, 3 or 4	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 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)
Hyperthyroidism	Grade 3 or 4	Grade 3 or 4– Hold until returns to adequate hormone levels based on laboratory values and restart dosing when toxicity resolves to Grade 1.	• Treat with non-selective beta-blockers (e.g. propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders.
Hypothyroidism	Grade 3 or 4	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 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 (e.g., endocrine consultation) • Exclude concomitant adrenal insufficiency (AM cortisol level)
In Japan Participants only: Myocarditis or pericarditis (Also refer to Section 6.6.1.1. for further details)	Grade 1 (including Grade 1 cardiac troponin elevation)	Discuss with GSK medical monitor regarding option to withhold or discontinue dosing	• As required as outlined below for Grade 2 and higher	• As agreed with GSK medical monitor

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 (ASCO 2018)**	**Action taken±**	**irAE management with corticosteroid and/or other therapies**	**Monitor and follow-up**
Myocarditis or pericarditis	Grade 2, 3 or 4	Permanently discontinue	• Administer high dose corticosteroids (1 g/day of IV methylprednisolone) for 3 to 5 days, followed by oral prednisone taper over 4 to 6 weeks based on improvement in cardiac function and biomarkers. • If no improvement in 24 hours, consider adding other potent immunosuppressive agents	• Ensure adequate evaluation (e.g. Urgent cardiology consultation) to confirm etiology and/or exclude other causes
Adrenal insufficiency	Grade 2, 3 or 4	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 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. • Ensure adequate endocrine evaluation (e.g. Endocrine consultation)
Uveitis	Grade 2 to 4	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.
Severe neurologic events (myasthenic syndrome/myasthenia gravis, Guillain Barré Syndrome, transverse myelitis)	Grade 2, 3 or 4	Permanently discontinue	Consider high dose corticosteroids and other therapies as needed. • It is highly recommended that Investigators discuss any AEs with the sponsor before using infliximab.	Ensure adequate evaluation (e.g., neurology consultation). Consider MRI of brain and/or spine depending on symptoms.

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 (ASCO 2018)	Action taken±	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
				• Consider inpatient management as clinically indicated.
Rash/ Skin reactions	Grade 3 or Suspected DRESS, SJS or TEN	Withhold	• Treat with high potency topical steroids to affected areas • Treat with prednisone	• Ensure adequate evaluation (e.g., urgent dermatology consultation) to confirm etiology and/or exclude other causes.
	Grade 4 or Confirmed DRESS, SJS or TEN	Permanently discontinue	Administer 1 to 2 mg/kg/day IV methylprednisolone and taper steroid when dermatitis is controlled	
Renal failure or nephritis	Grade 2 with creatinine >1.5 to ≤3×ULN	. . Restart dosing when toxicity resolves to Grade 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 (e.g., nephrology consultation) to confirm etiology and/or exclude other causes.
	Grade 3 or 4 with creatinine >3×ULN	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 (e.g., nephrology consultation, renal biopsy) to confirm etiology and/or exclude other causes. • Consider inpatient care
Hemophagocytic lymphohistiocytosis	Any grade	Permanently discontinue		
Other irARs	Based on severity and type of reaction (Grade 2 or 3)	Restart dosing when toxicity resolves to Grade 1	Based on severity of AE, administer corticosteroids. When controlled, taper steroid.	Ensure adequate evaluation to confirm etiology and exclude other causes
	Grade 4 or recurrent Grade 3	Permanently discontinue		
	Grade 1 or 2	Withhold		

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 (ASCO 2018)	Action taken±	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
Recurrence of AEs after resolution to ≤Grade 1	Grade 3 or 4	Permanently discontinue	• Based on severity of AEs, administer appropriate treatment until symptoms improve to ≤Grade 2	

Abbreviations: AE=adverse event; ALT=alanine aminotransferase; AST=aspartate aminotransferase; HRT=hormone replacement therapy; irAR=immune related adverse reaction; DRESS= Drug reaction with eosinophilia and systemic symptoms; PD-1=programmed cell death protein 1; SJS=Stevens Johnson syndrome; T1DM=Type 1 diabetes mellitus; TEN=toxic epidermal necrolysis.

NOTES:

1. *For participants with liver metastasis who begin treatment with Grade 2 AST or ALT, if AST or ALT increases by ≥50% relative to baseline and lasts for at least 1 week, then the participant should be discontinued

*For endocrine associated conditions, ASCO guidelines suggest consideration can be given to restarting drug in those with Grade 4 events once the condition is stabilised with hormone therapy; for study 208850, which only permits missing 3 doses of GSK3745417, stabilisation of a Grade 4 condition is unlikely to be achieved in the protocol defined timeframe and therefore participants with Grade 4 events should permanently discontinue study drug.

6.6.1. Management of Infusion Reactions or Severe Cytokine Release Syndrome (sCRS)

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

Infusion Reaction

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.

Cytokine Release Syndrome

Table 17 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].

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, tryptase and coagulation, as well as C-reactive protein (CRP) labs;
- In addition, troponin, and N-terminal pro B-type natriuretic peptide (NT-proBNP) / BNP tests should be monitored for participants with CRS grade ≥2 as clinically indicated;

- Central tests:
  - Central testing of samples will no longer be conducted.When CRS is suspected, obtain blood for the following tests: See Table 16 below for local testing:

Table 16 Biomarker Panel

Note: With this amendment, samples for cytokines/chemokines and PK will no longer be taken at the time of CRS event

Biomarker	Relationship to Adverse Event
Serum tryptase[a]	IgE-related infusion reaction (Allergic/anaphylaxis) [Schwartz, 2006]
Serum ferritin[a]	Elevated in CRS [Lee, 2019]
Serum cytokine/chemokine panel[b] (IFNγ*, TNFα*, IL-2*, IL-4, IL-6*, IL-8, IL-10*, IL-12p70, IL-13, IL-1β*, IP-10, MCP-1, MIP-1α, MIP-1β, IFNβ	*Reported to be elevated in CRS [Lee, 2019]
GSK3745417 plasma PK[c]	To be determined

Abbreviations: CRS= Cytokine Release Syndrome; IFNγ = Interferon gamma; TNFα = Tumor necrosis factor alpha; IgE: immunoglobulin E; IL = Interleukin

a. Performed by investigator designated local laboratory if available; otherwise performed by GSK designated laboratory
b. With this Amendment, samples for central testing of cytokines and chemokines will no longer be collected.
c. With this Amendment, a sample for central testing of plasma PK will no longer be collected..

Assessment and management of neurological signs and symptoms associated with CRS should include consideration of concurrent occurrence of Immune-effector cell-associated neurotoxicity syndrome (ICANS). See Section 6.6.1.2 for further details.

Table 17 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	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]

Grade	Clinical Presentation for Grading Assessment[1,2]	Management Guidelines
	(>6 L/minute), facemask, non-rebreather mask, or venturi mask not attributable to any other cause[3]	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 (e.g.: CPAP, BiPAP, intubation and mechanical ventilation)[8]	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[9]	

1. Fever is defined as temperature ≥38°C not attributable to any other cause. The constitutional symptoms of CRS, such as myalgia, arthralgia, and malaise, are by themselves nonspecific; however, when coincident with fever in the expected timeframe, the etiology of CRS is more likely. In patients who have CRS then receive antipyretic or anticytokine 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.
8. Intubation of a patient without hypoxia for the possible neurologic compromise of a patent airway alone or for a procedure is not, by definition, grade 4 CRS. By extension, a patient experiencing seizures in which a compromised airway affects oxygenation and intubation reverses such deficits is not considered to have grade 4 CRS, because the seizure rather than CRS is the cause of the hypoxia. Furthermore, a patient who remains intubated for a neurologic cause is not considered to have CRS when the other signs of CRS have resolved.
9. Grade 5 CRS is defined as death due to CRS in which another cause is not the principle factor leading to this outcome.

Source: Lee, 2019

In the event of an infusion reaction following administration of dostarlimab, the subsequent doses of dostarlimab should be delayed for 6 to 24 hours CCI [redacted]

Dose reduction for CRS

In the event of Grade 2 CRS outside the DLT period, 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 0.1 mg.

Table 18 GSK3745417 ± Dostarlimab Infusion Reaction Dose Modification and Treatment Guidelines

NCI CTCAE Grade[a]	Treatment[b]	Premedication at Subsequent Dosing (Dostarlimab Only)
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hr	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: • IV fluids • Antihistamines • NSAIDs • Acetaminophen • Narcotics Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 CCI [redacted] Otherwise dosing will be held until symptoms resolve and the participant should be premedicated for the next scheduled dose. **Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study intervention.**	Participant may be premedicated 1.5h (± 30 minutes) prior to infusion of dostarlimab with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of analgesic).[c]
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: • Epinephrine** • IV fluids • Antihistamines • NSAIDs • Acetaminophen • Narcotics • Oxygen • Pressors • Corticosteroids Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. **Participant is permanently discontinued from further study drug treatment.**	No subsequent dosing

a. For further information, please refer to the Common Terminology Criteria for Adverse Events v5.0 (CTCAE) at http://ctep.cancer.gov

b. Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration.

c. Administration should be omitted if previously administered as per prophylaxis for GSK3745417 (Appendix 13).

6.6.1.1. Cardiac Monitoring and Dose Modification Guidelines

In study 208850 examining GSK3745417 in participants with advanced solid organ tumours, one case of immune-mediated perimyocarditis has been observed, with a likely causal relationship to GSK3745417. On-study monitoring of troponins and cardiac function (using ECHO or MUGA) is required.

BNP (or NTproBNP) should be measured at screening and then on study as clinically indicated.

Troponin should be measured at baseline and then every 3 weeks on study as per the revised SoA (Section 1.2.1). As of this Amendment, Troponin testing at a central laboratory will no longer be required. A troponin sample will continue to be assessed at a local laboratory for purposes of subject management. Whenever possible, troponin I will be assayed by the local laboratory. However, 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 and be evaluated by the same reader at study centre.

All ECHO/MUGA data will be transferred and reviewed centrally by an independent cardiologist.

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

- Troponin is elevated ≥2x 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 ≥2x ULN without symptoms requires withholding GSK3745417 while awaiting repeat troponin value. A repeat troponin ≥2x ULN requires withholding GSK3745417 and awaiting cardiology consult. It is likely that additional cardiac imaging will be required to fully determine the nature of the event; the cardiology consult should guide the choice of imaging. In participants with asymptomatic troponin elevations, GSK417 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

(Schneider, 2021) 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.

6.6.1.2. Neurological Adverse Events on Study

Neurological DLTs (including severe headache, confusion, and hallucinations) considered possibly related to cytokine release as a result of study drug have been observed in the FTIH solid tumor Study 208850. Given that GSK3745417 is an immune-stimulatory agent, there may be potential for Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS). Although ICANS has not been observed in the development programme to date, all participants should have baseline brain imaging and full neurological assessment prior to starting study. Baseline assessment should also include use of the ICE-Encephalopathy Assessment Tool for Grading of ICANS (see below). In the event of mental state changes on study, or any new neurological symptoms potentially consistent with ICANS, additional regular testing with the ICE-encephalopathy assessment tool should be used based in investigator judgement and institutional guidelines. A specialist neurology consult (and further neurological imaging) should also be obtained in the event of new neurological symptoms or mental state changes on study

ICANS is a disorder characterized by a pathologic process involving the central nervous system following any immune therapy that results in the activation or engagement of endogenous or infused T-cells and/or other immune effector cells. Symptoms or signs of ICANS can be progressive and may include aphasia, altered level of consciousness, impairment of cognitive skills, motor weakness, seizures, and cerebral edema. However, ICANS-like symptoms in cancer patients may be due to other causes ranging from mild to moderate somnolence and confusion as a result of sedating medications, to seizures in relation to CNS tumors. The possible contribution of other medications, underlying disease and/or co-morbidities should be evaluated when considering a diagnosis of ICANS. A neurological consult and appropriate imaging should be considered in order to exclude other causes.

6.6.1.3. Grading of ICANS

Lee et al. [Lee, 2019] have developed a new grading system for ICANS which incorporates the use of a modified version of the CARTOX 10-point neurological assessment tool termed Immune Effector Cell-Associated Encephalopathy (ICE) (Table 19). Points are assigned for each of the tasks in Table 19, which are performed correctly. Normal cognitive function is defined by an overall score of 10. The ICE should be used to monitor all participants for ICANS.

Table 19 ICE-Encephalopathy Assessment Tool for Grading of ICANS

Task	ICE Points
Orientation to: year, month, city, hospital	Total of 4 points (one point for each)
Name three objects, for example point to: clock, pen, button	Total of 3 points (one point for each)

Task	ICE Points
Follow simple commands (for example, “Show me 2 fingers” or “Close your eyes and stick out your tongue”	1 point
Write a standard sentence, e.g. ‘our national bird is the bald eagle’	1 point
Count backwards from 100 in tens	1 point

Abbreviation: ICE = Immune Effector Cell-Associated Encephalopathy; ICANS= Immune Effector Cell-Associated Neurotoxicity Syndrome.

Scoring: 10, no impairment; 7-9; grade 1 ICANS; 3-6, grade 2 ICANS; 0-2, grade 3 ICANS; 0 due to patient unarousable and unable to perform ICE assessment, grade 4 ICANS

The ICE score is used in grading of ICANS in adults as presented in Table 20.

Table 20 Grading of Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE score[1]	7 to 9	3 to 6	0 to 2	0 (Participant is unarousable and unable to perform ICE)
Depressed level of consiousness[2]	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse. Stupor or coma
Elevated ICP/cerebral edema	N/A	N/A	Focal/local edema on neuroimaging[4]	Diffuse cerebral edema on neuroimaging; decerebrate or decorticate posturing; or cranial nerve VI palsy; or papilledema[3]; or Cushing's triad
Motor findings[5]	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or paraparesis
Seizure	N/A	N/A	Any clinical seizure focal or generalized that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (>5 min); or Repetitive clinical or electrical seizures without return to Baseline in between

Abbreviations: ICANS= Immune Effector Cell-Associated Neurotoxicity Syndrome; ICE = Immune Effector Cell-Associated Encephalopathy; CSF = cerebrospinal fluid; ICP = Intracranial Pressure; N/A = not applicable.

1. See Table 19 for ICE. A patient with an ICE score of 0 may be classified as grade 3 ICANS if awake with global aphasia, but a patient with an ICE score of 0 may be classified as grade 4 ICANS if unarousable.
2. Depressed level of consciousness should be attributable to no other cause (e.g., no sedating medication)
3. Papilloedema grading is performed according to the modified Frisén scale.
4. Intracranial hemorrhage with or without associated edema is not considered a neurotoxicity feature and is excluded from ICANS grading.
5. Tremors and myoclonus associated with immune effector cell therapies do not influence ICANS grading

This table is based on Lee, 2019.

6.6.1.4. Monitoring for Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)

The ICE score must be obtained at baseline prior to dosing with GSK3745417, and then on study as clinically indicated in patients experiencing new neurological symptoms or mental state changes.

6.6.1.5. Management of ICANS

A neurology consultation should be obtained for all participants with ICANS for thorough neurological evaluation, and recommendations for further testing such as electroencephalogram (EEG) and neuroimaging as indicated.

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:
    - chemistry, hematology, ferritin and coagulation, as well as C-reactive protein (CRP) labs.

Grade 1 ICANS is primarily managed with supportive care. Across several trials, tocilizumab has failed to resolve symptoms of ICANS, despite alleviating severe CRS (Maus, 2020). It remains to be determined whether targeting IL-6R in isolation during established CRS is insufficient to prevent subsequent neurotoxicity or if the lack of efficacy is due to tocilizumab's inability to cross the blood–brain barrier. It has been postulated that tocilizumab may worsen ICANS and therefore an assessment of treatment priority may be required between the severity of CRS and ICANS. Alternative IL-6 blockade such as siltuximab or the IL-1 antagonist, anakinra, have been proposed as potential alternatives, but data are lacking on their safety and efficacy.

Corticosteroids have been successfully used for the management of ICANS and seizure prophylaxis has been implemented in some studies, but the ideal dose and duration have not yet been determined (Maus, 2020).

In the event of ICANS, Investigators should follow institutional guidelines for symptom management, or refer to the SITC guidelines (Maus, 2020). Additional guidance on assessment and grading of ICANS can also be found in Lee 2019, (Lee, 2019).

