TITLE PAGE

Protocol Title: A phase I, open-label, dose-escalation study to investigate the safety, pharmacokinetics, pharmacodynamics and clinical activity of GSK3368715 in participants with solid tumors and DLBCL

Protocol Number: 207675/ 03

Short Title: FTIH study of GSK3368715 in participants with solid tumors and DLBCL

Development Phase: Phase I

Compound Number: GSK3368715

Sponsor Name and Legal Registered Address:

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PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 03	05-Dec-2019
Amendment 02	22-Feb-2019
Amendment 01	12-Jul-2018
Original Protocol	02-May-2018

Amendment 03: 05-DEC-2019

This amendment applies to all sites participating in the conduct of the study.

Overall Rationale for the Amendment:

Protocol Amendment 3 includes the following:

- Updated clinical safety guidelines, clinical pharmacology, and the risks/mitigation strategy following the temporary pause in enrolment due to venous thromboembolic events (VTE) that have been observed in the dose escalation phase of the study. Also, the risk of biopsy collection has been added to the benefit/risk assessment table.

- Changes to exclusion criteria to exclude participants who have 3 or greater Khorana score, and exclude participants who have prior history of VTE.

- Addition to allowed anti-coagulation therapy - the use of oral anticoagulation using Factor Xa inhibitors such as Apixaban and Rivaroxaban is allowed on trial. Anticoagulation with oral Vitamin K antagonists such as Warfarin is not allowed.

- Addition of exploratory coagulation markers and minor changes to other exploratory biomarkers being collected in the dose escalation phase of the study (Part 1).

- Changes and clarifications made in the Schedule of Activities Tables; clarification of time windows for PK and PD samples, changes to some of the PK and PD sampling time points in the dose escalation and PK/PD cohorts in Part 1 and telemetry only required for doses of > 200mg.

- Changes to DLT and stopping/exclusion criteria for QRS and VTEs, and update to the telemetry assessment.

- Addition of food effect cohort into Part 1.

- Addition of tablet formulation.

- Further clarifications added to the sample size determination section.

- Addition of albumin in the clinical labs table (Table 9, Appendix 2).
- Addition of guidelines of management of toxicity for VTEs in Appendix 12
- Addition of Appendix 13 (Khorana score)
- Administrative changes made throughout the document.

Section # and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis	Addition of PK/PD cohort and food effect into the overall design, also PK in fed and fasted state added to the objectives/endpoints. VTE DLT criteria mentioned in the "Intervention groups and duration" section.	To add text to make it clear that the PK/PD and food effect cohorts are included in Part 1 of the study. A brief statement has been added to this section around the new DLT criteria for any venous thrombo-embolic events.
Section 1.2 schema	New schema added.	To add clarity around the dose escalation, food effect and PK/PD cohort(s) in Part 1, and the planned transition of capsules to tablets in the food effect cohort and in Part 2 of the study.
Schedule of Activities tables, Section 1.3	Updates to Table 1 to Table 3. Changes in some of the PK and PD sampling collection times, clarification on time windows for certain PK and PD samples, addition of exploratory coagulation markers, up to 48 hour urine collections added to the PK/PD cohort, tumor imaging must include chest CT at screening and at all timepoints as stated in the Schedule of Activities tables	To add clarity. PK and PD sampling time points have been adjusted to ensure that the maximum blood volume is not exceeded for any participant enrolled onto the study. Tumor imaging – Chest CT scan added to further assess the participant, due to the incidence of embolic and thrombotic events observed to date in the dose escalation phase of the study.
Schedule of Activities tables, Section 1.3	Table 4 added – food effect cohort added to Part 1	To determine the effect of a high-fat, high-calorie meal on the bioavailability of GSK3368715 at or near the RP2D
Section 2.2.1.4 Clinical safety of GSK3368715	Detail added on the VTE events that have occurred on the study. This led to a temporary pause in enrolment in the dose escalation phase of the study.	To explain the rationale for the temporary pause in enrolment. This section now includes additional guidelines for management of any VTEs and to ensure participant safety going forward as enrolment will re-commence.

Section # and Name	Description of Change	Brief Rationale
Section 2.2.1.5 Clinical Pharmacology of GSK3368715	Updated information on the pharmacokinetics of the compound.	To add the latest information on the pharmacokinetics of the compound.
Section 2.3.1 Risk assessment	Addition of the VTE risk and the mitigation strategy around this risk. Addition of risk of biopsy collections.	To add details on the VTE risk, and the procedures that are being put in place in this current amendment to mitigate that risk. To add details on the risk of biopsy collections and the mitigation strategies for this risk.
Section 2.3.2 Benefit assessment and Section 2.3.3 Overall Benefit/Risk Conclusion	Addition of a sentence detailing some evidence of stable disease observed to date in the study (in dose escalation).	To provide a brief statement of some evidence of stable disease observed to date in the study (in Part 1, dose escalation).
Section 3, Objectives	To add in another exploratory objective into Part 1- the addition of some coagulation biomarkers.	To collect more data in Part 1 of the study on coagulation biomarkers, to gain more information to help with the safety assessments of any further potential VTEs.
Section 4.1.Overall Design, Section 4.1.1 Part 1 (dose escalation phase)	To add in text around the occurrences of the VTEs and the plans for re-initiation of enrolment.	To update the study design of Part 1 of the study.
Section 4.1.1.1 Food effect cohort	To add in details of the food effect cohort.	To add clarity and update the study design of Part 1 to include a food effect sub-study.
Section 4.1.3 Dose limiting toxicity	To add in details of the VTEs and the plans in place if more VTEs were to occur on re-initiation of the study.	To add clarity.
Section 4.1.4 Dose Escalation committee	Minor additions around VTEs and the DLT criteria.	To add clarity.
Section 4.2 Scientific rationale for study design	Added in details of the food effect study.	To gain more information of the bioavailability of GSK3368715 when administered in the fed and fasted state.

Section # and Name	Description of Change	Brief Rationale
Section 4.3.2	Addition of a new section, Dose Justification for Food Effect Sub cohort	Details of a new food effect cohort added to this protocol amendment.
Section 5.1, Inclusion criterion, number 2	To include patients enrolled in the food effect sub-study.	To add clarity.
Section 5.2, Exclusion criteria	Update to criterion 8 (e) to allow for a QRS interval of <110 ms at screening or baseline Addition of a new exclusion criterion (16) - a participant is considered high-risk for VTE as defined by either Khorana Score of >=3 or prior medical history of VTE	QRS interval value was updated following review of clinical safety data, to broaden eligibility This new exclusion criterion 17 is being added in this current amendment to mitigate the risk of further VTEs occurring in participants, once re-enrolment starts,
Section 5.3.1, Meals and dietary restrictions	Addition of text for the food effect sub-study	To add clarity for the food effect cohort.
Section 6.1, Study Intervention	Addition of tablets	A tablet formulation is in development and will be introduced into the study
Section 6.7 Concomitant therapy Section 6.7.1 Prohibited medications	Update to the allowed anti-coagulation therapy, to include the use of oral anticoagulation using Factor Xa inhibitors such as Apixaban and Rivaroxaban on the trial. Prohibited medications - Anticoagulation with oral Vitamin K antagonists such as Warfarin is not allowed	Due to the risk of venous thromboembolism among cancer patients, additional anti-coagulation therapies (oral anticoagulation using Factor Xa inhibitors such as Apixaban and Rivaroxaban) are being allowed on the trial.
Section 7.1.3, QRS interval stopping criterion	Updated text added (an increase in the QRS interval of > 20 ms from baseline).	Based on evaluation of cardiac clinical safety data from 207675
Section 7.1.4 PR interval stopping criteria	Updated text added (an increase in the PR interval to >250 msec in	Based on evaluation of cardiac clinical safety data from 207675

Section # and Name	Description of Change	Brief Rationale
	participants without pre-existing AV-block).	
Section 8.2.5 Telemetry	Text updated (continuous telemetry initially for at least 24 hours from the start of dose for the first 10 participants at each dose level >200 mg).	Based on evaluation of cardiac clinical safety data from 207675. Telemetry is only required for doses >200mg.
Section 8.6, Pharmacokinetics	Additional text to explain the sampling for the dose escalation, PK/PD cohort and the food effect cohort.	To add clarity.
Section 8.7 Pharmacodynamics	Some minor additions to the exploratory biomarkers being collected.	To allow for additional exploratory biomarkers to be collected.
Section 8.9 Biomarkers and translational research	Removal of Circulating Cell-free DNA/RNA Analysis. Addition of coagulation markers (Section 8.9.5).	Circulating Cell-free DNA/RNA analysis will be removed from this amendment. Exploratory coagulation biomarkers will be collected to gain more information to help with the safety assessments of any further potential VTEs.
Section 9.2 Sample Size Determination	Addition of some further details.	To add clarity.
Section 9.2.1.1 Operating characteristics of the safety stopping rule for VTE events in dose escalation	Addition of a new subsection to add detail on the operating characteristics of the safety stopping rule for VTE events in dose escalation.	To add clarity around the safety stopping rule for VTE events in the dose escalation phase of the study.
Section 9.6.3.2Statistical analysis of pharmacokinetic data	Addition of a new subsection to add detail on the statistical analysis of the PK data obtained from the food effect cohort.	New food effect cohort added, so this text is providing details of the statistical analysis of the PK data that will be obtained in this cohort.
Section 10.2, Appendix 2, Clinical laboratory tests, Table 9	Clinical laboratory tests – addition of albumin in the clinical chemistry panel.	To add clarity. Albumin was omitted from this table in error, in the previous protocol amendment.
Section 10.12,	Inclusion of text around	To add guidance for the investigators

Section # and Name	Description of Change	Brief Rationale
Appendix 12, Guidelines for management of toxicity	VTEs in the Dose Adjustment/Stopping Safety Criteria table	around what to do if any future VTEs occur on the study.
Section 10.13, Appendix 13, Khorana score	New appendix added.	To add clarity for the determination of Khorana scores. Addition of a table showing "Predictive model for chemotherapy-associated VTE".
Section 10.3.5 Reporting of SAE to GSK	New text added for capturing SAEs on paper CRF (as back-up option).	To add details for the possibility of capturing SAEs on a paper CRF (as a back-up option to the preferred electronic data capture in the eCRF).
Section 10.3.6 Definition of AESI	Section deleted.	Deleted text as there are no AEs of special interest stated in this study.