6.6.2. Management of Renal Events

Table 21 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 • Repeat serum creatinine levels every 24 hours • Perform diagnostics to identify root cause • Discuss with Sponsor/Medical Monitor • If serum creatinine returns to baseline level within one week, or cause found not attributable to study intervention, resume study treatment • If serum creatinine remains elevated more than one week without a known cause, permanently discontinue treatment • Nephrology consultation is highly recommended
Abnormal urinalysis findings, including hematuria	• Perform diagnostics to identify root cause • Nephrology consultation is highly recommended if cause is not known

6.6.3. Management of Thrombophlebitis

CCI [redacted]

6.7. Dose Delay

CCI [redacted].

During the GSK3745417 CCI [redacted] (monotherapy or combination), if there is a dose delay between 1 and 3 days, the procedures at the original scheduled visit (including dosing) should be performed as soon as possible. If the delay is >3 days, the visit and dose(s) will be considered missed.

During the GSK3745417 CCI [redacted] dosing schedules (monotherapy or combination), if there is a dose delay between 1 and 7 days, the procedures at the original scheduled visit (including dosing) should be performed as soon as possible. If the delay is >7 days, the visit and dose(s) will be considered missed.

During all the dosing schedules, subsequent doses should be administered at least 5 days apart.

Dosing delays or omissions are permitted in the case of medical/surgical events or for logistical reasons not related to study therapy (e.g., elective surgery, unrelated medical events, participant vacation, and/or holidays, but not for participants' decision to delay or omit treatment). If a dose (visit) is missed, participant should wait for the next scheduled dose to resume treatment. In individual cases, where in the judgement of an investigator waiting a full cycle to resume treatment after delay (skipping dose) related to toxicity

which has resolved would be detrimental to patient's health, the PI should contact Medical Monitor to discuss an earlier re-start.

The reason for any dose delay must be documented in the participant's eCRF and clinic record.

Participants with infusion delays equivalent to 3 consecutive missed doses should discontinue study treatment(s) unless the treating investigator and sponsor agree there is strong evidence supporting continued treatment.

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

Study participants who continue to benefit from study intervention beyond the data cut-off date will continue to have access to study intervention until the EOS as defined in Section 4.3 and Section 4.6. There is no planned intervention following the EOS. The investigator is responsible for ensuring that consideration has been given to the post-study care of the participant's medical condition.

New therapy should be documented on the CRF (if applicable). Every effort should be made to complete the required discontinuation of study treatment and follow up evaluations prior to initiating further therapy or dosing of an investigational agent

6.8.1. Continued Access to Study Intervention After Data Cut-off prior to EOS

Participants receiving study treatment at the time of the final analysis data cut-off date may continue to receive GSK3745417 and/or dostarlimab, if in the opinion of their treating physician, they are benefiting from continued treatment, and they do not meet any protocol-defined treatment discontinuation criteria (see Section 7.1). Study treatment will continue until a study treatment discontinuation criterion (see Section 7.1), as assessed by the investigator, has been met.

Participants who continue study treatment in the PACT phase will be cared for in accordance with local standard clinical practice. Additional guidance on treatment with the study drug and participant management is provided in the SRM. Participants will continue to be monitored for all SAEs, AEs leading to treatment discontinuation, overdoses, and pregnancy cases while receiving study treatment. Information relating to participant care will be recorded on participant medical records, with the exception of SAEs, AEs leading to treatment discontinuation, overdoses and pregnancy cases that must continue to be reported to GSK. Investigators must report all SAEs, AEs leading to treatment discontinuation, overdose and pregnancy cases until 90 days after the participant's last dose of study treatment in accordance with Section 11.3.5 (Reporting of Serious Adverse Events). Post final analysis data cut-off date, reporting and follow up of SAEs, overdose and pregnancy cases will be done via paper forms (see SRM for details). For dispensing of study treatment and maintaining study drug accountability in the PACT

phase please refer to the SRM. All other assessments will revert to standard of care at their site.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

Participants will receive study intervention for the scheduled time period, unless 1 of the following occurs earlier: disease progression (as determined by iRECIST), death, unacceptable toxicity or stopping criteria are met.

7.1. Discontinuation of Study Intervention

In addition to the above, study intervention might be permanently discontinued for any of the following reasons:

- Deviation(s) from the protocol
- Withdrawal of consent by participant or proxy
- Discretion of the investigator
- Participant loss to follow-up by the investigative site
- Closure or termination of the study
- Criteria described in Section 6.7 (Dose Delay)
- Female participant who becomes pregnant while on study treatment
- Criteria for discontinuation of study treatment(s) as described in Section 6.6 (Dose Modification Guidelines) have been met
- Criteria described in Section 7.1.2 (QTcF Stopping Criteria) have been met
- Criteria described in Section 7.1.3 (Stopping Rules for Clinical Deterioration) have been met

Note: Participants enrolled in Part 2A combination therapy of GSK3745417 with dostarlimab who require permanent discontinuation of one of the study interventions due to toxicity in a given treatment combination must permanently discontinue both interventions (unless continued treatment with the remaining agent is agreed upon by the treating investigator and Sponsor/Medical Monitor) in that combination and the reason for discontinuation must be recorded. The TDV should be conducted within 30 days of the last dose of study treatment(s).

The primary reason for discontinuation must be documented in the participant's medical records and eCRF. If the participant voluntarily discontinues from treatment due to toxicity, 'AE' will be recorded as the primary reason for permanent discontinuation on the eCRF.

Participants discontinuing from GSK3745417 monotherapy due to confirmed radiological disease progression will be allowed to transition to GSK3745417 combination with dostarlimab.

The assessments required at the TDV should be completed within 30 days of the last dose of study intervention(s).

All participants who discontinue from study treatment will undergo safety assessments at the time of discontinuation and during post-study treatment follow-up as specified in the SoA (Section 1.2.1). Participants will be followed up for safety until 90 days after last dose, until start of subsequent anticancer therapy or until death, whichever comes first.

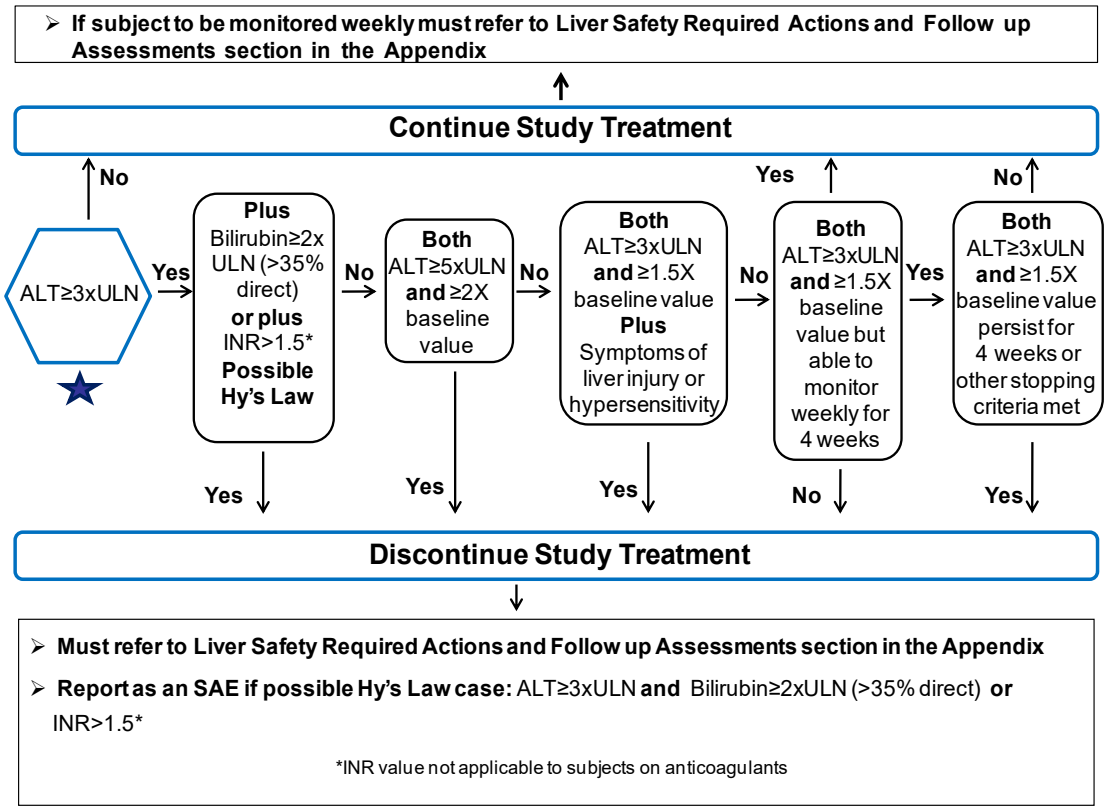
7.1.1. Liver Chemistry Stopping Criteria

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 2.
  OR
- In the presence of abnormal liver chemistry not meeting protocol-specified stopping rules, if the Investigator believes that it is in the best interest of the participant.

Participants with HCC and positive for HBV: Participants with ALT elevations ≥1.5x baseline, or an increase in ALT deemed clinically significant by the investigator, should have additional HBsAg and HBV DNA tests performed as clinically indicated to exclude a viral flare. These Participants should also have liver imaging to determine whether an increase in tumor size, or increase in liver metastases if present, may be contributing to the ALT elevation.

Figure 2 Liver Stopping and Monitoring Event Algorithm



Refer to Appendix 6 for required Liver Safety Actions and Follow up Assessments.

7.1.1.1. Study Intervention Restart or Rechallenge after Liver Stopping Criteria Met

If participant meets liver chemistry stopping criteria, do not restart/rechallenge participant with study intervention unless all of the following occurs:

- GSK Medical Governance approval is granted
- Ethics and/or IRB approval is obtained, if required, and
- Separate consent for intervention restart/rechallenge is signed by the participant

Note: If study treatment was interrupted for suspected drug-induced liver injury, the participant should be informed of the risk of death, liver transplantation, hospitalization, and jaundice and re-consented before resumption of dosing.

Refer to Appendix 6 for details on the restart/rechallenge process.

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

7.1.2. QTc Stopping Criteria

The QTcF correction formula *must* 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 of time 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

See the SoA (Section 1.2.1) for data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that need to be completed.

7.1.3. Stopping Rules for Clinical Deterioration

As indicated in Appendix 9, in order to adequately assess the antitumor effect of immunotherapeutic agents, participants experiencing apparent progression as defined by RECIST version 1.1 guidelines may continue to receive treatment until progression is confirmed at a subsequent imaging assessment at least 4 weeks later as indicated by iRECIST guidelines. These considerations should be balanced by clinical judgment as to whether the participant is clinically deteriorating and unlikely to receive benefit from continued study treatment. The following parameters should be considered by the Investigator prior to treating participants beyond confirmed progression as defined by iRECIST:

- Disease progression is not rapid as assessed by the Investigator
- Participant continues to meet all eligibility criteria as assessed by the Investigator
- Participant is tolerating study intervention
- Participant has stable performance status (ECOG PS 0-1)

- Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (e.g. CNS metastases)
- Participant has provided written informed consent prior to receiving additional study drug.

In cases where deterioration was assessed in the investigator's opinion to have occurred after a clinical event and is attributable to disease progression, is unlikely to reverse with continued study treatment or managed by supportive care (e.g., bisphosphonates and/or bone directed radiotherapy, thoracentesis, or paracentesis for accumulating effusions), study treatment should be discontinued. The decision to stop treatment should be discussed with the Sponsor's Medical Monitor. Examples of events that may, in the investigator's opinion, indicate a lack of clinical benefit and should result in the discontinuation of study drug include, but are not limited to, the following at the time of progression:

- ECOG PS decrease of at least 2 points from baseline, or a decrease considered clinically significant
- Clinically relevant worsening of laboratory values
- Skeletal related events defined by the following:
  - pathologic bone fracture in the region of cancer involvement
  - cancer related surgery to bone, and/or
  - spinal cord or nerve root compression
- Rapid progression of disease at critical anatomical sites requiring urgent medical intervention
- Development of new CNS metastases
- Any setting where the initiation of new antineoplastic therapy has been deemed beneficial to the participant even in the absence of any such documented clinical event.

7.2. Participant Discontinuation/Withdrawal from the Study

A participant may withdraw from the study at any time at his/her own request (withdrawal of consent) or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance or administrative reasons.

At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA. See SoA (Section 1.2.1) 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 a 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 or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the SoA (Section 1.2). Under this amendment, study procedures and their timing are summarised in SoAs in Section 1.2.1.

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.

If assessments are scheduled for the same nominal time, it is recommended that the assessments should occur in the following order: 12-lead ECG, vital signs, and blood draws. The timing of the assessments should allow the blood draw to occur at the exact nominal time.

The timing and number of planned study assessments may be altered during the course of the study based on newly available data (e.g., to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring for the following assessments: safety, PK, pharmacodynamics/biomarker, or other assessments.

The change in timing or addition of time points for any planned study assessments must be approved by the relevant GSK study team member and then archived in the study Sponsor and site study files, but this will not constitute a protocol amendment.

The IRB/ IEC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the Informed Consent Form.

This section lists the procedures and parameters of each planned study assessment. The exact timing of each assessment is listed in the SoAs (Section 1.2).

CCI

CCI

[redacted]

8.1.2. Tumor Growth Kinetics

CCI

[redacted]

8.2. Safety Assessments

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

8.2.1. Physical Examinations

A complete physical examination will be done at screening and TDV and will include assessments of the CV, Respiratory, Gastrointestinal and Neurological systems. Height and weight will also be measured and recorded.

A brief physical examination will be done at all other time points and will include assessments of the skin, lungs, CV system, and abdomen (liver and spleen).

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

For melanoma participants, a full body dermatological examination will be performed by a dermatologist (or suitably qualified physician) to identify abnormal skin lesions within the 28-day screening period. All findings will be photographed and identified during screening. Brief skin examinations will be performed as indicated in the SoA (Section 1.2.1) or more frequently as necessitated. Wherever possible, the same physician

should perform these examinations. Follow-up skin examinations by a referral dermatologist should be conducted if clinically indicated by the ECOG PS.

The PS will be assessed using the ECOG scale (Section 11.10) as specified in the SoA (Section 1.2.1).

8.2.2. Vital Signs

Vital sign measurements to be measured in semi-supine position after 5 minutes rest will include temperature, systolic and diastolic blood pressure, and heart rate. For study participants in Japan only, pulse oximetry for oxygen saturation will also be conducted as part of vitals as outlined in Table 5.

Vital signs will be measured more frequently on dosing days of GSK3745417 and dostarlimab. See Section 1.2.1 for details.

If a participant develops a fever, refer to Section 6.6 for fever management guidelines.

8.2.3. Electrocardiograms

Twelve-lead ECGs will be obtained at each planned ECG assessment during the study using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTcF intervals. Refer to Section 7.1.2 for QTcF stopping criteria and additional QTcF readings that may be necessary.

Before each ECG test, the participant should be at rest for approximately 10 minutes. The participant should be in the semi-recumbent or supine position; the same position must be used for all subsequent ECG tests.

ECG measurements will be performed in triplicate at Screening (all within a 5-minute time period), then as single ECG measurements. If QTc interval prolongation is observed during the study, triplicate ECG measurements will be performed.

8.2.4. Holter Monitoring for QT Assessment

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 at planned time points indicated in the SoA (Section 1.2). Holter monitoring may be waived for individual participants upon approval from GSK.

Holter monitoring will not be conducted in participants in the combination dose escalation (Part 2A).

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.

8.2.5. Neurological Assessments

In the event of neurological symptoms and/or signs, treating physician may consider serial neurological examinations (i.e., Immune Effector Cell-Associated Encephalopathy [ICE]), neurological consultation and appropriate imaging. These are described in more detail in Section 6.6.1.2.

All participants who experience neurological AEs will be graded according to CTCAE (version 5.0); any participants with ICANs will be graded according to the grading system described in Section 6.6.1.3.

8.2.6. Follow-Up Phone Call

After the first 6 doses of study intervention (monotherapy and combination), participants should be contacted between 24 hours and 72 hours following discharge from the clinic/hospital. The purpose of this phone-call is to assess for any AEs or cytokine related symptoms.

8.2.7. Clinical Safety Laboratory Assessments

Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA Section 1.2.1 and Appendix 15 for the timing and frequency.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 30 days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered significantly abnormal by the investigator or medical monitor.

If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified, and the sponsor notified.

All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA Section 1.2.1.

8.2.8. Chest Imaging (Japan cohort Only)

CCI [redacted]

8.3. Adverse Events and Serious Adverse Events

The definitions of an AE or SAE can be found in Appendix 3. All toxicities will be graded using National Cancer Institute - Common Toxicity Criteria for AEs (NCI-CTCAE), version 5.0 and as outlined in Section 4.1.2.