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A phase I, open-label, dose-escalation study to investigate the safety, pharmacokinetics, pharmacodynamics and clinical activity of GSK3368715 in participants with solid tumors and DLBCL

Short Title: First time in human (FTIH) study of GSK3368715 in participants with solid tumors and Diffuse Large B-Cell Lymphoma (DLBCL)

Rationale: Arginine methylation mediated by protein arginine methyltransferases (PRMTs) is an important post-translational modification of proteins involved in a diverse range of cellular processes such as gene regulation, ribonucleic acid (RNA) processing, deoxyribonucleic acid (DNA) damage response, and signal transduction. Type I PRMTs are responsible for asymmetric dimethylation of arginine (ADMA) residues. Mis-regulation and overexpression of PRMT1 (a type I PRMT) has been associated with a number of solid and hematopoietic cancers. In non-clinical models, inhibition of the Type I PRMT family by the small molecule GSK3368715 leads to inhibition of tumor cell growth across tumor types with cytotoxic response observed in lymphoma, acute myeloid leukemia (AML) and a subset of solid tumor cell lines. Pre-clinical data indicate that the anti-proliferative activity of GSK3368715 is enhanced in tumor models in which the enzyme Methylthioadenosine phosphorylase (MTAP) is lost due to a deletion of the chromosome 9p21 locus. These homozygous deletions of chromosome 9p21 are frequent and occur in approximately 15% of all human cancers affecting in addition to MTAP, the critical tumor suppressors p16-INK4A and p19-ARF.

This first-time-in-human (FTIH), open-label, dose-escalation study will assess the safety, pharmacokinetics (PK), pharmacodynamics (PD), and preliminary clinical activity of GSK3368715 in participants with relapsed/refractory Diffuse-large B-cell lymphoma (DLBCL) and selected solid tumors with frequent MTAP-deficiency.

Emerging pre-clinical data support the clinical development of combination regimens of GSK3368715 with novel, active agents such as the small-molecule PRMT5 inhibitor, GSK3326595 and/or with approved oncology therapies.

Objectives and Endpoints:

Objectives	Endpoints
Part 1: Dose Escalation	
Primary	
• Determine RP2D and schedule of GSK3368715 administered orally to participants with advanced stage solid tumors	• Incidence of dose limiting toxicity (DLT) • Incidence and severity of adverse events
Secondary	
• Evaluate the preliminary clinical activity of GSK3368715	• Best overall response
• Characterize the PK of GSK3368715, including PK in the fed and fasted state from the food effect sub-study	• PK parameters (Maximum observed concentration [Cmax], time to reach Cmax [Tmax], Area under the concentration-time curve [AUC], others) • PK parameters (Cmax, Tmax and AUC) in the fed and fasted state from the food effect sub-study
Part 2: Dose Expansion	
Primary	
• Evaluate the preliminary clinical activity of GSK3368715	• Objective response rate (ORR)
Secondary	
• Characterize the safety of GSK3368715 administered at the RP2D and schedule to participants with DLBCL, pancreatic cancer, NSCLC, and bladder cancer	• Incidence and severity of adverse events
• Further evaluate the clinical activity of GSK3368715	• Progression-free survival (PFS)
• Characterize the PK of GSK3368715	• PK parameters (Cmax, Tmax, AUC, others)

Overall Design: The study will consist of two parts. In Part 1 (Dose Escalation) escalating doses of GSK3368715 will be evaluated in participants with selected solid relapsed/refractory tumors. This will include at least one PK/PD cohort, and a food effect cohort. Based on safety and tolerability, and the PK/PD characteristics, a Recommended Phase 2 Dose(s) (RP2D) and schedule(s) of GSK3368715 will be established. In Part 2, this RP2D(s) will be further investigated in two expansion cohorts. Enrolment in the expansion cohorts will be limited to participants with DLBCL (Expansion Cohort 2A) and relapsed/refractory solid tumors (Expansion Cohort 2B) where MTAP deletion occurs at a frequency of approximately ≥25% (pancreatic, bladder, and non-small cell lung cancer).

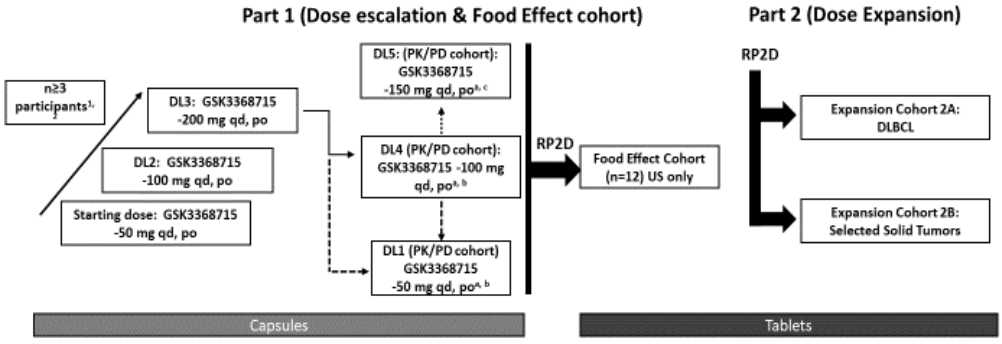
Number of Participants: It is estimated that up to approximately 60 participants will be enrolled in Part 1. In Part 2, approximately 141 participants will be recruited into Expansion Cohort 2A (~36 participants) and Expansion Cohort 2B (~ 105 participants). Additional tumor-specific cohort(s) and combinations may be added by protocol amendment, based upon emerging pre-clinical data, or clinical data.

Intervention Groups and Duration: In Part 1 of the study, the participants will initially receive GSK3368715 orally. This will include at least one PK/PD cohort and a food effect cohort. The Dose Limiting Toxicity (DLT) period is 21 days, and under protocol amendment 3, there is an addition of a VTE-specific DLT period of 8 (±1) weeks or until study discontinuation whichever occurs sooner. An end of treatment CT image is required if the participant withdraws before the end of the DLT observation period. Alternative dosing schedules and intervention cycles may be investigated. In Part 2, the participants are expected to receive the RP2D established in Part 1. In case of unexpected toxicities, alternative GSK3368715 doses may be explored in Part 2.

The study includes a screening period, an intervention period and follow up. Participants will be screened for eligibility beginning approximately 4 weeks before the start of intervention. Participants with confirmed partial response (PR) or complete response (CR) will be followed for response duration and may be eligible for additional intervention with GSK3368715 at the time of relapse/progression if determined to be deriving clinical benefit in the opinion of the investigator and with approval from the study Medical Monitor.

1.2. Schema

GSK3368715 Dose Escalation, PK/PD cohort(s) and a food effect cohort (Part 1) and Dose Expansion (Part 2)



a. Participants with advanced/refractory solid tumors.
b. Under protocol amendment 03, enrollment will resume in the 100 mg PK/PD cohort and the 50 mg PK/PD cohort.
c. Dose escalation will be limited to 50 mg increments.

Abbreviations: DL: GSK3368715 dose level; DLBCL: Diffuse-large B-cell lymphoma; po: oral dosing; qd: daily dosing

1.3. Schedule of Activities (SoA)

- A signed, written informed consent form (ICF) must be obtained from the participant prior to any study-specific procedures or assessments being performed. Protocol waivers or exemptions are not allowed except for immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the Schedule of Activities table, are required for study conduct.
- The timing of each assessment is listed in the Schedule of Activities (Table 1 and Table 2). Whenever vital signs, 12-lead electrocardiograms (ECGs) and blood draws are scheduled for the same nominal time, the assessments should occur in the following order: 12-lead ECG, vital signs, and blood draws. The timing of the assessments should allow the blood draw to occur at the exact time. Detailed procedures for obtaining each assessment are provided in the Study Reference Manual (SRM).
- The timing and number of planned study assessments, including safety, laboratory, imaging, tumor biopsy, pharmacokinetic (PK), and pharmacodynamic (PD)/biomarkers, may be altered during the study based on newly available data (e.g., to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.
- Any changes in the timing or addition of time points for any planned study assessments must be approved and documented by the relevant study team member and then archived in the sponsor and site study files, but these changes may not constitute a protocol amendment. The Institutional Review Board (IRB)/Independent Ethics Committee (IEC) will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the Informed Consent Form (ICF.)

Table 1 Screening Procedures

Procedure[1]	Notes
Informed consent	Informed consent can be signed within 45 days prior to first dose (following the signing of the ICF, all screening assessments for eligibility will begin approximately 4 weeks before the start of intervention)
Demography	
Medical History (past and current)	
Inclusion/Exclusion Criteria	
Disease Characteristics	
Anticancer Therapy	
Participant Registration	Participant registration will occur after all screening assessments have been performed and the participant has met all eligibility requirements
Echocardiogram/MUGA	ECHO/MUGA required within 28 days prior to first dose. If an ECHO or MUGA was done at baseline, then that same test should be used for further evaluations
Full Physical Examination	See Section 8.2.1 for details
ECOG Performance Status	For definitions, see Appendix 11.
Vital Signs	
Height and weight	
Holter monitoring	Screening Holter monitoring for 24 hours
12-lead ECG (Triplicate)	
HIV, HBsAg, HCV Antibody Screening	If test performed within 3 months prior to first dose of study intervention, testing at screening is not required.
Hematology/Clinical Chemistry	Refer to Appendix 2 for a complete listing of protocol required lab assessments.
Troponin (I or T)	
Pregnancy test	Required for females of child bearing potential. A serum pregnancy test should be done at screening. Must be done ≤7 days of first dose.
Tumor Imaging	Must be obtained up to 4 weeks (28 days) before the first dose. Must include CT Chest. Must include CT abdomen if history of documented intra-abdominal disease for disease staging.
Tumor biopsy	Part 1: A fresh biopsy, obtained during screening, is preferred however, an archival tumor specimen is acceptable if it is not feasible to obtain a fresh biopsy. Part 1 **PK/PD cohort(s) only**: A fresh biopsy (and consent for an on-therapy biopsy) is required for enrollment in this cohort. Part 2: A fresh biopsy, obtained during screening, is preferred, however archival tumor specimen is acceptable if it is not feasible to obtain a fresh biopsy. An archival tumor specimen must have been obtained within 6 months of starting study drug unless approved by the study Medical Monitor.

1. All assessments performed at Screening must be performed within 14 days prior to first dose unless otherwise specified in Table 1.

Table 2 Schedule of Activities (SoA) for Dose Escalation (Part 1)

Procedure	DLT period (Days 1-21)[3]								D22[3]	Continuation[3]	TDV[1]	Follow-up	Notes
	D1[2]	D2	D3	D4	D8	D11	D15	D16					
Safety													
AE / SAE Review	SAEs from signing of ICF to 90 days after last dose AESIs from first dose until 90 days after last dose AEs from first dose until TDV visit												See footnote 1 for TDV visit window. (See Section 8.3.1)
Concomitant Medication	Continuous from first dose												All concurrent medications will be collected until at least 30 days after the last dose of study intervention.
Brief Physical Examination	X				X		X		X	Q1W	X		See Section 8.2.1 for details
ECOG PS	X				X		X		X	Q4W	X		See Appendix 11 for definitions.
Vital Signs	X				X		X		X	Q4W	X		
Telemetry	X				X								Telemetry only required for doses > 200 mg and must start at least 60 min pre-dose and be continuous for 24h post-dose. See Section 8.2.5.
Holter monitoring	X				X		X		X				Holter monitoring must start at least 60 min pre-dose and be continuous for 24h post-dose.
12-lead ECG (Triplicate)	X	X	X		X		X		X	Q1W	X		On serial PK days (Day 1, 8 and 15), triplicate ECGs will be obtained at or about the time of each PK sample collection, as described in the SRM. On other days, triplicate ECGs will be obtained pre-dose.
Laboratory Assessments (Safety) – perform assessments pre-dose on each dosing day													
Clinical Chemistry, Urinalysis and Coagulations	X				X		X		X	Q1W	X		Refer to Appendix 2 for complete list of required laboratory assessments.
Hematology	X			X	X	X	X		X	Q1W	X		Hematology twice per week for the first two weeks (see Section 2.3.1). Refer to Appendix 2 for complete list of required laboratory assessments.
Pregnancy test					X				X	Q4W	X		Perform only in women of child bearing potential (WOCBP). Pregnancy tests during intervention phase and at discontinuation may be either serum

Procedure	DLT period (Days 1-21)[3]								D22[3]	Continuation[3]	TDV[1]	Follow-up	Notes
	D1[2]	D2	D3	D4	D8	D11	D15	D16					
													or urine. Final pregnancy test must be performed within 150 days after last study intervention.
Study intervention													
Administer study drug	X			←==========Daily Dosing==========→									A dose will be administered on Day 1, no dose will be given on Day 2 or Day 3 of the first cycle, after which, daily dosing will occur through the remainder of cycle 1 and all subsequent cycles. GSK3368715 should be administered in a fasted state at approximately the same time of day (± 4 h), with no food for 1 hour before and 2 hours after each dose. See Section 5.3.1 for dosing instructions on serial PK days.
Efficacy Assessment													
Tumor Imaging. Must include CT Chest. Must include CT abdomen if history of documented intraabdominal disease.										Week 9 Day1 then every 8 weeks until Week 33 Day 1 and then Q16W	X		Disease assessments will be performed until disease progression. Participants who discontinue for reasons other than PD will also be followed until the start of subsequent anti-cancer intervention. CR or PR should be confirmed as per response criteria in Appendix 10.
Patient Reported Outcomes													
Telephone interview (Part 2 only)										Week 9	X		Qualitative telephone interview to be completed within 21 days following the week 9 disease assessment and then again following the TDV. Participants who have the TDV within 30 days of the week 8 interview are not required to repeat the interview
Follow-up for Survival												Q12W	Participants will be followed every 12 weeks for survival and subsequent anti-cancer therapy. The survival follow-up visit will commence after discontinuation of study treatment. Participants should be contacted every 12 weeks (±2 weeks)

Procedure	DLT period (Days 1-21)[3]								D22[3]	Continuation[3]	TDV[1]	Follow-up	Notes
	D1[2]	D2	D3	D4	D8	D11	D15	D16					
													until death, termination of the study or participant has been followed for 2 years.
Tumor Specimens													
Tumor biopsy (Optional unless participant is in PK/PD cohort, see Table 3 below)		(X)											On intervention biopsies are optional (unless medically indicated) for individual participant(s)
Pharmacokinetics (PK), Pharmacodynamics (PD) and Pharmacogenomics (Genomics Research)													
PK plasma samples (parent drug and metabolites profiling for participants are in PK/PD cohort, see Table 3 below).	X	X	X	X	X		X	X	X	Q4W			On Day 1, patients will be administered GSK3368715 as a single oral dose followed by a 72 h intervention-free period to evaluate PK of the parent compound and its metabolites in plasma samples. Plasma metabolites will be analyzed at the timepoints indicated in Table 3 below. PK samples following Day 1 dose will be collected at Pre-dose, 15 ± 5 min, 30 ±5 min, 1h ± 5 min, 1.5h ± 5 min, 2h ± 10 min, 3h ± 10 min, 4h ± 10 min, 6h ± 30 min, 8h ± 30 min, 12h ±2h, 24h ±2h, 48h ± 2h, 72h ± 2 hrs post-dose. The 48 hr and 72 hr timepoints could be removed with emerging data. PK samples on Day 8 will be collected at Pre-dose, 1.h ± 5 min and 4h ± 10 min. PK samples on Day 15 will be collected at Pre-dose, 30 ±5 min, 1h ± 5 min, 2h ± 10 min, 3h ± 10 min, 4h ± 10 min, 6h ± 30 min, 8h ± 30 min, 12h ±2h, 24h ±2h (prior to next dose) post-dose. On Day 22) and then every 4 weeks during the continuation phase, only pre-dose PK samples should be collected. All pre-dose PK samples should be collected within 2h prior to the dose being administered.
Plasma for circulating free	X				X		X		X				Plasma for circulating free MMA, ADMA and/or SDMA will be collected pre-dose on Day 1 and 4h

Procedure	DLT period (Days 1-21)[3]								D22[3]	Continuation[3]	TDV[1]	Follow-up	Notes
	D1[2]	D2	D3	D4	D8	D11	D15	D16					
ADMA and SDMA (for Part 1, and PK/PD cohorts only)													post-dose ± 30 minutes) on Days 8,15 and 22. Refer to collection details within the SRM.
Plasma for exploratory biomarkers	X	X			X		X		X	X	X		Plasma for circulating biomarker analysis will be collected pre-dose on Day 1, 4h post dose ± 30 minutes on Days 2, 8,15 and 22, at first disease assessment and at TDV. Refer to collection details within the SRM.
Blood for TCR sequencing	X						X			X	X		Whole blood for TCR sequencing will be collected pre-dose on Days 1, 15, at first and second disease assessments and TDV. Refer to collection details within the SRM.
Whole Blood for PD biomarkers (for Part 1 and PK/PD cohort only)	X						X		X				Whole Blood for biomarker analysis will be collected pre-dose on Day 1, 4hrs post-dose ±30 minutes on Day 15, and pre-dose and 4h post-dose ±30 minutes on Day 22. Refer to collection details within the SRM.
Whole blood for biomarker analysis (PAX tube)	X				X		X				X		PAX whole blood samples will be collected pre-dose on Day 1, 4hr post-dose ± 30 minutes on Days 8 and 15 and on the TDV visit. Refer to collection details within the SRM.
Plasma and Serum for Coagulation markers	X				X		X		X				Plasma and serum samples will be collected pre-dose on Day 1 and 4hr ± 30 minutes post-dose on Days 8, 15 and 22.
Genetic sample	X												Informed consent must be given prior to sample collection. See Appendix 5.

Abbreviations: ADMA = asymmetric dimethylation of arginine; AE = Adverse event; AE = Adverse event of special interest; CR = Complete response; D = Day; ECG = Electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = End of intervention; h = hour; HBsAg = Hepatitis B surface antigen; HCV = Hepatitis C Virus; HIV = Human Immunodeficiency Virus; MUGA = Multigated (radionuclide) angiogram; PD = Pharmacodynamic; PK = Pharmacokinetic; PR = Partial response; SAE = Serious adverse event; SCR Screening; SDMA = symmetric dimethylation of arginine; SRM = Study Reference Manual; TCR = T-cell receptor; TDV = Treatment Discontinuation Visit; Q1W = Once every week; Q3W = Once every 3 weeks Q4W = Once every 4 weeks; Q8W = Once every 8 weeks.

1. The assessments required at the study intervention discontinuation visit must be completed within 30 days from the date that study intervention was discontinued and must occur prior to the start of subsequent anti-cancer therapy; the window for this visit is +10 days.
2. Day 1 assessments significantly different from screening assessments, especially those that are inconsistent with eligibility criteria, should be immediately discussed with the sponsor PRIOR to initiating study intervention. Day 1 labs may be skipped if screening labs were drawn Day -3, Day -2 or Day -1.
3. Visit Windows: With the exception of Screening and Week 1 visits (Day 1, 2, 3 and 4) and unless otherwise specified, assessments performed from Day 8 on will have a ± 3 day window. For Screening and Day 1 visits, all procedures must be completed before first dose.

Table 3 Schedule of Activities (SoA) (PK/Biomarker/Metabolite Cohort[s])

PK/PD/Biomarker/Metabolite Cohort(s); Samples collected in this section are in addition to any samples collected in Table 2													
Procedure	**First Intervention Period (Days 1-21)**									**Continuation**	**TDV[1]**	**Follow-up**	**Notes**
	D1	D2	D3	D4	D8	D11	D15	D16	D22				
Plasma (metabolite profiling)	X	X	X	X			X	X					Metabolites of GSK3368715 will be analyzed by utilizing samples collected for PK plasma as described in Table 2. Plasma metabolites will be analyzed from PK plasma samples collected on Day 1 at Pre-dose, 15 ± 5 min, 30 ±5 min, 1h ± 5 min, 1.5h ± 5 min, 2h ± 10 min, 3h ± 10 min, 4h ± 10 min, 6h ± 30 min, 8h ± 30 min, 12 ±2h, 24 ±2h, 48 ± 2h, 72 ± 2 hrs post-dose. The 48 and 72 hr timepoints could be removed with emerging data. On Day 15 PK samples for metabolites will be collected at Pre-dose, 30 ±5 min, 1h ± 5 min, 2h ± 10 min, 3h ± 10 min, 4h ± 10 min, 6 ± 30 min, 8h ± 30 min, 12 ±2h, 24 ±2h, (prior to next dose) post-dose. All pre-dose PK samples should be collected within 2h prior to the dose being administered
Urine (48-hour collection for PK and metabolite profiling)	0-24h	24-48h					0-24h						A separate container will be used to collect urine from the time of dosing until 24h post-dose and 24-48h on Days 1 and 24 h post dose on Day 15.
Tumor biopsy							X						On intervention biopsies are required between Day 15 and Day 20. Additional timepoints may be considered for biopsies after discussion between sponsor and investigator, if participants consent, for a maximum of 4 study related biopsies per participant.