The investigator and any qualified designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or the study, or that caused the participant to discontinue the study intervention (see Section 4.3).

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

All SAEs that are deemed related to study participation will be collected from the time of consent until the time points specified in the SoA (Section 1.2.1). Therefore, any SAEs assessed as related to study participation (including protocol-mandated procedures, invasive tests, or change in existing therapy) as well as those related to study drugs will be recorded from the time a participant consents to participate in the study.

AEs will be assessed and documented at each visit from first dose until the TDV. AESIs and SAEs will be collected until 90 days after the last dose or until start of subsequent anticancer treatment, whichever comes first (Section 1.2.1).

Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the case report form (CRF) not the AE section.

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

Investigators are not obligated to actively seek AEs or SAEs after the conclusion of the study participation. However, if the investigator learns of any SAE or 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.

For participants in the PACT phase of the study, GSK will continue to collect safety information including SAEs, AEs leading to treatment discontinuation, overdose and pregnancy cases via paper forms which will be reported directly to GSK. SAEs, AEs leading to treatment discontinuation, overdose and pregnancy cases will be reported during the PACT treatment period and for up to 90 days after last dose. Additionally, any SAEs that are ongoing at the time of the final data cut-off must be followed up to resolution unless the event is considered by the investigator unlikely to resolve, or the participant is lost to follow-up. Updates to these events will also occur via paper forms

directly to GSK. GSK retains the right to request additional information for any participant with ongoing AE(s)/SAE(s) at EOS, if judged necessary.

8.3.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

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 Appendix 3), 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 a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

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

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

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

8.3.5. Pregnancy

Details of all pregnancies in female participants will be collected after the start of study intervention and until 150 days following the last dose of study intervention.

If a pregnancy is reported, the investigator should inform GSK within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 4.

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered an SAE.

8.3.6. Cardiovascular and Death Events

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

The CV CRFs are presented as queries in response to reporting of certain CV Medical Dictionary for Regulatory Activities (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

An event which is part of the natural course of the disease under study (i.e., disease progression or hospitalization due to disease progression) does not need to be reported as an SAE.

Death due to disease under study is to be recorded on the death eCRF form.

However, if the underlying disease (i.e., progression) is greater than that which would normally be expected for the participant, or if the investigator considers that there was a causal relationship between treatment with study treatment(s) or protocol design/procedures and the disease progression, then this must be reported as a SAE.

NOTE: If either of the following conditions apply, then the event must be recorded and reported as a SAE (instead of a disease-related event):

- 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 treatment with study treatment(s).

8.3.8. Guidelines for Events of Special Interest

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(s) are provided in Section 6.6.

Please also refer to Appendix 11 for AEs of Special Interest.

8.4. Treatment of Overdose

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

There is no specific antidote for overdose with GSK3745417. In the event of a suspected overdose, it is recommended that the appropriate supportive clinical care should be instituted, as dictated by the participant's clinical status.

An overdose of dostarlimab is defined as any dose that is ≥20% than 1000 mg Q6W.

In the event of an overdose, the investigator should:

- Contact the Medical Monitor immediately.
- Closely monitor the participant for AE/SAE and laboratory abnormalities until study intervention can no longer be detected systemically (at least 48 hours).
- Document the quantity of the excess dose as well as the duration of the overdosing in the CRF.
- 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).

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

8.5. Pharmacokinetics – Blood and Urine

Blood samples for PK analysis of GSK3745417, dostarlimab and ADA will be collected at the time points described in the SoA (Section 1.2). The actual date and time of each blood sample collection will be recorded in the eCRF. The timing of PK samples may be altered and/or PK samples may be obtained at additional time points to ensure thorough PK monitoring. Details on PK blood sample collection, processing, storage, and shipping procedures are provided in the SRM. Plasma samples may be analyzed for other compound-related metabolites and the results reported under a separate DMPK, GlaxoSmithKline protocol. ADAs will be analyzed in a tiered approach using electrochemiluminescence (i.e., screening, confirmation, titer, and neutralizing antibody assay), if appropriate.

Collection of urine CCI [redacted] should enable a quantitative assessment of parent drug GSK3745417 and qualitative or quantitative assessment of drug metabolites in this matrix. Metabolite-related results may be reported under a separate DMPK, GlaxoSmithKline protocol. The pre-dose collection will be a single voiding. For post-dose collection intervals, the actual start and stop time and date for each urine sample collection interval will be recorded. The volume pre-dose and during each collection intervals will also be recorded. The timing of the urine samples may be altered and/or urine samples may be obtained at additional time points to ensure thorough urine

PK monitoring. Details on PK urine sample collection, processing, storage, and shipping procedures are provided in the SRM.

PK, ADA and urine sample collection may be terminated when sufficient data have been collected.

8.6. Anti-Drug Antibodies

Serum samples will be collected for the presence of antibodies that bind to dostarlimab. See Section 1.2.1 for the timing of sample collection. The actual date and time of each blood sample collection will be recorded in the eCRF. The timing of immunogenicity samples may be altered and/or may be obtained at additional time points to ensure thorough immunogenicity monitoring. The collected immunogenicity blood samples will be held and processed in the future, as necessary.

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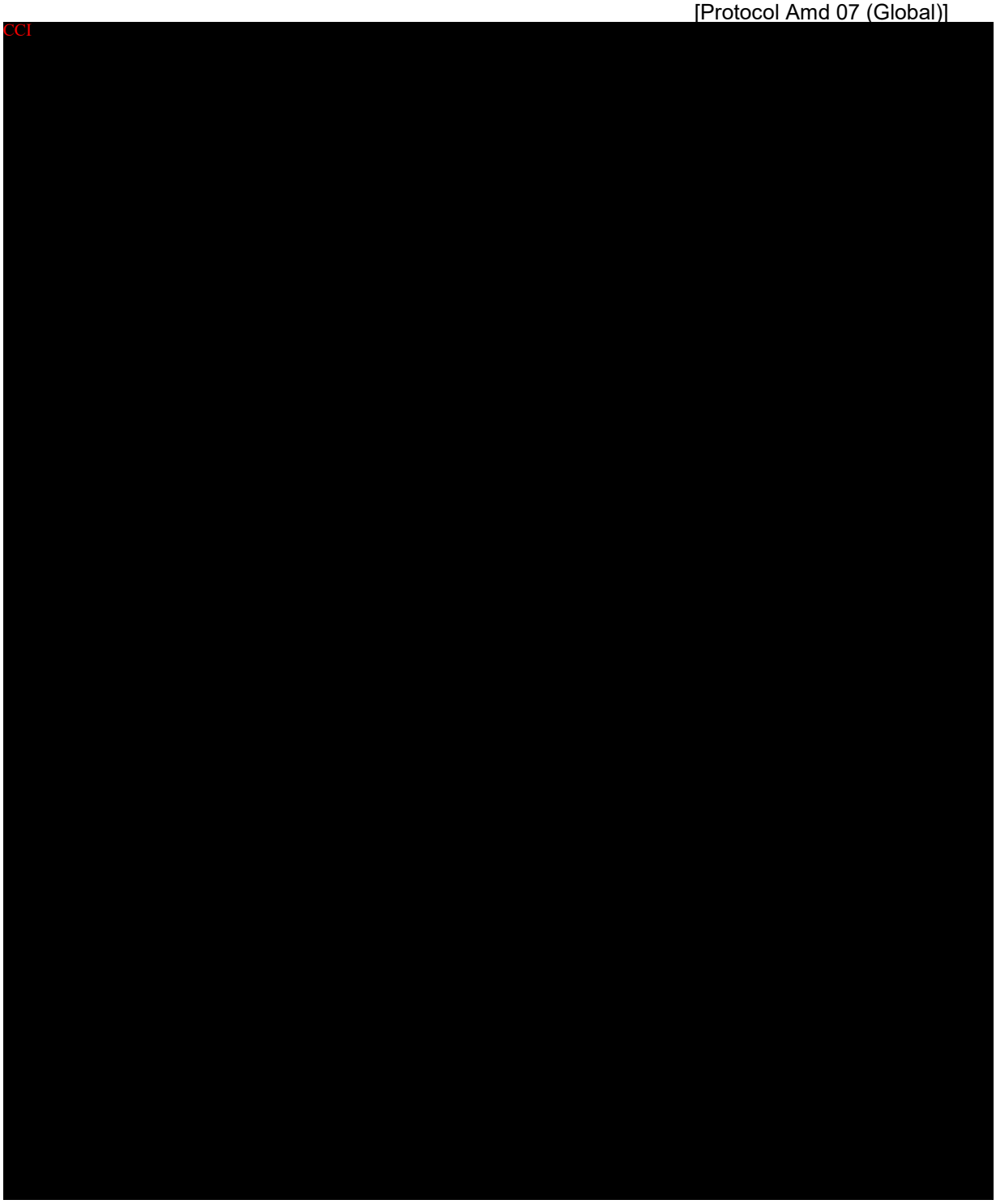

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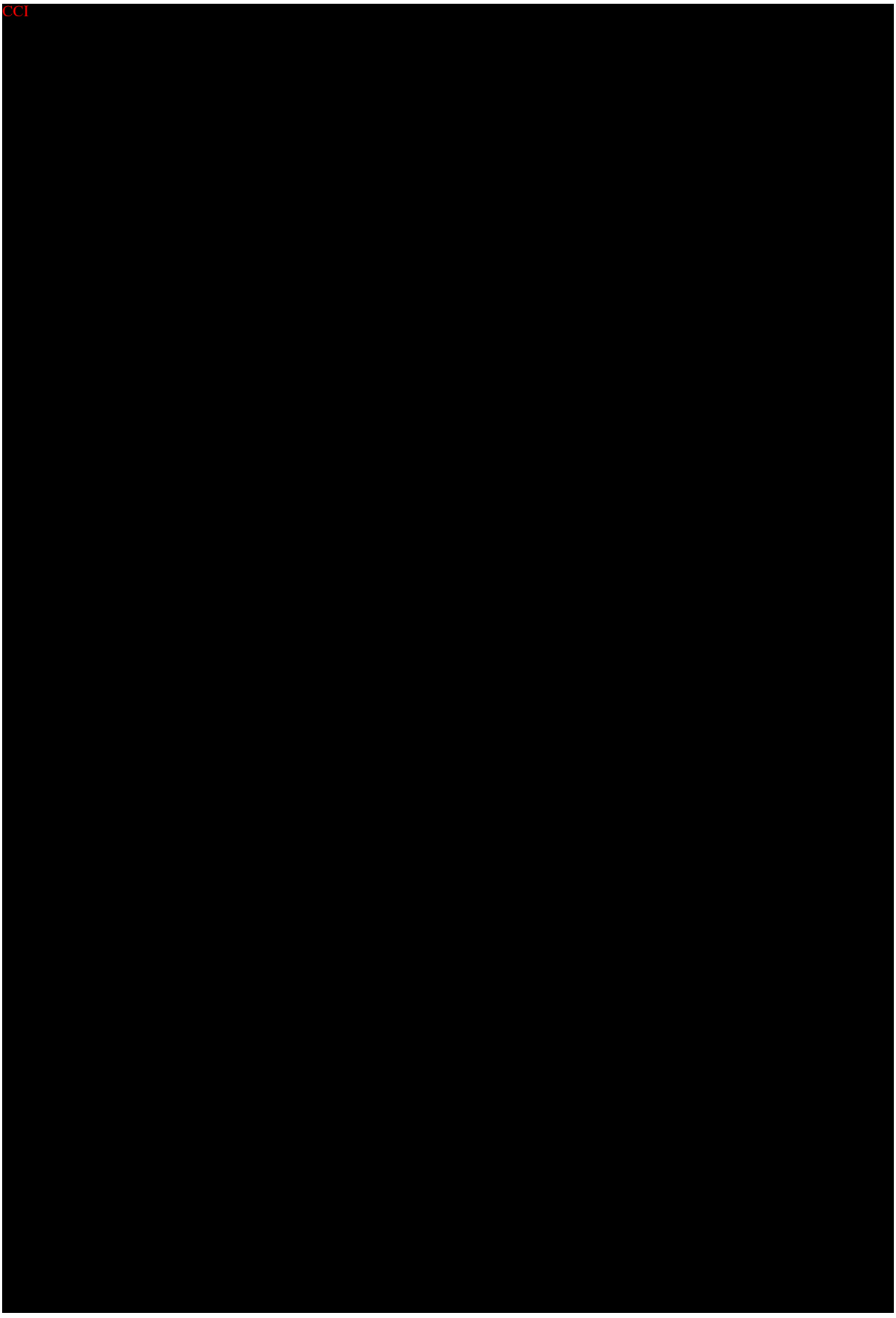

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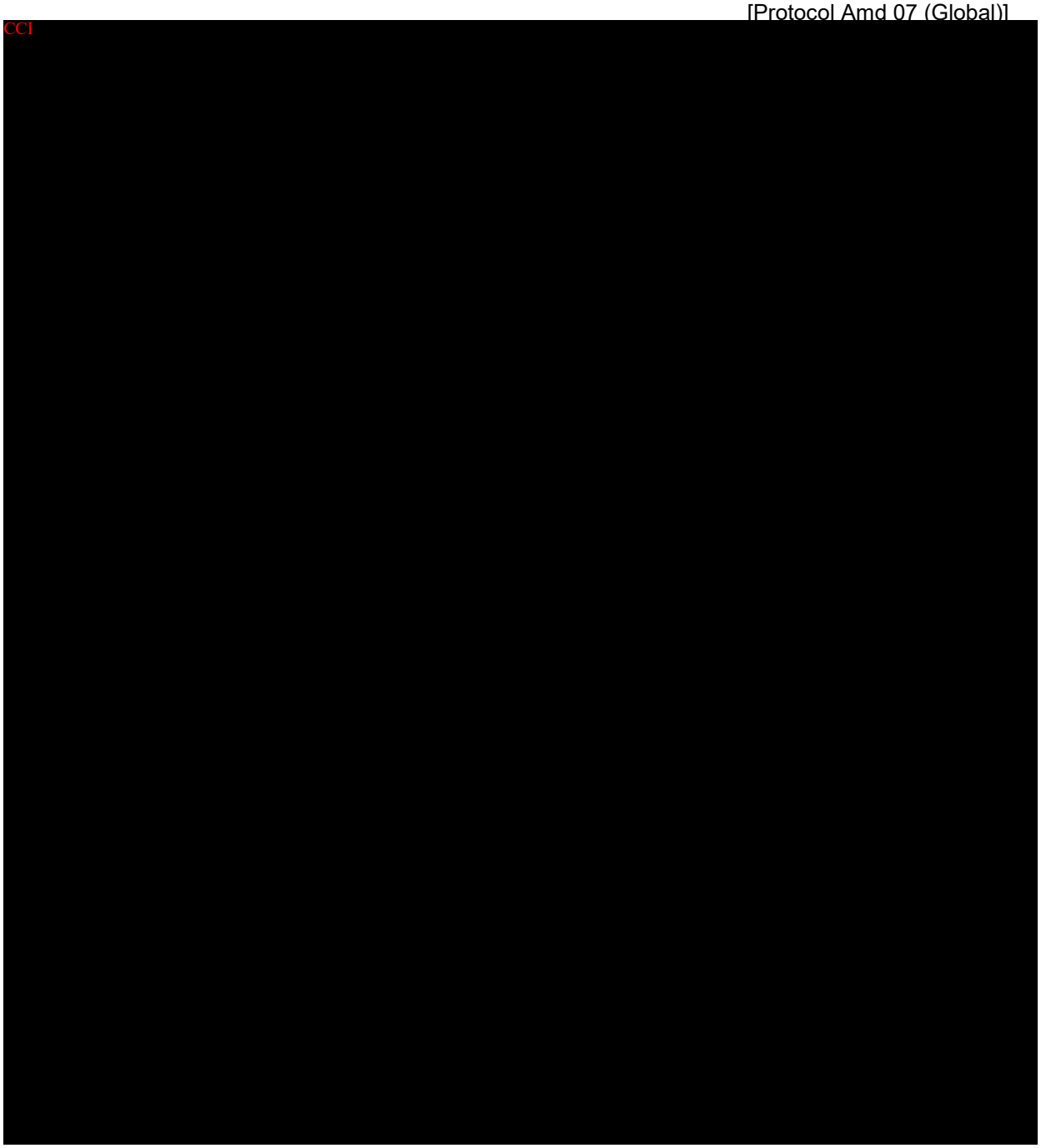

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11. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

11.1.1. Regulatory and Ethical Considerations

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

11.1.2. Financial Disclosure

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

11.1.3. Informed Consent Process

The investigator or his/her representative will explain the nature of the study including the risk and benefits, to the participant or his/her legally authorized representative and answer all questions regarding the study.