1. The assessments required at the treatment discontinuation visit (TDV) must be completed within 30 days from the date that study intervention was discontinued and must occur prior to the start of subsequent anti-cancer therapy; the window for this visit is +10 days

Table 4 Schedule of Activities (SoA) (Food effect cohort)

Food effect cohort (Section 4.1.1.1); samples collected in this section are in addition to any samples, studies, and visits described in Table 2)[3]										
	D1	D2	D3	D4	D5 [4]	D6	D7	D8	D9 and beyond	
Administer study drug[1]	X				X				←----------daily dosing---------->	
Plasma PK samples[2]	X	X	X	X	X	X	X	X	X[3]	

1. Study drug should be administered in fed or fasted state, based on assignment as described in Section 4.1.1.1
2. PK samples on Days 1 and 4/5 should be collected at 0 (pre-dose), 0.25h ± 5 min, 0.5h ± 5 min, 1h ± 5 min, 1.5h ± 5 min, 2h ± 10 min, 3h ± 10 min, 4h ± 10min, 6h ± 30 min, 8h ± 30 min, 12h ± 2h, 24± 2h, 48± 2h and 72± 2h hours post dose
3. Refer to Table 2 for subsequent PK sample requirements
4. In order to accommodate clinic schedules, the Day 5 dosing (including all PK assessments) may be performed one day earlier (on Day 4), i.e. Days 5 to 8 would shift to Days 4 to Day 7, and then all subsequent PK assessments from then on would follow the same schedule as in Table 2

NOTE: Participants in the food effect sub-study are subject to all screening, safety, PK, and efficacy evaluations detailed in Table 1 and Table 2. Samples collected in this section are in addition to any samples collected in Table 2, with the exception of Day 1-8 PK collections, in which the time points in Table 4 supersede those in Table 2

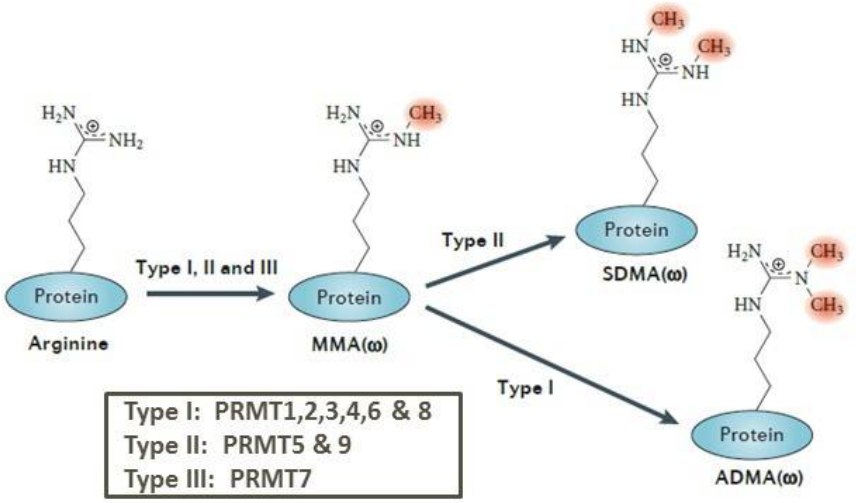
Any participant who experiences vomiting at or between 0.25-3 h will be removed from statistical analysis of PK comparability between fasted/fed state

2. INTRODUCTION

2.1. Study Rationale

Arginine methylation is an important post-translational modification of proteins involved in a diverse range of cellular processes such as gene regulation, ribonucleic acid (RNA) processing, deoxyribonucleic acid (DNA) damage response, and signal transduction. This protein arginine methylation is catalysed by a family of protein arginine methyltransferases (or PRMTs) which can be differentiated into the three classes of Type I, Type II and Type III enzymes. As shown in Figure 1, all three PRMT classes produce the intermediate monomethylarginine (MMA). This intermediate is subsequently converted by Type I PRMTs to generate Asymmetrical Dimethylated Arginine (ADMA) and by Type II PRMTs to generate Symmetrical Dimethyl Arginine (SDMA).

Figure 1 Arginine methylation by PRMTs



Yang and Bedford, Nature Reviews Cancer, 2013

The Type I class of PRMTs comprises the individual enzymes PRMT1, -3, -4, -6, and -8. Due to sequence similarities, PRMT2 is regarded as a type I enzyme as well, but catalytic activity has not been demonstrated so far. Apart from PRMT8, which has been found in brain tissue and HEK 293 (T) cells only, type I PRMTs are ubiquitously expressed.

Among the Type I class of PRMTs, the individual enzyme PRMT1 is the predominant Type I PRMT generating ~85% of cellular ADMA levels [Pawlak, 2000; Dhar, 2013]. Mis-regulation and overexpression of PRMT1 (a type I PRMT) has been associated with a number of solid and hematopoietic cancers [Yoshimatsu, 2011; Yang, 2013]. The link between PRMT1 and cancer biology has largely been through regulation of methylation of arginine residues found on relevant substrates. In several tumor types, PRMT1 can drive expression of aberrant oncogenic programs through methylation of histone H4 [Zhao, 2008; Shia, 2012; Takai, 2014], as well as through its activity on non-histone substrates [Wei, 2014]. In many of these experimental systems, disruption of the

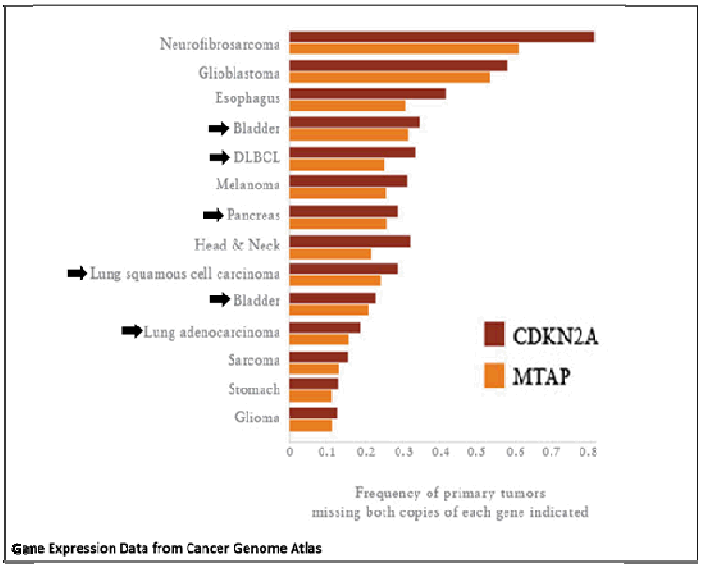
PRMT1-dependent ADMA modification of its substrates decreases the proliferative capacity of cancer cells [Cheung, 2007; Yang, 2013].

In non-clinical models, inhibition of the Type I PRMT family by GSK3368715 leads to inhibition of tumor cell growth across tumor types with cytotoxic response observed in lymphoma, acute myeloid leukemia (AML) and a subset of solid tumor cell lines. Additionally, GSK3368715 induces tumor growth inhibition and regression in mouse models, as a single agent and in combination with PRMT5 inhibition or anti-PD-1 immunotherapy. These results indicate that GSK3368715 may lead to anti-tumor activity and provide a novel therapeutic mechanism for the intervention of hematological and solid tumors alone and in combination with other anti-tumor agents.

MTAP Deficiency as a potential Biomarker for GSK3368715 Activity

The activity of GSK3368715 is frequently enhanced in cancer cell lines that are deficient in the enzyme Methylthioadenosine phosphorylase (MTAP). MTAP is a critical enzyme in the methionine salvage pathway that metabolizes 2-methylthioadenosine (MTA), leading to the regeneration of methionine and adenine. MTAP deficiency is caused by a homozygous gene deletion. The gene for MTAP is located on the human chromosome 9p21 (chr9p21) locus. This locus also includes the gene for the Cyclin Dependent Kinase Inhibitor 2A (CDKN2A) which encodes the two critical tumor suppressors p16-INK4a and p19-ARF. The chr9p21 locus, is deleted in approximately 15% of all human tumors leading to a combined loss of the p16-INK4a and p19-ARF tumor suppressors and a deficiency in MTAP expression as shown in Figure 2.

Figure 2 Frequency of homozygous deletion of CDKN2A (p16-INK4a) and MTAP in Primary Tumor Tissues



➡ = Primary tumor tissue for expansion cohorts

MTAP deficiency can be detected across multiple human solid and hematologic malignancies including approximately up to 40% of glioblastoma, 25% of melanoma,

pancreatic adenocarcinoma, and Diffuse-large B-cell lymphoma (DLBCL) as well as 15% of non-small cell lung cancers (NSCLC).

Deficient MTAP enzymatic activity in ch9p21 mutant tumor cells leads to an increase in the intracellular levels of the MTAP metabolite, MTA. MTA has been shown to be a potent inhibitor of the enzymatic activity of the important Type II PRMT enzyme PRMT5. In consequence, accumulation of intracellular MTA in MTAP-deficient tumor cells results in lower cellular levels of PRMT-5 mediated SDMA generation.

Based on these observations, Part 2 of the FTIH study will investigate the hypothesis that the therapeutic index of GSK3368715 is enhanced in MTAP-deficient tumors in which endogenous PRMT5 is partially inhibited, thereby sensitizing cells to Type 1 PRMT inhibition. This FTIH is designed as an open-label, dose-escalation study to assess the safety, pharmacokinetics (PK), and pharmacodynamics (PD) of GSK3368715 and to evaluate the preliminary clinical activity in participants with frequently MTAP-deficient relapsed/refractory DLBCL and selected solid tumors harbouring deletions of MTAP or wild type MTAP in Part 2.

2.2. Brief Background

2.2.1. GSK3368715

An overview of the nonclinical studies of GSK3368715 are provided below. Detailed information concerning the biology, pharmacology, PK, and safety can be found in the Investigators' Brochure (IB) [GlaxoSmithKline Document Number 2017N334333_02].

GSK3368715 is a potent, reversible, S-adenosyl methionine (SAM) uncompetitive, inhibitor of Type I PRMTs 1, 3, 4, 6, and 8 (K_i^{*app}= 1.5/81.0$^{\#}$/19.0/2.4/2.0 nM; $^{\#}$ K_i^{app}). A crystal structure of GSK3368715 with PRMT1 reveals that the compound is bound in the protein substrate binding pocket. GSK3368715 inhibits asymmetric arginine dimethylation leading to accumulation of MMA with a cellular EC_{50} = 13.6 ± 0.3 nM.

2.2.1.1. Nonclinical Safety

The systemic toxicity of GSK3368715 has been evaluated in rats and dogs administered GSK3368715 orally (once daily) for up to 4 weeks. Recovery was assessed following a 4-week or 2-week off-dose period in the rat and dog, respectively, in which time the majority of the findings had partially or completely recovered, with the exception of testicular and epididymidal changes which had progressed and is not uncommon for this limited recovery interval, and in the thymus and lymph nodes. Screening genotoxicity studies have also been conducted; GSK3368715 was not genotoxic, and does not pose a phototoxic risk as it does not absorb in the UV/vis range. Summaries of principal findings following single and repeat dosing of GSK3368715 and a comparison of systemic exposures achieved in these studies are presented below additional details regarding the principal toxicological findings can be found in the IB [GlaxoSmithKline Document Number 2017N334333_02].

The dose-limiting toxicities observed in the rat and the dog following repeat administration of GSK3368715 were gastrointestinal effects associated with poor

tolerability including body weight loss/decreased body weight gain. Microscopic erosions/ulcerations were observed in the GI tract of the rats (stomach) and dogs (oral cavity and upper gastrointestinal tract). These findings were resolved at the end of the two week off-drug period for the dog, but reversibility was not assessed at doses that caused gastrointestinal effects in rats.

Mild, reversible changes in hematopoietic cellularity were noted in the bone marrow of the rat and the dog. The effect on red cell mass persisted through the off-dose period and reflected effects on erythropoiesis that occurred during dosing but expected to be fully recovered based on recovery and rebound of reticulocyte counts and the bone marrow regenerative response observed at the end of the off-dose phase. Complete blood counts will be monitored regularly in this protocol (see Section 2.3.1).

Lymphoid changes were observed the thymus, mesenteric lymph node, spleen, and gut-associated lymphoid tissues (GALT) in rats were likely due to test item effects on the T lymphocytes; thymus changes correlated, in part, to lower white blood cell and lymphocyte counts. In the dog, decreased lymphoid cellularity in the GALT of the small intestine (ileum), mesenteric lymph nodes and thymus associated with reversible decreases in lymphocyte counts was observed and remained unchanged after a 2-week off-dose period. Based on the magnitude of the changes in circulating peripheral lymphocytes, these changes were considered non-adverse.

Reversible liver changes (hypertrophy in rat, and vacuolation in rat and dog) and increases in liver-associated enzymes were observed in the rat and dog. These changes were associated with microsomal enzyme induction in the rat. These changes are monitorable and clinically manageable (see Section 2.3.1).

Testicular effects including degeneration in seminiferous tubules in the dog were detected at all doses in the rat and the dog. These changes are not considered dose-limiting for oncology products. Contraceptive requirements are detailed in Appendix 4.

Dose-dependent functional cardiovascular effects were seen in rats and dogs at exposures relevant to the maximal predicted clinical exposure including increased heart rate, blood pressure and increased PR and QRS intervals; these changes correlated with exposure to GSK3368715. The NaV1.5 channel is inhibited by GSK3368715 (IC_{50} = 168 µM (at 2Hz)); therefore, the cardiovascular effects may be due to a direct effect on the NaV1.5 channel which is primarily associated with cardiac tissue. Changes in QT and QTc were seen at doses above the maximum tolerated dose (MTD) following six doses of GSK3368715 (Total maximum observed concentration [Cmax] of 10-40ug/mL, ~20-80X predicted human efficacious exposure). No structural and/or morphological cardiac effects related to administration of GSK3368715 were observed in either species at any doses. Increased cardiovascular monitoring will be implemented in this protocol (See Schedule of Activities Table Section 1.3).

Based on the histopathology changes and increased liver-associated serum enzyme activity and bilirubin, a no observed adverse effect level (NOAEL) in the rat was not determined. The severely toxic dose in 10% of the rats (STD 10) was 150 mg/kg/day

(mean AUC(0-t) 35.4 μg.h/mL, mean Cmax 4.59 μg/mL; gender averaged based on Day 28 values).

Based on adverse pathology in the digestive tract and in the testes noted at all doses, a no observed adverse effect level (NOAEL) could not be determined in the dog. Based on the moribundity of male dogs given 25 mg/kg/day, the highest non-severely toxic dose (HNSTD) was 15 mg/kg/day (mean AUC(0-t) 10.6 μg.h/mL, range 7.86 to 17.5 μg.h/mL mean Cmax 3.34 μg/mL, range 2.42 to 4.74 μg/mL [gender-averaged based on Day 28 values]).

2.2.1.2. Nonclinical Pharmacokinetics

The nonclinical pharmacokinetics of GSK3368715 was similar across species. Oral bioavailability was moderate to high (28% in mice, 100% in rats and 68% in dogs). Steady-state volume of distribution was high in all species (about 18, 27 and 39 times total body water in mouse, rat and dog, respectively). *In vivo*, GSK3368715 had high clearance in dogs and rats and moderate clearance in mouse with a low intrinsic clearance in microsomes and hepatocytes from humans but moderate intrinsic clearance in rat, dog and high in mouse hepatocytes. In vitro, GSK3368715 binding to plasma proteins varied between species and percent unbound was around 35.7% in mice, 35.9% in rats and 71.8% in dog and 64.2% in human at a concentration of 1μM. In a qualitative assessment of the metabolic profile, GSK3368715 primarily showed multiple metabolites formed via N-demethylation and O-dealkylation/oxidation. In human liver microsomes, GSK3368715 did not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP3A4/5, however it did inhibit CYP2D6 (IC50 = 22.6 μM). GSK3368715 half-life was 5.5 hours in the mouse, 7 hours in the rat and 12 hours in the dog.

2.2.1.3. Nonclinical Activity and Pharmacodynamics

GSK3368715 inhibits growth in cancer cell lines across tumor types when tested. The concentration of GSK3368715 required for 50% growth inhibition (gIC_{50}) was less than or equal to 2μM in 43% of all cell lines tested, including 80% of AML, 71% of melanoma, 70% of lymphoma, and 60% of kidney cancer cell lines. Cytotoxicity was most frequently observed in cell lines from AML and lymphoma, where 50% and 56% of cell lines had negative growth index values, respectively.

When tested in mouse xenograft studies, GSK3368715 induces tumor growth inhibition in lymphoma, breast, pancreatic and renal cell carcinoma models, with tumor regression observed at daily doses ≥ 150 mg/kg. Mouse models using human lymphoma and renal cell carcinoma cell lines indicate that 100% tumor growth inhibition is achieved at >90% of the maximal PD response, as measured by MMA induction in tumors.

In lymphoma cell lines, GSK3368715 induces gene expression changes that impinge upon key mechanisms central to lymphomagenesis, including but not limited to, inhibition of MYC and B-cell lymphoma protein 6 (BCL6) transcriptional programs. Additionally, treatment of lymphoma and breast cancer cell lines with GSK3368715 induces thousands of alterations in splicing, including intron retention and exon skipping, consistent with changes in arginine methylation of numerous substrates of Type I PRMTs linked to splicing and RNA metabolism. Additionally, GSK3368715 demonstrates

immunomodulatory activity through upregulation of interferon pathways and pro-inflammatory gene expression signatures in tumor cells. Together, these data suggest that multiple cancer relevant mechanisms are perturbed by GSK3368715 intervention.

2.2.1.4. Clinical Safety of GSK336715

The first and to date only active clinical study evaluating GSK3368715 is this first time in human study 207675. In this study, GSK3368715 has been administered as an oral capsule dosed once daily to patients with solid tumors. As of the clinical data cut-off date, 23 October 2019, three daily oral dose levels (50 mg, 100 mg and 200 mg) have been evaluated.

2.2.1.4.1. Adverse Events and Dose Limiting Toxicities

A summary of adverse events is included in the GSK3368715 Investigator's Brochure [GlaxoSmithKline Document Number 2017N334333_02]. As of the clinical data cut-off date, 23 October 2019, two (2) participants had DLTs in the 200 mg cohort Dose Level 3 (DL3). The first participant, a 72-year old male, experienced a Grade 3 thrombocytopenia in the context of progressive intra-abdominal metastases and portal/splenic vein thrombosis and was hospitalised. The investigator considered the event to be unrelated to GSK3368715. The second participant, a 68-year old male, experienced a Grade 3 atrial fibrillation. The investigator considered the event to be related to GSK3368715, however, the participant had pre-existing atrial ectopy and increased atrial area. These events led to permanent discontinuation of study drug.

In addition, there were eight (8) adverse events (four serious and four non-serious) of venous thromboembolism reported. None of them were considered drug-related by the investigators.

2.2.1.4.2. Venous Thromboembolism

The sponsor paused enrolment of the study on 12 September 2019 due to the unexpected incidence of venous thromboembolism (VTE). As of 25 September 2019, eight (8) out of 19 participants (42%) experienced VTE.

- 1/3 (33%) participants receiving DL1 (50 mg). None reported as SAE.
- 1/4 (25%) participants receiving DL2 (100 mg). None reported as SAE.
- 6/12 (50%) participants receiving DL3 (200 mg). Of those, 4/12 (33%) were SAEs.

The four (4) VTE cases reported as SAEs described two males and two females with a mean age of 67 years old. The time to onset in these VTEs were inconsistent, ranging from one day to 8 weeks after starting study drug. One VTE SAE event was fatal (i.e. participant who developed acute VTE after only one day drug exposure with existing chronic VTE). Of note, this participant had a very recent history of VTE, and entered the trial on anticoagulation with low molecular weight heparin. The other three VTE SAE events were considered resolved with sequelae after treatment with anticoagulant drugs. Among cases reported as an SAE, only one participant resumed study drug while on anticoagulant therapy, with a negative re-challenge. However, he permanently discontinued study drug approximately eight weeks later, due to disease progression. In

one participant, venous compression by locoregional disease progression (i.e. new lesions in pancreas/splenic vein thrombosis) could not be ruled out as a confounding factor. Two of the SAE cases were confounded by prior or concurrent history of VTE.

In addition, four (4) VTE cases were reported as non-serious AEs (one at 50 mg [DL1], one at 100 mg [DL2] and 2 at 200 mg [DL3]). For these participants (two females and two males), the mean age at the time of the VTE was 57 years old. The time to onset ranges from 4 to 8 weeks. Among these four (4) non-serious cases, only one resumed study drug while on anticoagulant therapy, with a negative re-challenge. Similarly, to the situation of the SAE cases, two participants locoregional disease progression could not be ruled out (i.e. new lesions in liver/portal vein thrombosis) and two participants were confounded by prior history of VTE.

One participant with an SAE of portal /plenic vein thrombosis also had an incidentally discovered mural aortic thrombus, this is to date the only case of arterial thromboembolism on this trial.

Due to the observed incidence of emobolic and thrombotic events, the study was put on enrolment pause and protocol amendment 3 now includes additional guidelines for management and stopping criteria for VTE..