Participants must be informed that their participation is voluntary and that they can withdraw their consent to participate for any reason or no reason at all. Participants or their legally authorized representative must be informed that they are free to take the Informed Consent home to discuss participation with members of their family or personal medical physician. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study, the date the written consent was obtained, and which persons were present when the study was explained to the potential participant or their legally authorized representative. The authorized person obtaining the informed consent must also sign the ICF.

Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.

A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.

Participants who are rescreened are required to sign a new ICF.

11.1.4. Data Protection

Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

11.1.5. Dissemination of Clinical Study Data

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the

opportunity to review the complete study results at a GSK site or other mutually -agreeable location.

GSK will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study participants, as appropriate.

The procedures and timing for public disclosure of the protocol and results summary and for development of a manuscript for publication for this study will be in accordance with GSK Policy.

GSK intends to make anonymized patient-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.

A manuscript will be progressed for publication in the scientific literature if the results provide important scientific or medical knowledge.

11.1.6. Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

Monitoring details describing strategy (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 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).

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

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

11.1.7. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definition of what constitutes source data can be found in The Monitoring Plan.

11.1.8. Study and Site Closure

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

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

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

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

11.1.9. 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.

11.2. Appendix 2: Clinical Laboratory Tests

Note: In this amendment, any tests conducted in a clinical laboratory will no longer be performed. Table 26 has been updated to reflect this change and now details the tests which will be performed by the local laboratory

- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 4.6.
- Additional tests may be performed at any time during the study as determined necessary by the investigator (e.g. for suspected CRS) or required by local regulations.
- Pregnancy Testing
  - Refer to Section 5.1 Inclusion Criteria for screening pregnancy criteria.
  - Negative serum pregnancy test is required within 72 hours prior to date of first dose of GSK3745417 on Day 1 and first dose of dostarlimab on Day 8 for females of childbearing potential; predose urine pregnancy test is required every 3 weeks for monotherapy arms with GSK3745417 and every 3 weeks for combination arms with GSK3745417 in co-administration with dostarlimab for the duration of the study, on the last day of treatment (if possible), at TDV, and at the Follow-Up visits.

Table 26 Protocol-Required Safety Laboratory Assessments

Local Safety Laboratory Assessments			
Laboratory Assessments	**Parameters**		
Clinical Chemistry[1]	BUN Creatinine Glucose eGFR	Potassium Sodium Calcium Total Protein Albumin	AST (SGOT) ALT (SGPT) Alkaline Phosphatase Total and direct bilirubin
Liver Function Test	AST (SGOT), ALT (SGPT), Alkaline Phosphatase, Total and direct bilirubin, Total Protein, Albumin in HCC and underlying HBV or HCV (see Section 1.2)		
Thyroid Function	Thyroid Stimulating Hormone, free T4, free T3		
Cardiac Function	Troponin I and/or T, BNP/NTproBNP		
Routine Urinalysis	Specific gravity pH, glucose, protein, blood, ketones by dipstick Microscopic examination (if blood or protein is abnormal)		
HBV monitoring for participants with HBV and HCC	HBV DNA		
Coagulation	PTT (or INR), PT/INR		
Other Screening Tests	Hepatitis B (HBsAg), HBe Antigen Quantitative HBsAg Hepatitis C (Hep C antibody) Serum Pregnancy test (as needed for WOCBP) For participants positive for HBV or HCV at Screening: HBV DNA, HBsAg, and HCV RNA		
Hematology, C-Reactive Protein, Ferritin, Coagulation, Tryptase	To be also conducted locally if CRS is suspected (Section 6.6.1)		
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit	RBC Indices: MCV MCH %Reticulocytes	WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils
Other	C-Reactive Protein		

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 6. All events of ALT ≥3 × upper limit of normal (ULN) and bilirubin ≥2 × ULN (>35% direct bilirubin) or ALT ≥3 × ULN and international normalized ratio (INR) >1.5, if INR measured, which may indicate severe liver injury (possible Hy's Law), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis).

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

11.3.1. Definition of AE

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

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil 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.

11.3.2. Definition of SAE

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

A SAE is defined as any untoward medical occurrence that, at any dose:
○ Results in death
○ Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AE. If a complication prolongs hospitalization or fulfils any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a **pre-existing** condition at baseline (prior to first dose of study drug) that did not worsen from baseline is not considered an AE.

Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
Is a congenital anomaly/birth defect
Other situations: • Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

11.3.3. Definition of Cardiovascular Events

Cardiovascular Events (CV) Definition:
Investigators will be required to fill out the specific CV event page of the CRF for the following AEs and SAEs: • Myocardial infarction/unstable angina • Congestive heart failure • Arrhythmias • Valvulopathy • Pulmonary hypertension • Cerebrovascular events/stroke and transient ischemic attack • Peripheral arterial thromboembolism • Deep venous thrombosis/pulmonary embolism • Revascularization (stent or CABG)

11.3.4. Recording and Follow-Up of AE and SAE

AE and SAE Recording

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

Assessment of Severity

The investigator will assess severity for each AE and SAE reported during the study and will grade it according to the NCI-CTCAE v 5.0. Other measures to evaluate AE and SAE may be utilized (e.g., National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE).

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 in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE

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

11.3.5. Reporting of SAE to GSK

SAE Reporting to GSK via Electronic Data Collection Tool

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

SAE Reporting to GSK via Paper CRF
• Facsimile transmission of the SAE paper CRF 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 CRF pages within the designated reporting time frames. • Contacts for SAE reporting can be found in the Study Reference Manual.

Note: During the PACT phase, all SAEs and pregnancies will be reported via paper CRFs.

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

11.4.1. Definitions

Woman of Childbearing Potential (WOCBP)

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

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

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with 1 of the following:
    - Documented hysterectomy
    - Documented bilateral salpingectomy
    - Documented bilateral oophorectomy

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

    Note: Documentation can come from the site personnel's: review of the participant's medical records, medical examination, or medical history interview.
3. Postmenopausal female
    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
        - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement >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 enrollment.

11.4.2. Contraception Guidance

• **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)

11.4.3. Collection of Pregnancy Information

Female Participants who become pregnant

- Investigator will collect pregnancy information on any female participant, who becomes pregnant while participating in this study.
- Information will be recorded on the appropriate form and submitted to GSK within 24 hours of learning of a participant's pregnancy.
- Participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow up information on participant and neonate, which will be forwarded to GSK. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.
- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study intervention by the investigator, will be reported to GSK as described in Appendix 3. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Any female participant who becomes pregnant while participating will discontinue study intervention.

11.5. CCI

CCI

[redacted]

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

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 6) • 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 perform liver event follow up assessments within **24 hr**	• 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

• 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 [redacted]
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

11.6.1. 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.

11.6.2. 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 x baseline and ALT <3xULN).

- 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 11.6.2 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 11.3.

11.7. Appendix 7: Estimated Glomerular Filtration Rate

CKD stage: Kidney Disease Outcomes Quality Initiative (KDOQI) CKD stages 3/4/5 defined by eGFR using the CKD Epidemiology Collaboration (CKD-EPI) formula [Levey, 2009].

$GFR = 141 \times \min(S_{cr}/\kappa, 1)^{\alpha} \times \max(S_{cr}/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018$ [if female] × 1.159 [if black] x 0.813 [if Japanese]

where:
S_{cr} is serum creatinine in mg/dL,
κ is 0.7 for females and 0.9 for males,
α is -0.329 for females and -0.411 for males,
min indicates the minimum of S_{cr}/κ or 1, and
max indicates the maximum of S_{cr}/κ or 1.

11.8. Appendix 8: NYHA Functional Classification System for Heart Failure

The New York Heart Association (NYHA) Functional Classification [NYHA, 1994] provides a simple way of classifying the extent of heart failure. It places participants in one of four categories based on the level of limitation experienced during physical activity:

Class	Symptoms
Class I (Mild)	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation or dyspnea (shortness of breath).
Class II (Mild)	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation or dyspnea.
Class III (Moderate)	Marked limitation of physical activity. Comfortable at rest, but less than ordinary physical activity results in fatigue, palpitation or dyspnea.
Class IV (Severe)	Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.

11.9. Appendix 9: Guidelines for Assessment of Disease, Disease Progression and Response Criteria – adapted from RECIST version

11.9.1. RECIST 1.1 Guidelines

Please note the following:

- The same diagnostic method, including use of contrast when applicable, must be used throughout the study to evaluate a lesion. Contrast agents must be used in accordance with the Image Acquisition Guidelines.
- All measurements must be taken and recorded in millimeters (mm), using a ruler or calipers.
- Ultrasound is not a suitable modality of disease assessment. If new lesions are identified by ultrasound, confirmation by CT or MRI is required.
- Fluorodeoxyglucose (FDG)-PET is generally not suitable for ongoing assessments of disease. However, FDG-PET can be useful in confirming new sites of disease where a positive FDG-PET scans correlates with the new site of disease present on CT/MRI or when a baseline FDG-PET was previously negative for the site of the new lesion. FDG-PET may also be used in lieu of a standard bone scan providing coverage allows interrogation of all likely sites of bone disease and FDG-PET is performed at all assessments.
- If PET/CT is performed then the CT component can only be used for standard response assessments if performed to diagnostic quality, which includes the required anatomical coverage and prescribed use of contrast. The method of assessment must be noted as CT on the eCRF.

Clinical Examination: Clinically detected lesions will only be considered measurable when they are superficial (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler/calipers to measure the size of the lesion, is required. [Eisenhauer, 2009]

CT and MRI: **Contrast enhanced CT with 5 mm contiguous slices is recommended.** Minimum size of a measurable baseline lesion must be twice the slice thickness, with a minimum lesion size of 10 mm when the slice thickness is 5 mm. MRI is acceptable, but when used, the technical specification of the scanning sequences must be optimized for the evaluation of the type and site of disease and lesions must be measured in the same anatomic plane by use of the same imaging examinations. Whenever possible, the same scanner should be used. [Eisenhauer, 2009]

X-ray: In general, X-ray should not be used for target lesion measurements owing to poor lesion definition. Lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung; however, chest CT is preferred over chest X-ray. [Eisenhauer, 2009]

Brain Scan: If brain scans are required, then contrast enhanced MRI is preferable to contrast enhanced CT.

11.9.2. Guidelines for Evaluation of Disease

Evaluation of Anticancer Activity

- RECIST version 1.1 guidelines will be used to determine the overall tumor burden at Screening, select target and non-target lesions, and in the disease assessments through the duration of the study [Eisenhauer, 2009].
- As indicated in RECIST version 1.1 guidelines:
    - Lymph nodes that have a short axis of <10 mm are considered non-pathological and must not be recorded or followed.
    - Pathological lymph nodes with <15 mm, but ≥10 mm short axis are considered non-measurable.
    - Pathological lymph nodes with ≥15 mm short axis are considered measurable and can be selected as target lesions; however, lymph nodes should not be selected as target lesions when other suitable target lesions are available.
    - Measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions, and recorded and measured at baseline. These lesions should be selected based on their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically).

Note: Cystic lesions thought to represent cystic metastases must not be selected as target lesions when other suitable target lesions are available.

Note: Measurable lesions that have been previously irradiated and have not been shown to be progressing following irradiation must not be considered as target lesions.

Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by CT or MRI) can be considered measurable. Bone scans, FDG-PET scans or X-rays are not considered adequate imaging techniques to measure bone lesions.

- All other lesions (or sites of disease) must be identified as non-target and must also be recorded at baseline. Non-target lesions will be grouped by organ. Measurements of these lesions are not required, but the presence or absence of each must be noted throughout follow-up.

11.9.3. Measurable and Non-Measurable Definitions

Measurable lesion:

A non-nodal lesion that can be accurately measured in at least one dimension (longest dimension) of

- ≥10 mm with MRI or CT when the scan slice thickness is no greater than 5 mm. If the slice thickness is greater than 5 mm, the minimum size of a measurable lesion

must be at least double the slice thickness (e.g., if the slice thickness is 10 mm, a measurable lesion must be ≥20 mm).

- ≥10 mm caliper/ruler measurement by clinical exam or medical photography.
- ≥20 mm by chest X-ray.

- Additionally, lymph nodes can be considered pathologically enlarged and measurable if:
  - ≥15 mm in the short axis when assessed by CT or MRI (slice thickness recommended to be no more than 5 mm). At baseline and follow-up, only the short axis will be measured. [Eisenhauer, 2009]

Non-measurable lesion:

All other lesions including lesions too small to be considered measurable (longest diameter <10 mm or pathological lymph nodes with ≥10 mm and <15 mm short axis) as well as truly non-measurable lesions, which include: leptomeningeal disease, ascites, pleural or pericardial effusions, inflammatory breast disease, lymphangitic involvement of the skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques [Eisenhauer, 2009].

Measurable disease: The presence of at least 1 measurable lesion. Palpable lesions that are not measurable by radiologic or photographic evaluations may not be utilized as the only measurable lesion.

Non-Measurable only disease: The presence of only non-measurable lesions.
Note: non-measurable only disease is not allowed per protocol.

11.9.4. iRECIST Guidelines

iRECIST is based on RECIST 1.1, but adapted to account for the unique tumor response seen with immunotherapeutic drugs. iRECIST will be used to assess tumor response and progression and make treatment decisions. When clinically stable, participants should not be discontinued until progression is confirmed according to the rules described below. This allowance to continue treatment despite initial radiologic PD takes into account the observation that some participants can have a transient tumor flare in the first few months after the start of immunotherapy, and then experience subsequent disease response. These data will be captured in the clinical database.

Clinical stability is defined as meeting all of the following:

- Absence of symptoms and signs indicating clinically significant progression of disease
- No decline in ECOG performance status
- No requirements for intensified management, including increased analgesia, radiation, or other palliative care

Any participant deemed **clinically unstable** may be discontinued from study treatment at site-assessed first radiologic evidence of PD. It is strongly preferred to obtain the repeat tumor imaging, when feasible, for confirmation of PD by iRECIST.

In a clinically unstable participant, if the investigator decides to continue treatment, following consultation with the sponsor medical monitor, the participant may continue to receive study treatment. The tumor assessment should be repeated at least 4 weeks and up to 8 weeks later to confirm PD by iRECIST. Images should continue to be sent into the central imaging vendor for potential central review.

If repeat imaging does not confirm PD per iRECIST and the participant continues to be clinically stable, study treatment may continue and follow the regular imaging schedule. If PD is confirmed, participants will be discontinued from study treatment.

If a participant has confirmed radiographic progression (iCPD) as defined below, study treatment should be discontinued; however, if the participant is achieving a clinically meaningful benefit, continuation of study treatment may be considered following consultation with the sponsor. In this case, if study treatment is continued, tumor imaging should continue to be performed following the intervals as outlined in Section 8.1 and submitted to the central imaging vendor.

Description of the iRECIST Process for Assessment of Disease Progression

Assessment at Screening and Prior to RECIST 1.1 Progression

Until radiographic disease progression based on RECIST 1.1, there is no distinct iRECIST assessment.

Assessment and Decision at RECIST 1.1 Progression

For participants who show evidence of radiological PD by RECIST 1.1 the investigator will decide whether to continue a participant on study treatment until repeat imaging is obtained (using iRECIST for participant management (see Table 27 and Figure 11). This decision should be based on the participant's overall clinical condition (See discussion of clinical stability in Section 11.9.1).

Tumor flare may manifest as any factor causing radiographic progression per RECIST 1.1, including:

- Increase in the sum of diameters of target lesion(s) identified at baseline to ≥20% and ≥5 mm from nadir:
    - Note: the iRECIST publication uses the terminology "sum of measurements", but "sum of diameters" will be used in this protocol, consistent with the original RECIST 1.1 terminology.
- Unequivocal progression of non-target lesion(s) identified at baseline
- Development of new lesion(s)

iRECIST defines response categories, including iUPD (unconfirmed progressive disease) and iCPD (confirmed progressive disease). For purposes of iRECIST assessment, the first

visit showing progression according to RECIST 1.1 will be assigned a visit (overall) response of iUPD, regardless of which factors caused the progression.

At this visit, target and non-target lesions identified at baseline by RECIST 1.1 will be assessed as usual.