2.2.1.4.3. Cardiac Safety

At the time of Amendment 3, a total of 19 participants have been dosed at 50-200 mg QD in study 207675 with GSK3368715. Concentration-QRS analysis with over 400 time-matched data points showed an equal number of negative and positive changed in QRS duration at all concentrations with a slope of almost zero. No systematic dose dependent increase in QRS duration or significant ventricular arrhythmias have been observed to date.

Based on these data, telemetry will no longer be required for any participants dosed at 200 mg or below under Protocol Amendment 3. See also the Investigator Brochure Version 2 [GlaxoSmithKline Document Number 2017N334333_02].

2.2.1.5. Clinical Pharmacology of GSK3368715

Pharmacokinetics (PK) of GSK3368715 is currently being evaluated after administration of single and repeat daily oral administration of GSK3368715 at doses of 50mg to 200mg in study 207675. Concentrations are detected in plasma 0.25 hours after oral administration with peak concentrations at around 1.0 hours on average, then GSK3368715 declines bi-exponentially with a mean terminal elimination half-life of 20-24 hours. A dose dependent increase in plasma exposures (both Cmax and AUC) of GSK3368715 were observed as doses increased from 50mg QD to 200 mg QD. Following multiple-dose administration, mean AUC was up to 2-4 fold higher on Day 15 as compared to Day 1 in all dose groups, except for participants PPD and PPD who showed much higher accumulation on Day 15 of 6-7 folds relative to Day 1.

2.2.2. Potential GSK3368715 Combination Regimens

2.2.2.1. GSK3368715 Combination with PRMT5 inhibition

Overexpression of another PRMT, PRMT5 has been shown in several cancers including glioma, lung cancer, melanoma, mantle cell lymphoma, multiple endocrine neoplasia, prostate, and gastric cancer. PRMT5 is the predominant type II PRMT that catalyzes the formation of symmetric dimethylated arginine (SDMA).

Co-intervention of cancer cells with GSK3368715 and a PRMT5 tool inhibitor (GSK3326591) results in a cytotoxic response in 57% of the cell lines treated compared with 18% and 11% for GSK3368715 and GSK3203591 as single agents, respectively.

Deletion of the *MTAP* gene results in the accumulation of its metabolite, 2-methylthioadenosine (MTA), a selective inhibitor of PRMT5 enzymatic activity [Kryukov, 2016; Marjon, 2016; Mavrakis, 2016]. Thus, MTAP deficiency may contribute to sensitivity and cytotoxic responses to GSK3368715 alone suggesting the potential utility of *MTAP* status as a predictive biomarker of response. Due to its genomic proximity to the tumor suppressor *CDKN2A(p16)*, the *MTAP* gene is frequently deleted in cancers including 40-56% of glioblastoma, 27-31% of pancreatic adenocarcinoma, 27-32% of bladder cancer, 25% of melanoma, 23% of lymphoma, and 9-28% of non-small cell lung carcinoma. GSK3368715 alone induces a cytotoxic response in a subset of pancreatic cancer cell lines deficient for MTAP. Together, these data indicate that GSK3368715 intervention in combination with PRMT5 inhibition, through MTAP loss or a small molecule inhibitor, has potent anti-tumor activity in cancer cell lines across multiple tumor types.

2.2.2.2. GSK3368715 Combination with Checkpoint Modulators

Cancer cell lines treated with GSK3368715 demonstrated altered expression of pro-inflammatory, immune response gene families including tumor necrosis factor alpha (TNF-α) and interferon-gamma (IFN-γ) suggesting an immunomodulatory effect. Therefore, the anti-tumor activity of GSK3368715 was evaluated in an immune-competent mouse tumor model as a single agent and in combination with the checkpoint modulator antibody anti-PD1. GSK3368715 alone and in combination with anti-PD1 has significant effects on tumor growth inhibition and provides enhanced survival benefit relative to control mice. Surviving animals from all single agent and combination dosing groups are resistant to re-challenge with tumor cells without additional dosing of either agent. Collectively, these data suggest GSK3368715 may provide durable anti-tumor effects in an immune-competent setting and synergize with immune system checkpoint modulators such as anti-PD1.

2.3. Benefit/Risk Assessment

The risk assessment and risk mitigation plan for the study are summarized below.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of GSK3368715 may be found in the Investigator's Brochure [GlaxoSmithKline Document Number 2017N334333_02].

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
GSK3368715		
Cardiovascular	Increased QRS and PR intervals in rat and dog.	• Exclusion of participants with cardiac abnormality • Increased cardiac monitoring as per Schedule of Activities (Section 1.3) • Cardiac stopping criteria (See Section 7.1.2)
Gastrointestinal	Ulcerations/erosions in the upper gastrointestinal tract in rat and dog associated with reduced food consumption, body weight loss, emesis, abnormal feces, and/or salivation.	• Exclusion of participants with significant malabsorptive gastrointestinal abnormalities • Guidelines for management of diarrhea, nausea, vomiting included in Appendix 12.
Hematologic/Lymphoid	Mild, reversible increased hematopoietic cellularity (with immature phenotype) in the bone marrow of rat and dog at tolerated doses; decreased cellularity at non-tolerated doses. Decreased lymphoid organ cellularity. Mild decreases in circulating RBC, WBC and/or platelets.	• Exclusion of participants with clinically significant bleeding • Laboratory assessments for complete blood counts • Guidelines for management of thrombocytopenia and anemia included in Appendix 12 • Dose stopping/modification criteria (Appendix 12)

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Hepatic	Reversible hepatocyte hypertrophy and vacuolation and increases in serum liver-associated enzymes in rat and dog.	• Exclusion of uncontrolled hepatic disease • Routine monitoring of liver chemistry • Stopping criteria/rechallenge guidelines (See Appendix 6).
Testicular/Reproductive Effects	Testicular effects including degeneration in seminiferous tubules in rat and dog.	• Male contraceptive language included in Appendix 4
Thromboembolic Risk	A higher than expected incidence of venous thromboembolism was observed in the first 19 participants treated on clinical study 207675.	• Change in inclusion/exclusion criteria, to exclude participants at high risk of VTE. • Extended monitoring time for VTE events to clear dose prior to dose escalation. • Include cohort stopping rules for VTE • Resume enrollment under protocol amendment 03 at reduced dose of 100 mg po daily • Limit dose escalation to 50 mg increments.
Study procedures		
Biopsy	A tissue biopsy is required in PK/PD cohorts to evaluate tumor expression of the biomarkers pathway. Risks associated with a tumor biopsy depend upon the location and type of biopsy performed. Pain, infection, bleeding may occur after the procedure. Additional risks depending on the location of the biopsy may include pneumothorax, pneumonia, injury to surrounding nerves or organs, hospitalization, and, rarely, death.	• Participants will be informed of the specific risks associated with the biopsy to be performed through the ICF. Participants at increased risk or not well suited to undergo a biopsy should not be enrolled in a cohort that requires a fresh biopsy. Participants will be treated according to local practice.

2.3.2. Benefit Assessment

Data obtained in this study may assist in growing the knowledge base on relapsed/refractory solid tumors and DLBCL and their treatment, or help identify individuals more likely to benefit or have side-effects from GSK3368715. Study participants may benefit from the medical tests and screening performed during the study. Four of 19 subjects treated to date have experienced a period of radiologically documented stable disease of at least 8 weeks duration.

2.3.3. Overall Benefit/Risk Conclusion

Epigenetic alteration resulting in the loss of gene expression by transcription silencing occur approximately 10- times more frequently than genetic alterations and have thus, long been thought of as a separate mechanism driving malignant transformation and carcinogenesis. However, data recently derived from the whole exome sequencing of thousands of human cancers have led to the unexpected discovery of a 'crosstalk' between the tumor genome and the epigenome caused by many inactivating mutations in genes that control the epigenome. These mutations have the potential to disrupt DNA methylation patterns, histone modifications and nucleosome positioning and hence, gene expression. Genetic alteration of the epigenome therefore contributes to cancer just as epigenetic process can cause point mutations and disable DNA repair functions. The 'crosstalk' between the genome and the epigenome offers new possibilities for manipulations of epigenetic alterations for cancer prevention, detection, and therapy.

The Type 1 protein arginine methyltransferases (PRMTs) are believed to be involved in this 'crosstalk'. Aberrant regulation and overexpression of PRMT1, a member of the Type I class of PRMTs has been associated with the development and dissemination of solid tumors and hematologic malignancies. Moreover, deficiency of MTAP, a gene that is frequently deleted concomitantly with the tumor suppressor p16 gene (also known as cyclin-dependent kinase inhibitor 2A), appears to sensitize tumor cells to cytotoxicity induced through Type 1 PRMT1 inhibition.

GSK3368715 is a first-in-class agent selectively targeting Type 1 PRMTs. In preclinical studies, GSK3368715 has demonstrated broad anti-tumor efficacy *in vitro* and *in vivo*. Loss of MTAP enhances sensitivity and cytotoxic response to GSK3368715 in select tumor types. These preclinical studies strongly support the clinical development of GSK3368715 in patients with solid tumors and hematologic malignancies initially as single agent and in the future potentially in combination with other intervention modalities. Tumor indications with more frequent MTAP deficiencies may be more susceptible to GSK3368715 induced cytotoxicity.

In this first time in humans (FTIH) study only participants with advanced stage solid tumors or relapsed/refractory DLBCL will be enrolled. All participants in this study will have exhausted all approved and effective therapies prior to receiving GSK3368715. The study protocol has been specifically designed to (i) carefully monitor all participants and thereby, minimize the clinical risk of intervention-related toxicities and to (ii) enrich the study population for tumor indications with higher sensitivity for GSK3368715 study intervention.