New lesions will be classified as measurable or non-measurable, using the same size thresholds and rules as for baseline lesion assessment in RECIST 1.1. From measurable new lesions, up to 5 lesions total (up to 2 per organ), may be selected as New Lesions – Target. The sum of diameters of these lesions will be calculated and kept distinct from the sum of diameters for target lesions at baseline. All other new lesions will be followed qualitatively as New Lesions – Non-target.

Assessment at the Confirmatory Imaging

At the confirmatory imaging visit assessment, the participant will be classified as progression confirmed (with an overall response of iCPD), or as showing persistent unconfirmed progression (with an overall response of iUPD), or as showing disease stability or response (iSD/iPR/iCR). Timing of confirmatory imaging is described in Table 27.

Confirmation of Progression

Progression is considered confirmed, and the overall response will be iCPD, if ANY of the following occurs:

- Any of the factors that were the basis for the initial iUPD show worsening
  - For target lesions, worsening is a further increase in the sum of diameters of ≥5 mm, compared to any prior iUPD time point
  - For non-target lesions, worsening is any significant growth in lesions overall, compared to a prior iUPD time point; this does not have to meet the "unequivocal" standard of RECIST 1.1
  - For new lesions, worsening is any of these:
    - An increase in the new lesion sum of diameters by ≥5 mm from a prior iUPD time point
    - Visible growth of new non-target lesions
    - The appearance of additional new lesions
- Any new factor appears that would have triggered PD by RECIST 1.1

Persistent iUPD

Progression is considered not confirmed, and the overall response remains iUPD, if:

- None of the progression-confirming factors identified above occurs AND
- The target lesion sum of diameters (initial target lesions) remains above the initial PD threshold (by RECIST 1.1)

Additional imaging for confirmation should be scheduled 4 to 8 weeks from the imaging on which iUPD is seen. This may correspond to the next visit in the original visit schedule. The assessment of the subsequent confirmation imaging proceeds in an identical manner, with possible outcomes of iCPD, iUPD, and iSD/iPR/iCR.

Resolution of iUPD

Progression is considered not confirmed, and the overall response becomes iSD/iPR/iCR, if:

- None of the progression-confirming factors identified above occurs, AND
- The target lesion sum of diameters (initial target lesions) is not above the initial PD threshold.

The response is classified as iSD or iPR (depending on the sum of diameters of the target lesions), or iCR if all lesions resolve.

In this case, the initial iUPD is considered to be pseudo-progression, and the level of suspicion for progression is "reset." This means that the next visit that shows radiographic progression, whenever it occurs, is again classified as iUPD by iRECIST, and the confirmation process is repeated before a response of iCPD can be assigned.

Management Following the Confirmatory Imaging

If repeat imaging does not confirm PD per iRECIST, as assessed by the investigator, and the participant continues to be clinically stable, study treatment may continue and follow the regular imaging schedule. If PD is confirmed, participants will be discontinued from study treatment or for participants in monotherapy dose escalation and eligible, crossover to receive combination therapy.

NOTE: If a participant has confirmed radiographic progression (iCPD) as defined above, but the participant is achieving a clinically meaningful benefit, continuation of study treatment may be considered following consultation with the Sponsor. In this case, if study treatment is continued, tumor imaging should continue to be performed following the intervals as outlined in Section 3 and submitted to the central imaging vendor.

Detection of Progression at Visits after Pseudo-Progression Resolves

After resolution of pseudo-progression (i.e., achievement of iSD/iPR/iCR), iUPD is indicated by any of the following events:

- Target lesions
  - Sum of diameters reaches the PD threshold (≥20% and ≥5 mm increase from nadir) either for the first time, or after resolution of previous pseudo-progression. The nadir is always the smallest sum of diameters seen during the entire trial, either before or after an instance of pseudo-progression.
- Non-target lesions

- If non-target lesions have never shown unequivocal progression, doing so for the first time results in iUPD.
- If non-target lesions have shown previous unequivocal progression, and this progression has not resolved, iUPD results from any significant further growth of non-target lesions.

- New lesions
  - New lesions appear for the first time
  - Additional new lesions appear
  - Previously identified new target lesions show an increase of ≥ 5 mm in the new lesion sum of diameters, from the nadir value of that sum
  - Previously identified non-target lesions show any significant growth

If any of the events above occur, the overall response for that visit is iUPD, and the iUPD evaluation process (see Assessment at the Confirmatory Imaging above) is repeated. Progression must be confirmed before iCPD can occur.

The decision process is identical to the iUPD confirmation process for the initial PD, with one exception: if new lesions occurred at a prior instance of iUPD, and at the confirmatory imaging the burden of new lesions has increased from its smallest value (for new target lesions, the sum of diameters is ≥5 mm increased from its nadir), then iUPD cannot resolve to iSD or iPR. It will remain iUPD until either a decrease in the new lesion burden allows resolution to iSD or iPR, or until a confirmatory factor causes iCPD.

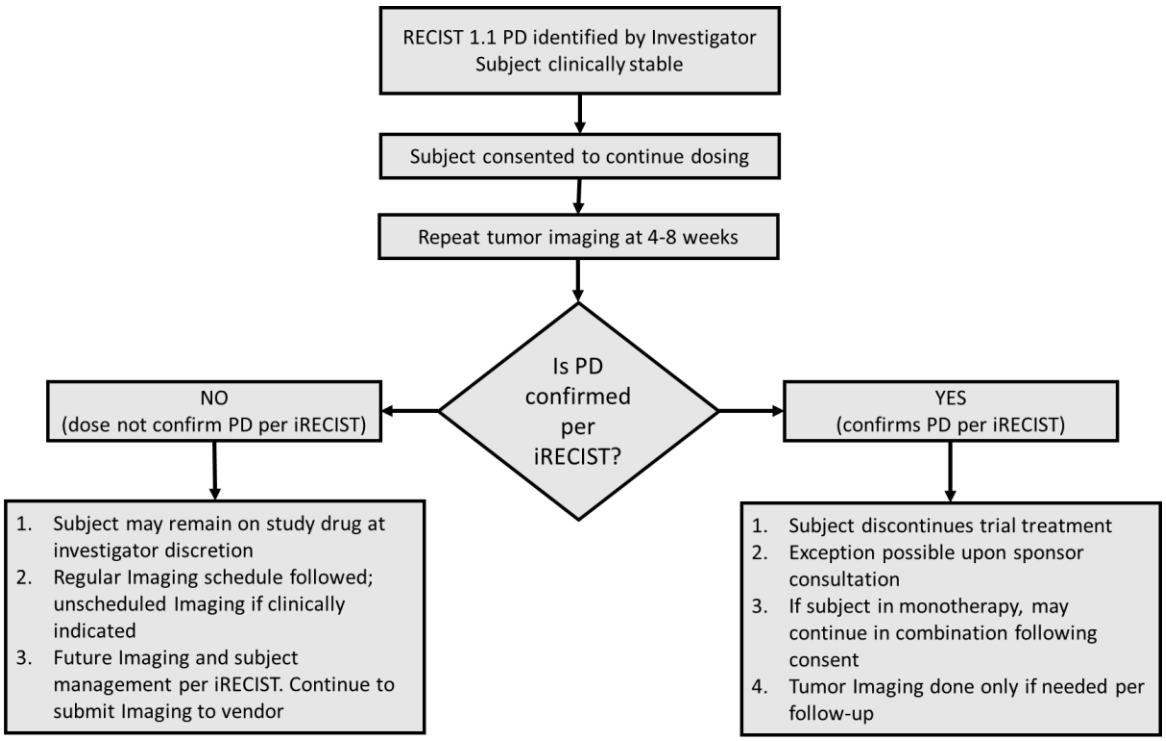
Additional details about iRECIST are provided in the iRECIST publication [Seymour, 2017].

Table 27 Imaging and Treatment after First Radiologic Evidence of Progressive Disease

	Clinically Stable		Clinically Unstable	
	Imaging	**Treatment**	**Imaging**	**Treatment**
First radiologic evidence of PD by RECIST 1.1	Repeat imaging at 4 to 8 weeks to confirm PD.	May continue study treatment at the investigator's discretion while awaiting confirmatory tumor imaging by site by iRECIST.	Repeat imaging at 4 to 8 weeks to confirm PD per investigator's discretion only.	Discontinue treatment
Repeat tumor imaging confirms PD (iCPD) by iRECIST per investigator assessment	No additional imaging required.	Discontinue treatment (exception is possible upon consultation with sponsor).	No additional imaging required.	Not applicable
Repeat tumor imaging shows iUPD by iRECIST per investigator assessment	Repeat imaging at 4 to 8 weeks to confirm PD. May occur at next regularly scheduled imaging visit.	Continue study treatment at the investigator's discretion.	Repeat imaging at 4 to 8 weeks to confirm PD per investigator's discretion only.	Discontinue treatment
Repeat tumor imaging shows iSD, iPR, or iCR by iRECIST per investigator assessment.	Continue regularly scheduled imaging assessments.	Continue study treatment at the investigator's discretion.	Continue regularly scheduled imaging assessments.	May restart study treatment if condition has improved and/or clinically stable per investigator's discretion. Next tumor imaging should occur according to the regular imaging schedule.

iCPD = iRECIST confirmed progressive disease; iCR = iRECIST complete response; iRECIST = modified Response Evaluation Criteria in Solid Tumors 1.1 for immune-based therapeutics; iSD = iRECIST stable disease; iUPD = iRECIST unconfirmed progressive disease; PD = progressive disease; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors 1.1.

Figure 11 Imaging and Treatment for Clinically Stable Participants after First Radiologic Evidence of PD Assessed by the investigator



11.10. 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.

11.11. Appendix 11: 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		

11.12. Appendix 12: Management Guidelines for CRS[a]

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 (e.g.: Continuous Airway Positive Pressure (CPAP), Bilevel Airway Positive Pressure 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 anticytokine 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.

a. Lee, 2019

11.13. Appendix 13: IRR/CRS Prophylaxis Regimen

Pre-medication	Dose	Administration	Action
Corticosteroid Medication			
Note: *Administer full (8 mg) dose of dexamethasone (or equivalent) noted below for first treatment dose. If no cytokine related reactions are observed then administer half (i.e.., 4 mg) the corticosteroid dose for second treatment dose. If no reactions after second dose, then administer half (i.e.., 2 mg) the corticosteroid dose for third treatment dose. If no reactions after the third dose, no further corticosteroids are required.* *Prophylactic corticosteroids may also be restarted as needed if cytokine related reactions of any grade occur and at a dose level at the discretion of the investigator after consultation with and approval by the sponsor.*			
Glucocorticoid	dexamethasone (8 mg) or equivalent	IV - administer approximately 30-60 minutes prior to the infusion	Required[a] – see above
Glucocorticoid	dexamethasone (4 mg) or equivalent	IV - administer approximately 30-60 minutes prior to the infusion	Required[a] – see above
Glucocorticoid	dexamethasone (2 mg) or equivalent	IV - administer approximately 30-60 minutes prior to the infusion	Required[a] – see above
Other Medications			
Antihistamine	diphenhydramine (50 mg) or equivalent	Oral - administer at least 1 hour (±15 minutes) prior to study drug **or** IV - start infusion approximately 15 to 30 minutes prior to study drug	Required
Antipyretic	acetaminophen (650 mg) or equivalent	Oral or IV- administer approximately 15 to 30 minutes prior to study drug	Required
H_2-antagonist	ranitidine (50 mg) or equivalent	IV - start infusion 30 (±15) minutes prior to study drug	Optional
Antiemetic	ondansetron (16 mg) or equivalent	IV - start infusion approximately 15 to 30 minutes prior to study drug	Optional

Abbreviations: CRS=cytokine release syndrome; IRR=infusion-related reaction; IV=intravenous.

a. Pre-infusion medications are only required up to and including the first treatment dose.

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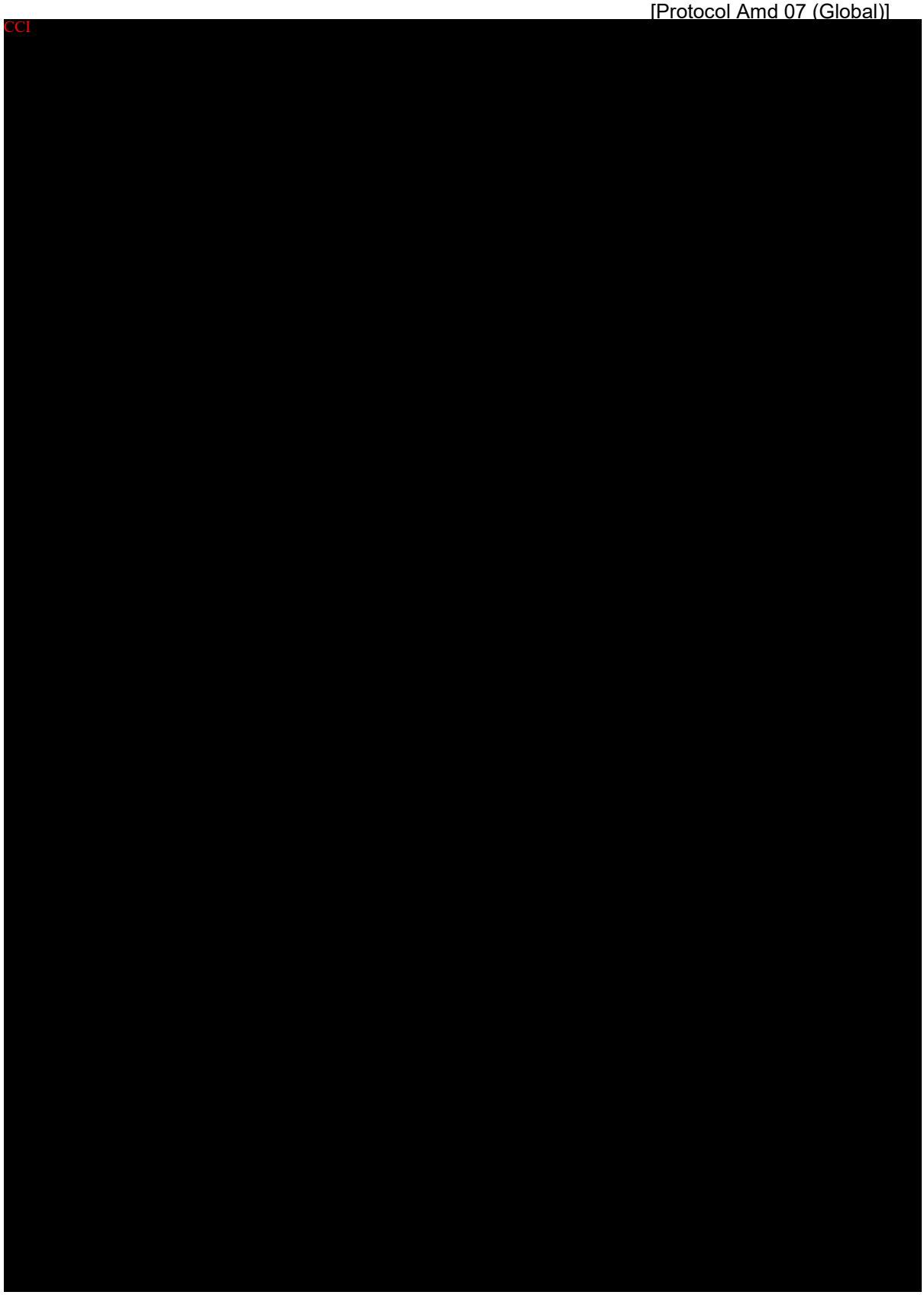