Considering the novel and very relevant mode-of-action, the anti-tumor activity observed in pre-clinical tumor models, the availability of a relevant biomarker for enrichment, and the clinical monitoring measures incorporated into this study protocol, the sponsor believes that the potential clinical benefit associated with GSK3368715 study intervention outweighs the risk of severe, intervention-emergent toxicities. This assessment is maintained after initial clinical evaluation in 19 participants in a Phase 1 population with advanced cancer without alternative therapeutic options.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Part 1: Dose Escalation	
Primary	
• Determine RP2D and schedule of GSK3368715 administered orally to participants with advanced stage solid tumors	• Incidence of DLT • Incidence and severity of adverse events
Secondary	
• Evaluate the preliminary clinical activity of GSK3368715	• Best overall response
• Characterize the PK of GSK3368715, including the PK in the fed and fasted state in the food effect sub-study	• PK parameters (Cmax, Tmax, AUC, others) • PK parameters (Cmax, Tmax and AUC) in the fed and fasted state in the food effect sub-study
Part 2: Dose Expansion	
Primary	
• Evaluate the preliminary clinical activity of GSK3368715	• Objective response rate (ORR)
Secondary	
• Characterize the safety of GSK3368715 administered at the RP2D and schedule to participants with DLBCL, pancreatic cancer, NSCLC, and bladder cancer	• Incidence and severity of adverse events
• Further evaluate the clinical activity of GSK3368715	• Progression-free survival (PFS)
• Characterize the PK of GSK3368715	• PK parameters (Cmax, Tmax, AUC, others)
Part 1 and Part 2	
Exploratory	
• Evaluate time to response (TTR), duration of response (DOR) and overall survival (OS) • Evaluate changes in PD biomarkers relevant to define the molecular mode-of-action of GSK3368715 • Investigate biomarkers such as, but not restricted to, MTAP deficiency and CDKN2A gene deletion, as potentially predictive of sensitivity or resistance to GSK3368715 • Characterize the relationship between PK, PD, and clinical activity of GSK3368715 • Evaluate the relationship of pharmacogenetic profile in host DNA and response to GSK3368715 therapy • Determine the impact of GSK3368715 on function and health-related quality of life • Determine the amount of GSK3368715 excreted in urine from participants in the	

PK/PD expansion cohorts
- Characterize the metabolic profile of GSK3368715 (in the PK/PD expansion cohorts
- Investigate biomarkers such as, but not restricted to, D-dimer, fibrinogen and Factor VIII to evaluate whether GSK3368715 affects the coagulation cascade

4. STUDY DESIGN

4.1. Overall Design

This is a first time in human (FTIH), open-label, repeat-dose, non-randomized, multicenter study to evaluate the safety, tolerability, PK, PD, preliminary clinical activity and establish a recommended dose of GSK3368715 in participants with refractory/relapsed solid tumors and DLBCL.

The study will consist of a dose-escalation phase, including at least one PK/PD cohort and a food effect cohort, (Part 1) and dose expansion phase (Part 2):

- **Part 1**: GSK3368715 doses will be escalated using the Neuenschwander continual reassessment method (N-CRM). The populations enrolled will be participants with selected solid relapsed/refractory tumors. Based on safety and tolerability, and the PK/pharmacodynamic characteristics of the molecule, recommended Phase 2 (RP2D) dose(s) and schedule(s) will be established.

- **Part 2**: the safety and preliminary clinical activity of GSK3368715 administered at the RP2D and schedule will be further evaluated in two expansion cohorts

    - **Expansion Cohort 2A**: Participants with relapsed/refractory Diffuse-large B-cell lymphoma (DLBCL)

    - **Expansion Cohort 2B:** Participants with selected relapsed/refractory solid tumors where MTAP deletion occurs at a frequency of approximately ≥25% (e.g., pancreatic, bladder, and non-small cell lung cancer).

Note: In both expansion cohorts, both MTAP proficient and deficient participants will be enrolled. Separate analysis will be conducted for MTAP deficiency or MTAP proficiency/wild type within each specific disease histology.

Based on the emerging safety- and molecular activity profile of GSK3368715 combination regimens with novel, active agents such as the small-molecule PRMT5 inhibitor, GSK3326595 and/or with approved oncology therapies may be considered. Rationale for these future combinations will be provided before the initiation of that combination and added by way of a protocol amendment.

The study includes a screening period, an intervention period and follow up. Participants will be screened for eligibility beginning approximately 4 weeks before the start of

intervention. Participants may continue treatment in the study until disease progression, unacceptable toxicity, or withdrawal of consent. For participants who discontinue intervention prior to a determination of PD, the follow-up period includes disease assessments every 8 weeks until documented PD. Following PD or for participants that discontinue study intervention, participants will be contacted every 12 weeks to assess survival status for 2 years from the start of the study. Participants with confirmed partial response (PR) or complete response (CR) will be followed for response duration.

Assessment of disease status will be performed by the Investigator in accordance with Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 and the latest version of Lugano Criteria for NHL.

4.1.1. Part 1: Dose-Escalation Phase

Cohort Size: The initial dose cohort(s) will include up to three participants per GSK3368715 dose level. Cohorts will be expanded at the first instance of a ≥ Grade 2 drug-related non-hematological toxicity. From there on, a minimum of 3 and a maximum of 12 DLT evaluable participants may be assigned to any single dose at the discretion of the Dose Escalation Committee (DEC) as outlined in the Dose Escalation Plan.

Replacement: If a participant fails to receive at least 75% of the planned doses within the 21-day DLT observation period for reasons other than toxicity (e.g., concurrent illness or disease progression), the participant will be replaced by additional participant(s) assigned to the same dose level and will not be counted as DLT evaluable.

Dose Escalation: After each dose cohort, a dosing recommendation for the next cohort will be made using the Neuenschwander Continual Reassessment Method (N-CRM) [Neuenschwander, 2008].

The N-CRM design makes use of a Bayesian logistic regression model relating dose and toxicity and is expected to locate the target dose level efficiently while minimizing the number of participants exposed to pharmacologically inactive or unsafe dose levels. The N-CRM method is fully adaptive and makes use of all DLT information, therefore is expected to locate the target dose level efficiently.

The N-CRM estimates, for each potential dose, the posterior probabilities that the DLT rate lies in each of four toxicity ranges:

- A dose falls in the **Under-dosing** range if the probability of a DLT at the dose is, 16%.
- A dose falls in the **Target** Toxicity range if the probability of a DLT at the dose is ≥16% and <33%.
- A dose falls in the **Excessive** Toxicity range if the probability of a DLT at the dose is ≥33%, and <60%.
- A dose falls in the **Unacceptable** Toxicity range if the probability of a DLT at the dose is ≥60%

At the time of each dose-escalation decision, 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%.
- VTE safety rules
  - Upon re-initiation of enrolment under Protocol Amendment 3, details of a VTE meeting the DLT criteria are given in Section 4.1.3 and in Table 6.
- Upon re-initiation of enrolment under Protocol Amendment 3 at 100mg , dose escalation steps will be considered in maximal steps of 50 mg, depending on the pharmacodynamic effects and the safety profile observed in previous cohorts, taking into consideration the updated DLT criteria (see Table 6).
- *Note*: GSK3368715 dose de-escalation is also possible using this method.

An updated posterior estimate of the dose-toxicity curve will also be provided at the time of the dose-escalation meeting. Further details about the N-CRM approach are provided in Section 9. Although the N-CRM will be used to recommend the next dosing level, the DEC (i) will review all available data, including safety, PK and PD data from current and prior cohorts, (ii) can halt or reduce the GSK3368715 dose based on clinical judgement at any time during the trial, and (iii) can recommend alternative schedule(s) if emerging data suggest that continuous daily dosing will result in excessive toxicity or limited efficacy (Section 4.1.4). *Note:* if an alternative schedule is evaluated, the starting dose at the time of a schedule change will be the dose for which the target toxicity level was not exceeded using once daily dosing schedule.

Dose Schedule: GSK3368715 will be dosed initially orally (po) Based on emerging safety-, PK-, and PD- data, the DEC may recommend to evaluate alternative dosing schedule(s). The starting dose for an alternative dosing schedule will not exceed the highest GSK3368715 dose declared safe by the DEC at the time of the proposed schedule change.

During dose escalation, the first dose will be staggered by at least 24 hours between the participants enrolled within a cohort. This staggered dosing start is not required for participants enrolling at previously cleared doses.

PK/PD/Metabolite/Biomarker-Cohort: At GSK3368715 dose levels near to the expected RP2D, the DEC may recommend to expand a cohort(s) to up to 12 participants for additional PK- and PD-, metabolite- and/or biomarker-sample collection.

Under protocol amendment 03, a 100mg PK/PD cohort will be opened on resuming enrolment, and a 50mg PK/PD cohort may be opened in parallel. An additional PK/PD cohort may be opened later at a different dose level. The total maximal number of participants enrolled on PK/PD cohorts will be approximately 30.

The DEC may mandate to:

(1) take pre- and post-dose tumor biopsies,

(2) collect additional urine-, plasma-, and/or whole blood samples, and/or
(3) perform ^{18}fluorodeoxyglucose (FDG) positron emission tomography (PET) (i.e. FDG-PET)/computer tomography (CT) (PET/CT) scan assessments. in the additional participants enrolled in these GSK3368715 cohort(s).

The intention is to generate more comprehensive data at therapeutically relevant GSK3368715 dose level(s) in order to (i) establish a dose-response curve for GSK3368715 on the basis of PD-biomarkers, (ii) further characterize the metabolism of GSK3368715, and/or (iii) investigate the molecular mode-of-action of GSK3368715 on the basis of exploratory biomarkers. Participants may be enrolled into these PK/PD/Metabolite/Biomarker cohort(s) even after the MTD and/or RP2D has been identified and study Part 2 has been initiated.

Maximum-tolerated Dose: MTD is the highest GSK3368715 dose that emerges from the evaluation of safety-, PK-, and PD-data guided by the N-CRM statistical design during the DLT evaluation period.

Recommended Phase 2 Dose: RP2D of GSK3368715 will be determined after review of all available safety-, PK-, PD-, and clinical efficacy data in accordance with the N-CRM design. The RP2D will be equivalent with the MTD or a lower GSK3368715 dose that provides adequate PK exposure and biologic activity with superior tolerability.

Note: If necessary, alternate dosing schedules can be explored to determine additional biologically active doses even after a RP2D is defined.

4.1.1.1. Food effect Cohort

Once a RP2D is identified, a food effect sub-study may be initiated. It will be an open-label, randomized, single dose, two period, cross over study to investigate the effect of a high-fat, high-calorie meal on the bioavailability of GSK3368715 with a tablet formulation at or near the RP2D. Initiation or completion of this sub-study is not required prior to initiating part 2. GSK3368715 dosing (fed then fasted, or fasted then fed) will be separated by at least 3days. A minimum of 12 participants in the United States may be enrolled in the sub-study. A participant requiring dose reduction or discontinuation from study before completion of at least 48 hours after dosing in fasted/fed state in the sub-cohort will be replaced by a new participant. All participants enrolled to the sub-study, on completion of their participation in this segment of the study, will continue on a daily dosing schedule until discontinuation criteria are met, as described in Section 7.1.

The food effect sub-study will be open to participants with histologically- or cytologically confirmed solid malignancies as described for Part 1 in Section 5.1.

The high-fat (approximately 50% of the total caloric content of the meal), high-calorie meal (approximately 800 to 1000 calories) will be the representative example given by the 2002 US Food and Drug Administration (FDA) guidance [FDA, 2002]. Additional details of the required meal will be provided in the SRM.