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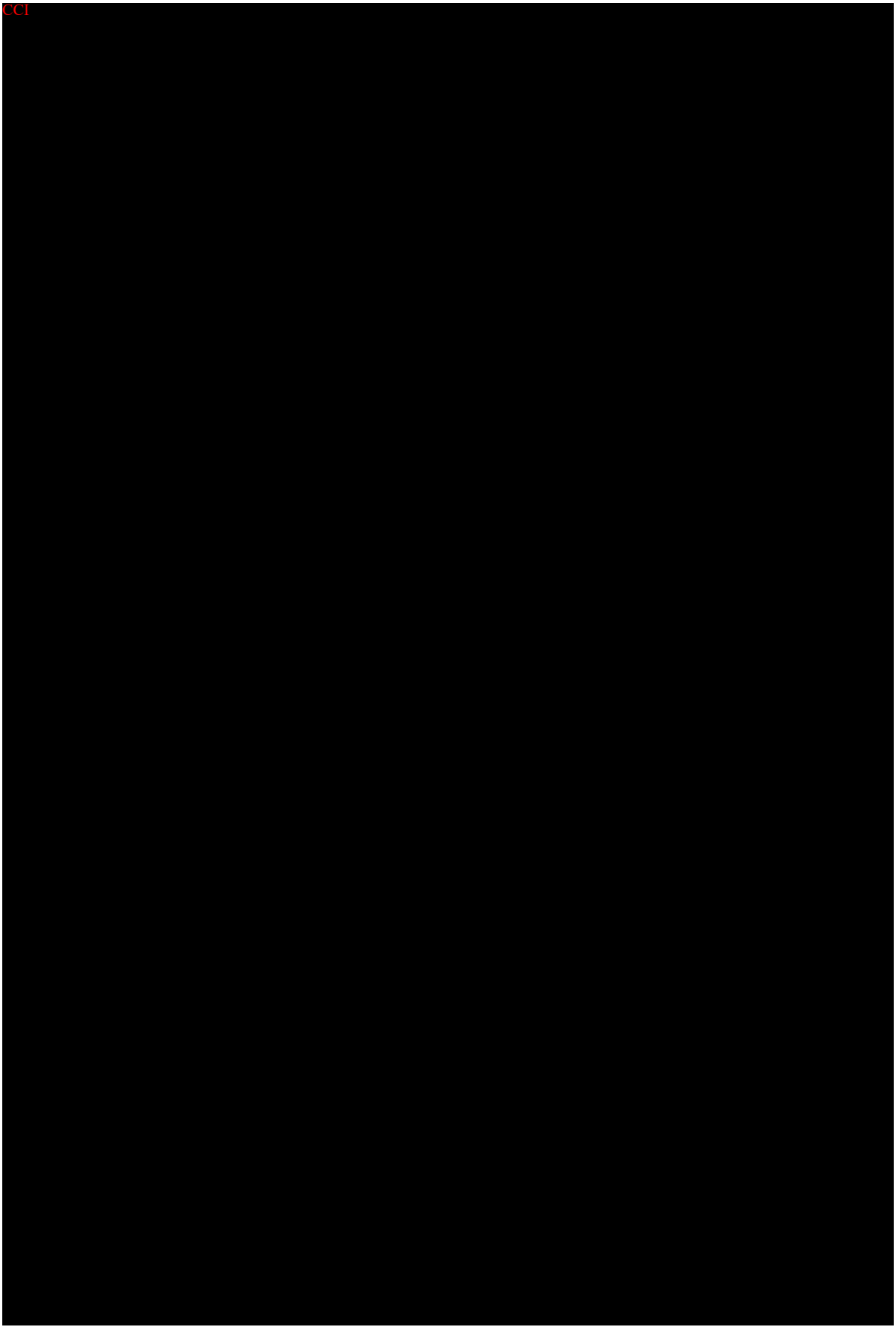

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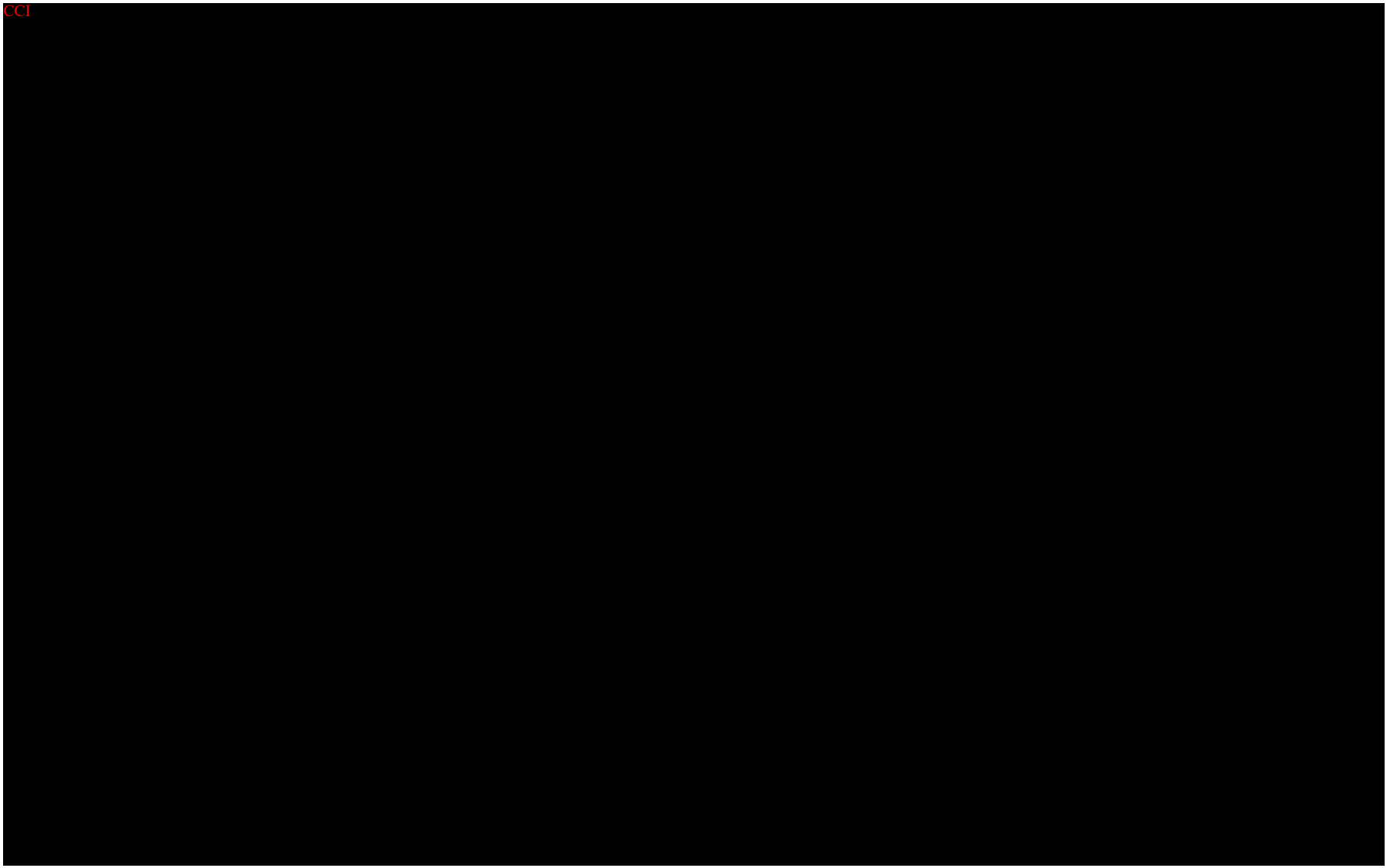

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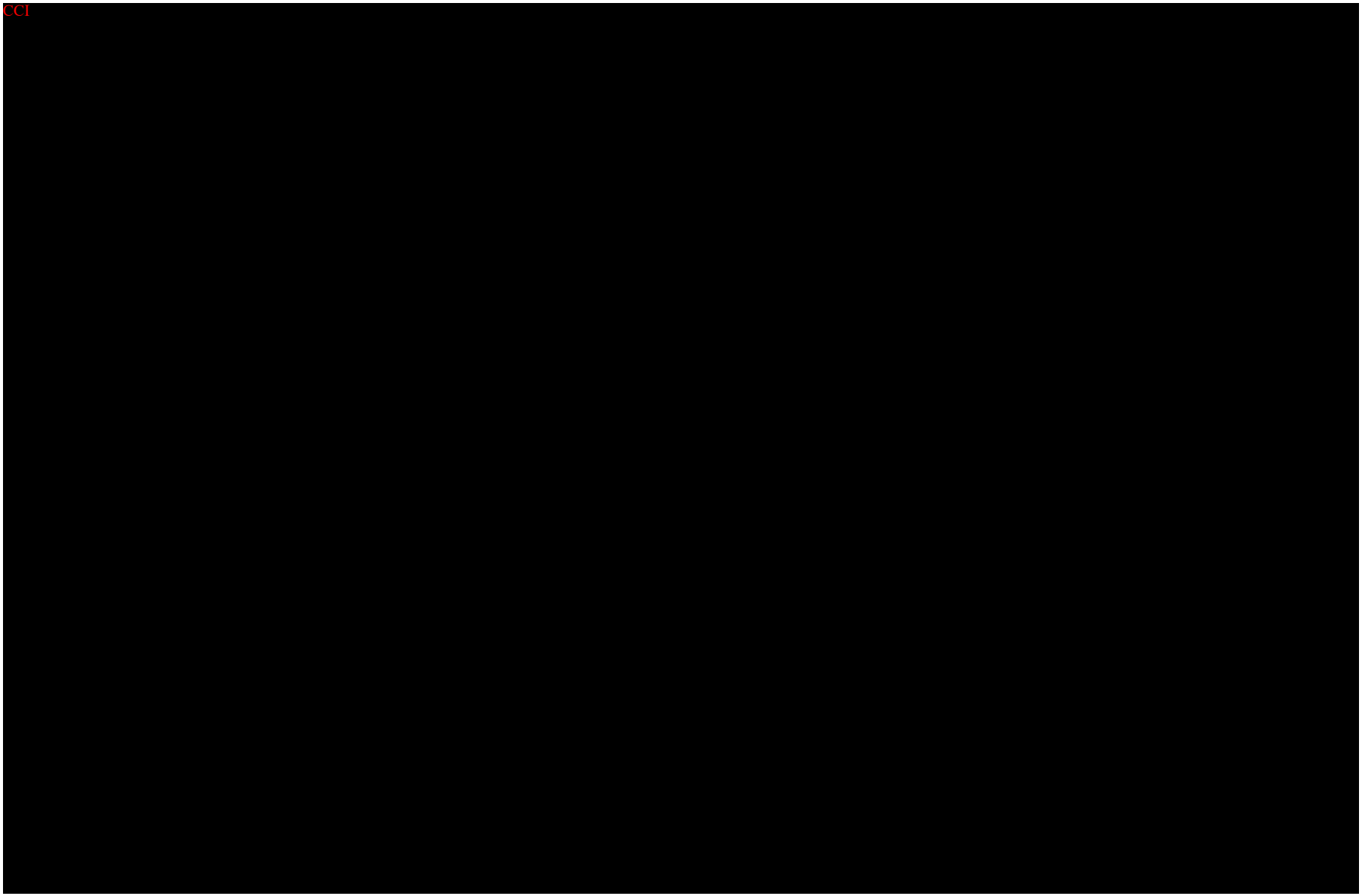

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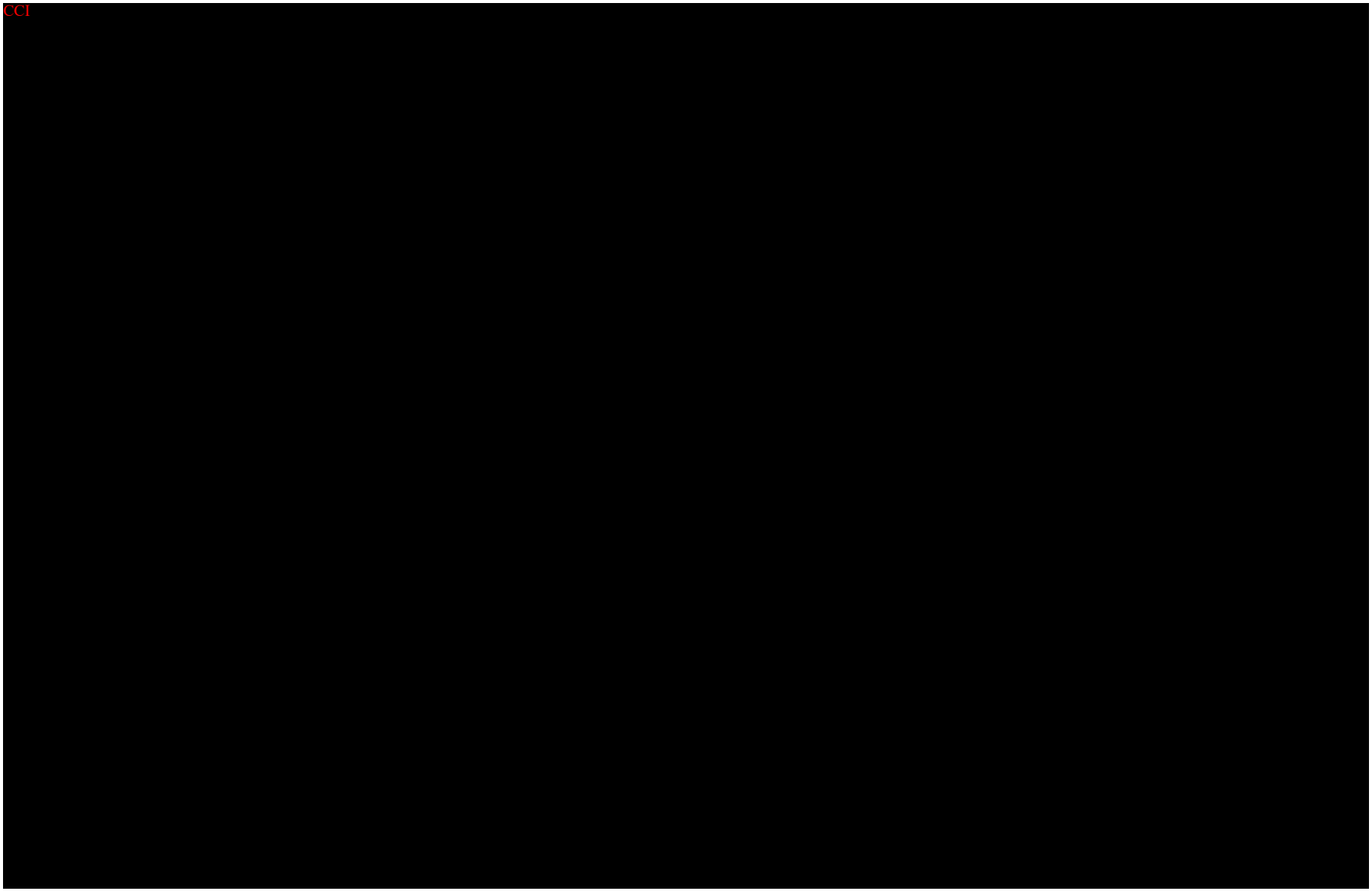

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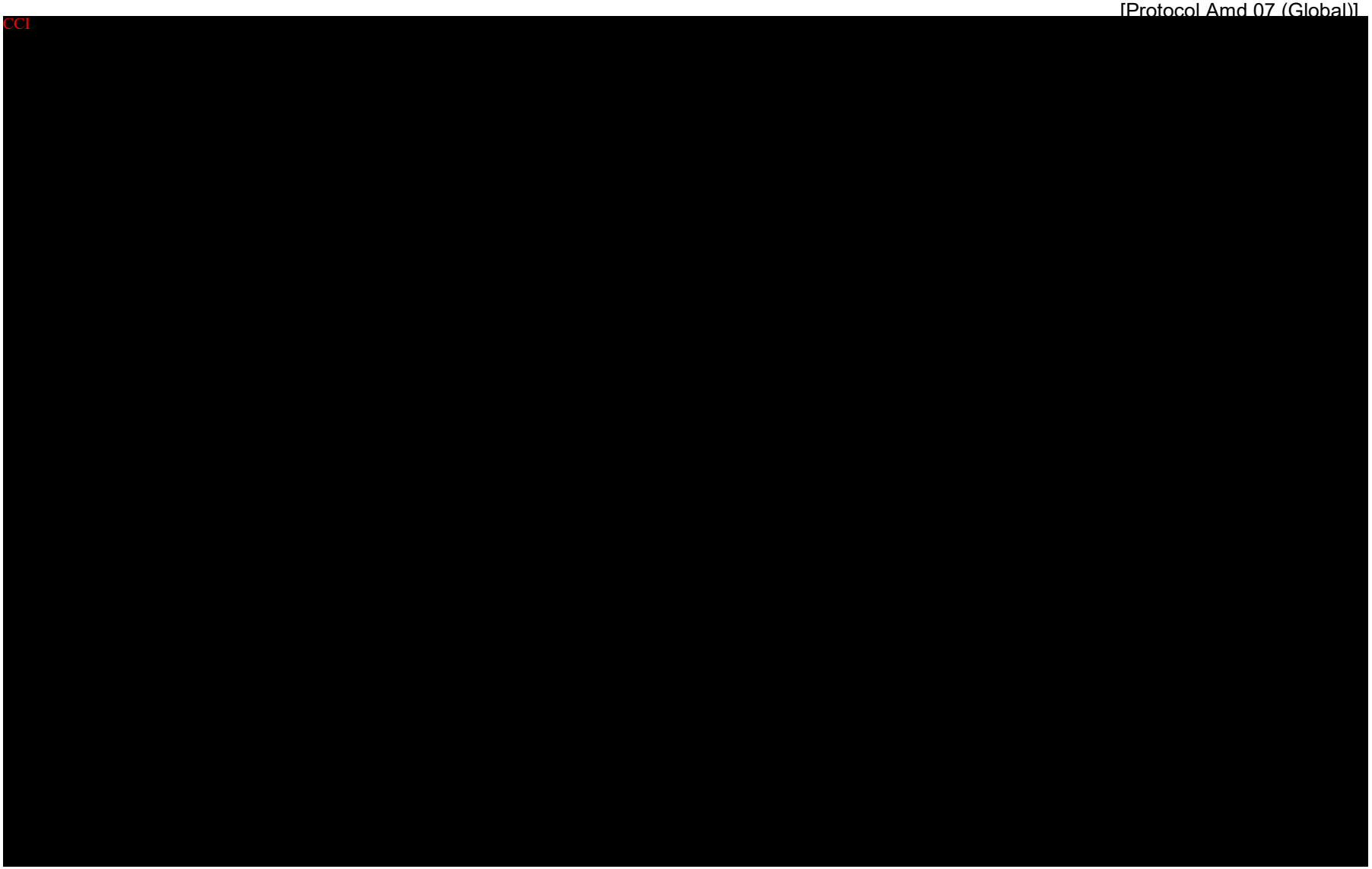

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Timepoint Definitions for assessments:

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g. All assessments performed at Screening must be performed within 28 days prior to first dose unless otherwise specified.
h. Procedures should be performed at all 6 weekly study interventions, unless otherwise specified
i. 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 CCI [redacted].
j. Procedures scheduled on study treatment administration days can be performed within 3 days prior to dosing day, unless otherwise specified.
k. Baseline ALT in Participants with HCC and positive for HBV or positive for HCV should be determined by taking the mean value of the screening ALT and the pre-dose Day 1 ALT.
l. CCI [redacted]

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11.17. Appendix 17: Protocol Amendment History

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

Amendment 1 (12-Dec-2018)

Section # and Name	Description of Change	Brief Rationale
Section 3: Objectives and Endpoints	CCI [redacted]	CCI [redacted]
Section 4.1: Study Design	Added wording that Parts 1B, 2A and 2B will start upon amendment only. Updated study design to remove MSS CRC expansion cohort. Updated dose escalation intervals not to exceed two-fold increments. Cohort size updated to be consistent with Appendix 13	
Section 4.1.2: Dose Limiting Toxicity	Specific criteria for Cytokine Release Syndrome (CRS) and non-hematologic toxicities were updated.	
Section 5.1: Inclusion Criteria	Clarified disease characteristics for advanced/recurrent solid tumors. Expanded population from selected solid tumors to all solid tumors.	
Section 7.1.3: Stopping Rules for Clinical Deterioration	Added considerations for treating participants beyond disease progression.	
Section 9.2.1: Dose Escalation	Updated with revised Bayesian prior and operating characteristics.	
Section 11.14: Appendix 14	Dose levels updated.	

Section # and Name	Description of Change	Brief Rationale
Whole Document	Minor typographical errors and inconsistencies corrected.	

Amendment 2 (27-Aug-2020)

Section # and Name	Description of Change	Brief Rationale
Section 1.1. Synopsis	Text related to pembrolizumab replaced with dostarlimab. A stipulation was added that, based on emerging data, addition of other combination partners or dose expansion cohorts could be added by protocol amendment. Deleted objectives and endpoints associated with dose expansion cohort [redacted] Number of participants were clarified so that approximately 140 participants will be in four dose escalation arms. The reference to cohorts was changed to refer to arms.	[redacted]
Section 1.2. Schema	Schema was updated	

Section # and Name	Description of Change	Brief Rationale
Section 1.3: Schedule of Activities (SoA)	Text related to pembrolizumab replaced with dostarlimab. CCI [redacted] Removed dose expansion cohort (including patient reported outcomes) details. Additional text added to clarify in-house monitoring duration for all visits. Additional text added for 12-lead ECG and Holter Monitoring. CCI [redacted] Updated consideration for follow-up call between 24- and 72-hours following discharge from the clinic/hospital. Safety laboratory assessment text updated to include HBV DNA, HBsAg sample timepoints and HCV antibody, and HCV RNA sample timepoints. Notes updated for Hepatitis B and C screening, pregnancy test, thyroid function, GSK3745417 CCI [redacted],	CCI [redacted]

Section # and Name	Description of Change	Brief Rationale
	CCI [redacted] Schedule for CCI [redacted] Footnote added to clarify that Baseline ALT in participants with HCC and historic/current HBV or historic HCV should be determined by taking the mean value of the screening ALT and the pre-dose Day 1 ALT.	
Section 2.1: Study Rationale	Combination partner changed from pembrolizumab to dostarlimab. Dose escalation Part 1 changed to Part 1A and Part 2 changed to Part 2A. Dose expansion Part 2 changed to Part 2B. Timing was updated for various assessments and time points.	CCI [redacted]
Section 2.2.1: GSK3745417	Combination partner changed from pembrolizumab to dostarlimab. Added wording that Parts 1B and 2B will start upon amendment based on emerging data.	
Section 2.2.2: Clinical Safety of GSK3745417	New Section with GSK3745417 newly emerging clinical safety data	
Section 2.2.3: Dostarlimab	New Section with dostarlimab use as an investigational drug added. Dostarlimab IB cross reference added. Dostarlimab IB edition updated.	

Section # and Name	Description of Change	Brief Rationale
Section 2.3: Benefit/Risk Assessment	Benefits, risks, and reasonably expected AEs of dostarlimab added.	CCI [redacted]
Section 3: Objectives and Endpoints	CCI [redacted] Deleted objectives and endpoints associated with dose expansion cohort CCI [redacted]	CCI [redacted]
Section 4.1: Overall Design	Dose escalation Part 1 changed to Part 1A and Part 2 changed to Part 2A. Two treatment arms changed to 4 treatment arms. CCI [redacted]	

Section # and Name	Description of Change	Brief Rationale
	Updated study design to remove dose expansion cohort and [redacted]. Cohort size updated to be consistent with Appendix 13.	
Section 4.1.1: Dose Escalation	Presentation of dose escalation for [redacted] Dose escalation criteria and dosing schedule updated for all the 4 treatment arms. Pharmacokinetic/[redacted] Footnote added to Table 6. [redacted] Cohorts permitted IRR/CRS prophylaxis added.	[redacted]
Section 4.1.2: Dose Limiting Toxicity	DLT text added for Monotherapy Arm A1 and Arm A2 and for combination therapy Arm A3 and Arm A4. DLT criteria for non-hematologic toxicity added with specifications: DLT criteria updated for any other non-hematologic toxicity: Grade ≥2 uveitis, eye pain, or blurred vision that does not resolve with topical therapy within 2 weeks	

Section # and Name	Description of Change	Brief Rationale
	Grade ≥2 immune-related endocrine toxicity that requires hormone replacement Grade ≥2 colitis or diarrhea that persists without resolution to Grade ≤1 for ≥7 days despite adequate steroid therapy DLT criteria for hematologic toxicity added with specifications.	
Section 4.1.3: Dose Escalation Committee	Text related to dose expansion monitoring deleted.	CCI [redacted]
Section 4.1.4: Tumor Types Enrolled During Parts 1A and 2A	Text related to dose expansion enrolment deleted.	
Section 4.1.5: Participant Re-Treatment	Added considerations for additional arms. Text updated to explain that participants must have completed at least 1 treatment period of GSK3745417 monotherapy without the occurrence of drug-related Grade ≥3 AE or serious adverse events (SAEs) of any severity Grade in the first 21 days of treatment. Clarification added that the GSK medical monitor must be consulted and approve the decision before crossover is permitted.	
Section 4.1.6: Study Duration	Study treatments table updated to include additional treatment arms.	

Section # and Name	Description of Change	Brief Rationale
Section 4.2: Number of Participants	Text related to participants in expansion cohorts, pharmacokinetic/CCI [redacted] Number of participants were clarified so that approximately CCI [redacted]	CCI [redacted]
Section 4.3: Participant and Study Completion	CCI [redacted]	
Section 4.4: Scientific Rationale for Study Design	Text added for dostarlimab. Expansion cohort deleted.	
Section 4.5.2: Justification of starting dose	Presentation of dose escalation for CCI [redacted]	
Section 4.5.3: Dostarlimab Dose Rationale	Dostarlimab dose rationale added.	
Section 5.1: Inclusion Criteria	Inclusion criteria added for participants with hepatocellular carcinoma (HCC) and historic/current HBV or historic HCV. One additional on-treatment biopsy criterion removed. Organ function table updated to include activated partial thromboplastin time and participants	

Section # and Name	Description of Change	Brief Rationale
	with HCC and historic/current HBV or historic HCV. Contraceptive method duration for participants receiving dostarlimab added. Urine pregnancy test removed, and duration of serum pregnancy test updated to 72 hours before the first dose of study intervention.	
Section 5.2: Exclusion Criteria	Exclusion criteria added for participants with hepatocellular carcinoma (HCC) and historic/current HBV or historic HCV. Prior treatment with checkpoint inhibitor PD-L2 added. Transfusion of blood products within 3 weeks per dostarlimab added. Exclusions only for Part 2A added to include known hypersensitivity to dostarlimab or associated excipients.	CCI [redacted]
Section 6.1: Study Intervention(s) Administered	Text updated to include Arm A1, Arm A2, Arm A3, and Arm A4. Added combination therapy monitoring. Dostarlimab dosing administration schedule added. Investigational product dosage/administration table updated.	
Section 6.3 Measures to Minimize Bias: Randomization and Blinding	Added allocation description per treatment arm.	

Section # and Name	Description of Change	Brief Rationale
Section 6.5.1: Permitted Medications and Non-Drug Therapies	Text updated to add prophylaxis of cytokine-related symptoms. Text updated to add non-mandatory prophylactic treatment of thrombosis.	CCI [redacted]
Section 6.5.2: Prohibited Medications and Non-Drug Therapies	Added considerations for additional prohibited medications.	
Section 6.6: Dose Modification	Added considerations for dose reduction. Dose modification and toxicity management guidelines for immune-related AEs table updated. Text added for adrenal insufficiency, uveitis, immune-related encephalitis, rash, renal failure or nephritis, and recurrence of AEs after resolution to ≤Grade 1. Line item added for Infusion-related reaction guidance and cross-referenced with Table 15. Biomarker panel table updated.	
Section 6.7: Dose Delay	Clarification added that during all the dosing schedules, subsequent doses should be administered at least 5 days apart. Conditions added for dosing delays or omissions.	
Section 7.1: Discontinuation of Study Intervention	Clarification added that participants discontinuing from GSK3745417 monotherapy will be allowed to	

Section # and Name	Description of Change	Brief Rationale
	crossover to GSK3745417 plus dostarlimab combination.	
Section 7.1.1: Liver Chemistry Stopping Criteria	Consideration added for participants with HCC and historic/current HBV.	CCI [redacted]
Section 8.1: Efficacy Assessments	Explanation added that in case if a fresh tumor tissue biopsy cannot be obtained, the reason for missed biopsy must be documented in the medical record.	
Section 8.2.3: Electrocardiograms	Explanation added that if QTc interval is prolonged during the study, triplicate ECG measurements will be performed.	
Section 8.2.5: Telemetry	Telemetry is only required for CCI [redacted] monotherapy arm.	
Section 8.2.6 Neurological Assessments	Text updated to add neurological examinations if clinically significant.	
Section 8.2.7: Follow-Up Phone Call	Updated consideration for follow-up call between 24- and 72-hours following discharge from the clinic/hospital.	
Section 8.4: Treatment of Overdose	Definition of dostarlimab overdose added.	

Section # and Name	**Description of Change**	**Brief Rationale**
Section 8.5. Pharmacokinetics	Added text associated with analysis of plasma samples.	CCI [redacted]
Section 8.6: Anti-Drug Antibodies	Consideration added for possession and processing of collected immunogenicity blood samples.	
Section 8.7.2: Tumor Tissue	Consideration added for biopsy schedule.	
Section 9: Statistical Considerations	Section revision due to addition of two arms and updated sample size.	
Section 9.2.1: Dose Escalation (Part 1A)	Updated with revised Bayesian prior and operating characteristics.	
Section 9.2.1: Dose Escalation	Text updated with simulation results under various scenarios.	
Section 9.2.2: Dose Escalation (Part 2A)	Added dose escalation plan in the combination arms. Deleted dose expansion plan.	
Section 9.4.1 Efficacy Analyses	Added description of exploratory efficacy endpoints. Deleted description of PFS, OS and TTR as exploratory efficacy endpoints.	
Section 11.2: Appendix 2: Clinical Laboratory Tests	Text updated for pregnancy testing and participants with HCC.	
Section 11.12: Appendix 12: Management Guidelines for CRS	Appendix revised according to the updated Cytokine Release Syndrome (CRS) management guidelines (Lee, 2019).	

Section # and Name	Description of Change	Brief Rationale
Section 11.13: Appendix 13: IRR/CRS Prophylaxis Regimen	Appendix includes list of premedications and regimen.	CCI [redacted]
Section 11.14: Appendix 14 Statistical Simulation Dose Levels	Dose levels and number of participants per dose cohort updated.	
Whole Document	Combination partner changed from pembrolizumab to dostarlimab. Pembrolizumab information deleted. Additional treatment arms added. Processes during dose expansion cohort deleted. Patient reported outcomes deleted. Minor typographical errors and inconsistencies corrected.	

Amendment 3 (16-OCT-2020)

Section # and Name	Description of Change	Brief Rationale
Section 1.3: Schedule of Activities (SoA)	Schedule for coagulation testing added to Table 1 and Table 2. Clarification of coagulation testing timepoints added in Table 3 and Table 4. Timepoint definition in footnotes – typos corrected (Table 1, Table 2, Table 3, Table 4).	CCI [redacted]
Section 4.1.1: Dose Escalation	Upper limit of target toxicity range changed from 35% to 33%	

Section # and Name	Description of Change	Brief Rationale
Section 4.4: Scientific Rationale for Study Design	Upper limit of target toxicity range changed from 35% to 33%	CCI [redacted]
Section 5.1: Inclusion Criteria	Addition of minimal age of study inclusion in South Korea as ≥ 19 years. Simplification of Table 11 with respect to PT/INR and PTT measurements. Addition of APTT.	
Section 5.2: Exclusion Criteria	Removed of option to enrol participants treated in CCI [redacted].	
Section 6.1: Study Intervention(s) Administered	Table 12. Dostarlimab dosage form: Supplied only as solution for infusion.	
Section 7.1.3. Stopping Rules for Clinical Deterioration	CCI [redacted]	
Section 9.2.1: Dose Escalation (Part 1A)	CCI [redacted]	
Section 9.2.2: Dose Escalation (Part 2A)		
Section 11.2: Appendix 2: Clinical Laboratory Tests	LFT at local lab for HCC subjects. PTT and PT/INR conducted at local lab.	

Amendment 4 (21-APR-2021)

Section Number	Description of Change	Brief Rationale
1.3.Synopsis Objectives Section 3. Objectives	CCI [redacted]	[redacted]
Synopsis	• Added clarification that the objectives presented are applicable to Part 1A/2A only	CCI [redacted]
1.3. SoA – Tables 1-5 Safety assessments 8.2.3 Electrocardiogram	• 12-Lead ECG at Screening to be taken in triplicate	
1.3. SoA – Tables 1-5 Safety assessments	• BNP or NTproBNP measurement added to Safety assessments at Baseline	
1.3 SoA – Tables 1-5 Safety assessments	• Periodic echocardiograms performed whist on treatment	
1.3. SoA – Tables 1-5 Safety assessments	• Troponin assessments modified for frequent monitoring.	
1.3. SoA – Tables 1-5 Safety assessments	• Additional clinical chemistry, CBC with differential and coagulation samples to be	

Section Number	Description of Change	Brief Rationale
	collected in the event of a CRS	
1.3. SoA – Tables 1-5 Efficacy assessments	CCI [redacted]	CCI [redacted]
1.3. SoA – Table 1-5 PK and Biomarkers	• Sample collection schedules modified with additional collections	
1.3. SoA – Table 1-5 Safety assessments	• Neurological assessment modified to include ICE monitoring	
1.2 Table 1 8.5 Pharmacokinetics	• Urine collection schedule added for GSK3745417 metabolite measurement	
1.3 SoA – Table 1	• Telemetry	
1.3 SoA – Table 3-5 Safety Assessments	• 24-hr In-house monitoring schedule modified	
1.3 SoA – Table 3-5 Safety Assessments 8.2.4 Holter monitoring	• Holter monitoring deleted	
1.3.New SoA table, Table 5. 4.1 Overall Design	• New SoA table for subjects from Part 1A that cross to combination treatment	
1.3 SoA – Tables 3-5, Section 4.1.1 Table 7	• CCI [redacted] monotherapy removed. Dosing starts with combination. Timing of	

Section Number	Description of Change	Brief Rationale
	many assessments have been amended accordingly	CCI [redacted]
CCI [redacted]		
1.3 SoA – Table 3	• Dosing day allowable window is ± 1 day	
2.3.1 Risk Assessment	• Cardiac effects updated based on event of perimyocarditis	
Section 4.1.2 Table 8	• Additional term of 'hematologic events' added to the existing DLT criteria for anemia, neutropenia and thrombocytopenia.	
Section 4.1.5. Participant retreatment	• Clarification re. allowing Part1A participants to crossover to combination added.	
Section 5.2 Excl Criteria	• Expanded neurological exclusion criteria to any CNS metastases (symptomatic or asymptomatic) located in the brainstem.	
Section 5.2 Excl Criteria	• Prior treatment with STING agonist criteria modified	
Section 5.2 Excl Criteria	• Participants with signs/symptoms suggestive of COVID-19 within 14	

Section Number	Description of Change	Brief Rationale
	days of study entry, or with known exposure to COVID-19 within 14 days prior to study entry	CCI [redacted]
1.3 SoA Tables 3-5, Section 6.1 Study intervention administered	• Monitoring time before combination therapy administration shortened to 30 mins (from 2 hours) • Clarification of monitoring time after dostarlimab therapy to at least 2 hours	
6.5.1 Permitted Medications and Non-Drug Therapies	• Addition of language to allow subjects in non-prophylaxis cohorts to be receive prophylaxis with steroid post DLT period for repeated Grade 2 and above CRS	
6.6. Dose Modification Table 15	• Language related to dose modification and toxicity management modified	
6.6.1 CRS Section and Table 16	• Language related to CRS management clarified. A new Table has been added for monitoring guidelines for CRS management	
6.6.1.1 Cardiac monitoring	• A new Section 6.6.1.1 Cardiac monitoring and dose modification guidelines added	
6.6.1.2 Neurological monitoring	• A new Section 6.6.1.2 Neurological Adverse Events On Study added	
6.6.1.3 Grading Immune Effector Cell-Associated	• A new Section 6.6.1.3 for grading ICANS added	

Section Number	Description of Change	Brief Rationale
Neurotoxicity Syndrome (ICANS)		
6.6.1.4. Monitoring ICANS	• A new Section 6.6.1.4 for monitoring ICANS added	CCI [redacted]
6.6.1.5. Management of ICANS	• A new Section 6.6.1.5 for managing ICANS added	
8.1.2. Tumor Growth Kinetics	• A new Section 8.1.2 added for tumor growth kinetics	
9.4.3.2. Immunogenicity Analyses	• A new Section 9.4.3.2 added for immunogenicity analyses	
11.9.4 iRECIST Guidelines	• Figure 11 updated	

Amendment 5/NET-1: 19-JUL-2021

Overall Rationale for the Amendment:

CCI [redacted]

Section Number and Name	Description of Change	Brief Rationale
	• Table 3: removed pregnancy test on Day 8 • Table 3: Changed vital signs from Week 8, 11, and 14, to Week 7, 10, and 13 • Table 1: Added sample for C-reactive protein at EOI+4 h • Table 5: CBC with Differential added: "If a participant experiences cytokine release syndrome, perform CBC with differential at EOI+8h too"	CCI [redacted]
4.1 Overall Design and Synopsis	Added definition of "enrolled"	
5.4 Screen Failure	Modified wording to define screen failre to exactly match boilerplate	
8.8 Genetics	Add boilerplate text on genetic samples	
9.1. Statistical Hypotheses	CCI [redacted]	
11.1.3 Informed Consent Process	Added "Including the risk and benefits"	Required per GSK template updates
11.3.5 Reporting to GSK via Electronic Data Collection Tool	Removed paragraph that starts "The investigator or…"	Required per GSK template V16
11.15. Appendix 15: Imaging Sub-study	This appendix describes the objectives, and all procedures specific to the Imaging Sub-study that will be conducted in Netherlands only	All procedures for the conduct of the Imaging Sub-study are described.
11.16 Appendix 16: Radiation Dose	New Appendix that describes how to estimate radiation dose	Appendix needed to support Imaging Sub-study

Amendment 6: 19-JAN-2022

CCI [redacted]

CCI [redacted]

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

A table of key changes from Protocol Amendment 4 to Amendment 6 is shown below:

Section Number and Name	Description of Change	Brief Rationale
1.1 Synopsis	• Additional text added to Overall Design referring to the inclusion of a CCI [redacted]	CCI [redacted]
1.2. Schedule of Activities (SoA)	• CCI [redacted] activities are described in Appendix 15	
	• Table 1- Table 5: 24 Hour In-House Monitoring: Added "Participants may be released after a 6-hour observation period… PK and CCI [redacted]	
	• Table 1- Table 5, AE/SAE Review revised • CCI [redacted]	
	• CCI [redacted]	
	• Table 1- Table 5: Added "predose" to urine pregnancy test and ≤72 h serum prior to first dose	
	• Table 1: Added sample for C-reactive protein at CCI [redacted]	

Section Number and Name	Description of Change	Brief Rationale
	• Table 1- Table 5: change CCI [redacted]	CCI [redacted]
	• Table 1 - Table 5, Table 29 – added timeframe for CCI [redacted]	
	• Table 1- Table 2: First on-treatment fresh CCI [redacted]	
	• Table 1 – Table 5: CCI [redacted]	
	• Table 1 – 5: additional timepoints CCI [redacted]	
	• Table 1 -3, 5: added changes CCI [redacted]	
	• Table 1- 2: changes added to GSK3745417 plasma PK timepoints collection	
	• CCI [redacted]	
	• Table 1- Table 5: revised definition of CCI [redacted]	
	• Table 3: 12-lead ECG changed from CCI [redacted] after the CCI [redacted]	
	• Table 1- Table 5, added clarifications for CCI [redacted]	

Section Number and Name	Description of Change	Brief Rationale
	• Table 3: CCI [redacted]	CCI [redacted]
	• Table 3: removed pregnancy test on Day 8	
	• Table 3: Changed vital signs from CCI [redacted]	
	• Table 2 and 4: additional text added to the timepoints for liver function test (LFT)	
	• CCI [redacted]	
2. Introduction	Updated Study Rationale, Background	
2.3.1 Risk Assessment	Updated table of rationale for risks and mitigation strategies	
2.3.2 Overall Benefit:Risk Conclusion	Removed first two paragraphs	
3 Objectives and Endpoints	Added footnote about CCI [redacted]	
4.1 Overall design	Added additional text for CCI [redacted]	
4.1.1. Dose Escalation and Synopsis	Added Dose escalation for GSK3745417 monotherapy in CCI [redacted]	
	Reduced time between first 3 participants to 48 hours (was 72)	
	Descriptions added to Dose Schedule and new section under subhead: CCI [redacted]	

Section Number and Name	Description of Change	Brief Rationale
4.1.3 Dose Escalation Committee	Added item 6: defining the role of DEC in deciding dose escalation	CCI [redacted]
4.1.5. Participant Re-treatment	Removed requirement for new participant number	
4.2. Number of participants	Added numbers of participants for CCI [redacted]	
4.4. Scientific Rationale for Study Design	Added "CCI [redacted]	
4.5.2. Dostarlimab Dose Rationale	Added clarification for CCI [redacted]	
5.1 Inclusion Criteria	Added Inclusion Criterion #10: "CCI [redacted] Update Table 12 eGFR cut-off	
5.2 Exclusion Criteria	Revised exclusion 12 to include #13 Revised Exclusion 28 (was 29): Known hypersensitivity to any of the study interventions or any of their exipients	
6.1. Study Intervention(s) Administered	Additional text added for observation period to allow less than 8 hours monitoring Table 13 updated	
6.3 Measures to minimize bias: Randomization and Blinding	Deleted: "The first dose level of Arm A4 will open only after that dose level of CCI [redacted] Reduced time between first 3 participants to 48 hours (was 72)	
6.5.1. Permitted medications and Non-Drug Therapies	Added additional text to the second paragraph "Growth Factors and Bisphosphonates"	
6.6. Dose Modification	Updated language	

Section Number and Name	Description of Change	Brief Rationale
	Table 14 for guidelines for immune-related AEs updated	CCI [redacted]
6.6.1 Management of Infusion Reactions or Severe Cytokine Release Syndrome	Table16 removed “and pressors” Added “If patient experiences symptoms consistent with pericarditis or myocarditis”	
6.6.1.4 Monitoring for Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)	Removed:” Brain MRI (or CT Scan if MRI not feasible) should be obtained for all participants at the time of Screening.	
6.7. Dose Delay	Removed Paragraph 6: “If a dose is missed, participant should perform all assessments indicated for the missed dose after 6th dose”	
7.1.1 Liver Chemistry Stopping Criteria 7.1.1.1 Study Intervention Restart or Rechallenge after Liver Stopping Criteria Met	Added “• In the presence of abnormal liver chemistry not meeting protocol specified stopping rules, if the Investigator believes that it is in the best interest of the participant.” Added “Note: If study treatment was interrupted for suspected drug-induced liver injury, the participant should be informed of the risk of death, liver transplantation, hospitalization, and jaundice and re-consented before resumption of dosing.”	
8.1 CCI [redacted]	Added Paragraph 2	
8.2.2 Vital Signs	Added pulse oximetry for oxygen saturation”	
8.2.5. Telemetry	Removed telemetry for the Part 1A, CCI [redacted] monotherapy	
CCI [redacted]		
8.3.1 Time Period and Frequency for Collecting AE and SAE Information	Revised Paragraph 2: “AEs at each visit….Until start of subsequent anticancer treatment (Section 1.3).”	

Section Number and Name	Description of Change	Brief Rationale
CCI [redacted]		
9.3 Populations for Analysis	Added DLT Evaluable (Part 1A and 2A) and CCI [redacted] populations	CCI [redacted]
CCI [redacted]		CCI [redacted]
9.5 Interim Analysis	Deleted "The Reporting and Analysis Plan will describe the planned interim analyses and subgroups in greater detail. …Any additional decision rules will be documented in RAP before the interim analysis."	
11.1.1 Regulatory and Ethical Consideration	Added next to last bullet:" • Notify significant/major protocol deviations to the EC/IRB, as well as findings of internal Quality Audits and CAPA's."	
11.1.3 Informed Consent Process	Added "Including the risk and benefits" Added in Paragraph 2: "and that they can withdraw their consent to participate for any reason or no reason at all. Participants or their legally authorized representative must be informed that they are free to take the Informed Consent home to discuss participation	

Section Number and Name	Description of Change	Brief Rationale
	with members of their family or personal medical physician." Added in Paragraph 3: "and which persons were present when the study was explained to the potential participant or their legally authorized representative."	
11.2 Appendix 2: Clinical Laboratory Tests	Revised first paragraph language Table 25:Added HBe antigen and Tryptase, and revised hepatitis test language	CCI [redacted]
11.3.5 Reporting of SAE to GSK	Removed paragraph that starts "The investigator or…"	
11.7 CKD-EPI Formula	Revised Title to Estimated Glomerular Filtration Rate Added factor for participants in Japan	
CCI [redacted]	This appendix describes the objectives, and all procedures specific to the CCI [redacted]	
11.16 Appendix 16: Radiation Dose	New Appendix that CCI [redacted]	

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Reason for signing: Approved	Name: PPD Role: Approver Date of signature: 04-Aug-2023 13:42:07 GMT+0000

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11.18. FRENCH-SPECIFIC REQUIREMENTS

This appendix includes all applicable requirements of French Public Health Code / specific local GSK requirements and identifies, item per item, the mandatory modifications or additional information to the study protocol.

1. Concerning the « SELECTION OF STUDY POPULATION AND WITHDRAWAL CRITERIA»

The following vulnerable subject populations will be excluded: minors, protected subjects, adult subjects not in condition to express their consent, subjects deprived of liberty, subjects receiving psychiatric cares, subjects hospitalized in a Health and Social Establishment for other purpose than the participation to the study.

A subject will be eligible for inclusion in this study if he /she is either affiliated to or beneficiary of a social security category (French Public Health Code Law L.1121-8-1). (Exception for a participant to a non-interventional study or to a participant to an interventional study if authorised by the Ethics Committee).
It is the investigator's responsibility to ensure and to document (in the source document - subject notes) that the subject:

- is either affiliated to or beneficiary of a social security category.
- has got an authorisation by the Ethics Committee.

2. Concerning the "STUDY GOVERNANCE CONSIDERATIONS"

- **In section "Regulatory and Ethical Considerations, including the Informed Consent Process" of study protocol**

  ⇒ Concerning **the process for informing the subject** and/or his/her legally authorized representative, the following text is added:

  French Patient Informed Consent is a document which summarizes the main features of the study and allows collection of the subject and/or his/her legally authorized representative written consent. It also contains a reference to the authorisation of ANSM and the approval from the French Ethics Committee.

  ⇒ **Concerning the management of the Patient Informed Consent Forms**, the following text is added:

  French Patient Informed Consent Form is in duplicate (triplicate for minor subject).

  The first page of the Patient Informed Consent Form is given to the investigator. The copy is kept by the patient or legally authorized representative.

- **NOTIFICATION TO THE HOSPITAL DIRECTOR**

  In accordance with Article L1123-13 of the French Public Health Code, the Hospital Director is informed of the commitment to the trial in her/his establishment. The Hospital Director is supplied with the protocol and any information needed for the financial disposition, the name of the investigator(s), the number of sites involved in his establishment and the estimated time schedule of the trial (R.1123-69).

- **INFORMATION TO THE HOSPITAL PHARMACIST**

  In accordance with Article R.1123-70 of the French Public Health Code, the Hospital Pharmacist is informed of the commitment to the trial in her/his establishment. The Pharmacist is supplied with a copy of the protocol (which allows her/him to dispense the drug(s) of the trial according to the trial methodology), all information concerning the product(s) of the trial (e.g. included in the IB), the name of the investigator(s), the number of sites involved in her/his establishment and the estimated time schedule of the trial.

- **Ethnic Origin**

  In accordance with the data privacy regulation, the ethnic origin, as any personal data, can only be collected if the collection of this data is strictly necessary and relevant for the purpose of the study.

- **TESTING OF BIOLOGICAL SAMPLES**

  In accordance with the French Public Health Code Law – article L1211-2, a biological sample without identified purpose at the time of the sample and subject's preliminary information is not authorized.

3. Concerning the "DATA MANAGEMENT" the following text is added:

Within the framework of this clinical trial, data regarding the identity of the investigators and/or co-investigators and/or the pharmacists if applicable, involved in this clinical trial, and data regarding the subjects recruited in this clinical trial (subject number, treatment number, subjects status with respect to the clinical trial, dates of visit, medical data) will be collected and computerized in GSK data bases by GSK or on its behalf, for reasons of follow up, clinical trial management and using the results of said clinical trial. According to the data privacy regulation, each of these people aforesaid has a right of access, correction and opposition on their own data through GSK (Clinical Operations Department).

4. Concerning Data Privacy

In accordance with the applicable data privacy regulation, personal data are processed in a manner that ensures appropriate security, including protection against unauthorized or unlawful processing and against accidental loss, destruction or damage, using appropriate technical or organizational measures. The processing is whether deemed to be compliant with one of the methodologies of reference **(MR-001)** or has been the subject of a request for authorization to the CNIL. The Investigator has, regarding the processing data related to her/him, a right of access, of rectification, erasure and of opposition with GSK in accordance with the legal provisions.

5. Investigational Product Accountability, Reconciliation, and Destruction

In specific situations where institutional practices dictate that the site disposes of and/or destroys IP prior to allowing the "monitor' to verify and document IP accountability, the following applies:
*"During the conduct of the Study, Investigational Product (IP) will be destroyed by the Institution prior to a GSK "**monitor**" conducting final investigational product accountability. Institution agrees that such destruction will comply with Institution's investigational product accountability procedures and will provide GSK with investigational product accountability logs and supporting documentation to verify adherence to 'Bonnes Pratiques Cliniques' (decision dated on the 24th of November 2006).*