Participants enrolled in the sub-study will be assigned to one of two sequences, as described in Table 5; equal numbers will be assigned to each sequence. The schedule of visits for participants enrolled in the sub-study is detailed in Table 4 in Section 1.3. Upon completion of the sub-study, all participants will continue to undergo scheduled assessments as described in Table 2. Additional details, including the process of sequence assignment, will be provided in the SRM.

Table 5 Food Effect Sub-Study

Food effect cohort (single dose administrations)			
Sample size	Sequence	Period 1 (W1D1)	Period 2 (W1D4/D5)
6	1	Fasted	Fed
6	2	Fed	Fasted

Fasted: Participants should take nothing by mouth apart from water and other medications for at least 8 hours prior to dosing and should continue fasting until at least 4 hours after administration of the morning dose. Participants should be administered the drug product with 240 mL (8 fluid ounces) of water. Water will be allowed as desired except for one hour before and after drug administration. Participants will receive standardized meals approximately 4 and 10 hours post dose.

Fed: Following an overnight fast (at least 8 hours), participants should start the recommended high fat, high calorie breakfast 30 minutes prior to administration of the drug product. Study participants should eat this meal in 30 minutes or less; however, the drug product should be administered 30 minutes after start of the meal. The drug product should be administered with 240 mL (8 fluid ounces) of water. No food should be allowed for at least 2 hours post-dose. Water will be allowed as desired except for one hour before and after drug administration.

4.1.2. Part 2: Expansion Cohorts

Part 2 (Dose Expansion) will start after the RP2D is determined in Part 1.

The intention of Part 2 is to (i) collect additional information on the safety and PK/PD characteristics of GSK3368715 and (ii) to evaluate the clinical activity of GSK3368715 in selected disease populations.

Part 2 will consist of two expansion cohorts:

- **Expansion Cohort 2A:** Up to 36 participants with DLBCL will be enrolled. Based on the assumed prevalence of MTAP deletions, it is expected that ~ 23 % of participants (or ~ 8 out of 36 participants) will present with DLBL deficient of MTAP.

  For DLBCL cohort (Part 2A), this cohort will be evaluated separately from the solid tumor cohorts (Part 2B). A Bayesian adaptive design based on hierarchical model will be used to allow interim monitoring of the response rate and allow information borrowing between the MTAP defined subgroups within the cohort. The interim futility analysis will be performed every 2-3 months with minimum of 5 additional evaluable participants from the entire cohort. The first interim futility analysis will be performed when at least 5 participants become evaluable from each of the MTAP defined subgroups. Data from both subgroups will be included in the analysis to form the Bayesian hierarchical model. Any subgroup with posterior probability of ORR > 10% sufficiently low (<20%) will be declared as ineffective and terminated for enrollment according to the design.

- **Expansion Cohort 2B:** Up to 105 participants with pancreas cancer, NSCLC, and bladder cancer, will be enrolled. The number of participants with a specific tumor histology in this cohort will is not fixed but will ultimately not exceed 35 participants of any specific tumor histology.

  The three tumor histologies were selected on the basis of the higher frequency of MTAP deletions which is assumed to be ~ 30% in pancreatic cancer, ~27-32% in bladder cancer, and ~9-28% in NSCLC.

  A Bayesian adaptive design based on hierarchical model will be used to allow interim monitoring of the response rate in this expansion cohort on ongoing basis. The design will also allow information borrowing across the three different histologies as well as between the MTAP defined subgroups within each histology. Participants enrolled in Part 1 who were treated at the RP2D of GSK3368715 and have the same disease histology as required for Expansion Cohort 2B will be included in the analyses as appropriate.

  The first interim futility analysis will be performed when at least 5 participants become evaluable from MTAP proficient subgroup within any cohort. Data from all participants across all tumor types in part 2B will be included in the analysis to form the Bayesian hierarchical model. Details about the futility rules are specified in Section 9.4.2.1.

MTAP-Testing for Expansion Cohort 2A and -2B: Homozygous deletion of the tumor suppressor protein p16 (CDKN2A) on chromosome 9p21 is prevalent in cancer (in ~ 15-40% of all cancers) and commonly (in more than 90% of instances [Huang, 2009; Kirovski, 2011; Su, 2014]) involves co-deletion of the adjacent gene for MTAP.

Because of the high frequency and prognostic relevance, molecular testing for p16 (CDKN2A)-deletion is commonly conducted and p16 is a marker present on most molecular panels. Local molecular testing for p16 (CDKN2A) deletion will be utilized to prospectively stratify the Part 2 population; and will be followed by retrospective central confirmatory MTAP-deletion testing.

It is expected that participants whose tumor harbors an MTAP-deletion or wild-type MTAP are equally represented in the 2 expansion cohorts. In expansion cohorts, the intention is to stratify enrollment such that approximately 50% of participants within each of the three solid tumor types and the DLBCL cohort have an MTAP deletion.

In order to achieve the expected number of participants whose tumor harbors a MTAP-deletion, prospective MTAP testing may be implemented if the local p16 (CDKN2A) testing does not deliver the required number of enriched participants in concordance with the retrospective MTAP testing.

4.1.3. Dose-Limiting Toxicity

All toxicities will be graded using National Cancer Institute – Common Toxicity Criteria for Adverse Events (NCI-CTCAE), version 5.

An AE is considered to be a dose-limiting toxicity (DLT) if the event is considered by the investigator to be clinically relevant and attributed (definitely, probably or possibly) to the study intervention during the first 21 days of intervention and meets at least one of the criteria listed in Table 6.

In addition, there are clear VTE DLT criteria:

- Upon re-initiation of enrolment under Protocol Amendment 3, any cohort in Part 1 with two (2) grade 2 venous thromboembolism (VTE) that requires systemic anticoagulation or ≥ grade 3 VTE in up to 6 participants will be considered not cleared and enrolment at this dose level and higher dose levels will be permanently stopped.
- Upon re-initiation of enrolment under Protocol Amendment 3, any cohort in Part 1 with ≥3 grade 2 venous thromboembolism (VTE) that requires systemic anticoagulation or Grade ≥3 VTEs out of up to 10 participants will be considered not cleared and enrolment at this dose level and higher dose levels will be permanently stopped.
- Upon re-initiation of enrolment under Protocol Amendment 3 at 100mg, dose escalation steps will be considered in maximal steps of 50 mg depending on the pharmacodynamic effects and the safety profile observed in previous cohorts, taking into consideration the updated DLT criteria (see Table 6).
- Grade 2 venous thromboembolism (VTE) that requires systemic anticoagulation or ≥ grade 3 VTE, regardless of investigator assessed causality, will be considered a DLT during the first 8 (± 1) weeks or until study discontinuation (e.g., disease progression), whichever occurs sooner.
- An end of treatment CT image is required if the participant withdraws before the end of the VTE DLT observation period (Table 6).

If an AE is considered related to the underlying disease it is not defined as a DLT.

Table 6 Dose-Limiting Toxicity Criteria

DLT criteria for Non-hematologic Toxicity	
AST or ALT	• Grade 3 • Grade 4 • ALT ≥ 5xULN • ALT ≥ 3xULN persists for ≥ 4 weeks • ALT ≥ 3xULN and bilirubin ≥ 2xULN (>35% direct bilirubin) • ALT ≥ 3xULN and INR >1.5, if INR measured • ALT ≥ 3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity
Nausea	• Grade 3 persisting >3 days despite BSC[a]
Vomiting	• Grade 3 or 4 persisting > 3 days despite BSC[a]
Diarrhea	• Grade 3 or 4 persisting > 3 days despite BSC[a]
Fatigue	• Grade 3 persisting > 5 days
Hypertension	• Grade 3 that cannot be controlled with medical therapy • Grade 4
ECG-change	• > 20 msec extension of the QRS-interval compared to baseline
Laboratory abnormality	• Grade 3 persisting > 3 days despite BSC[a] • Grade 4
Any other	• Grade 2 leading to frequent dose interruptions despite BSC[a] and limiting GSK3368715 dosing to <80% of expected dose • Grade 2 requiring delay of GSK3368715 administration for > 14 days • Grade ≥3

DLT criteria for Hematologic Toxicity	
Neutropenia	• Grade 3 persisting > 3 days despite BSC[a] • Febrile neutropenia • Grade 4
Thrombocytopenia	• Grade 3 persisting > 3 days despite BSC[a] • Grade 3 associated with clinically significant hemorrhage • Grade 4
Any other[b]	• Grade 2 and 3 leading to frequent dose interruptions despite BSC[a] and limiting GSK3368715 dosing to < 80% of expected dose • Grade 3 persisting > 3 days despite BSC[a] • Grade 4
Venous Thromboembolism	• Grade 2 venous thromboembolism (VTE) that requires systemic anticoagulation or VTE Grade ≥3 during the first 8 (± 1) weeks or until study discontinuation (e.g., disease progression), whichever occurs sooner.

ALT=alanine aminotransferase; AST=aspartate aminotransferase; BSC=best supportive care; DLT=dose-limiting toxicity; ECG=electrocardiogram; ULN=upper limit of normal

a. Best supportive care if available, according to institutional standards
b. With the exception of lymphocytopenia

For participants who experience a toxicity that meets the criteria of DLT, administration of GSK3368715 will be held pending management and resolution of the toxicity.

Participants who withdraw from the study before completing 21 days of intervention for reasons other than DLT may be replaced at the discretion of the sponsor.

Guidance for the management of toxicity, including dose modification algorithms, is provided in Appendix 12.

4.1.4. 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. The DEC will be chaired by the GSK medical monitor and membership will include a GSK scientist, GSK pharmacovigilance physician, GSK statistician, GSK pharmacologist, along with additional GSK staff as appropriate and all participating investigators.

In Part 1, 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, as defined in the Dose Escalation Plan. Although the escalation of the GSK3368715 dose will be guided by the N-CRM, the DEC can override this recommendation.

In Part 2, the members from the DEC will continue to routinely assess cumulative safety data as a safety evaluation team. This team may decide to stop further enrolment if intervention-emergent toxicity is determined to result in an unfavourable change in participant risk/benefit.

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

1. Modify the dose escalation of GSK3368715 proposed by the N-CRM based on clinical judgement. *Note:* GSK3368715 dose steps will not exceed 50 mg dose increments under protocol amendment 03.
2. Investigate alternative dosing regimens
3. Modify the timing, frequency, and/or type of safety assessments performed during study conduct
4. Request intervention of additional participants at previously completed dose levels for the purpose of obtaining additional safety, PK, PD, metabolite, or biomarker data (i.e. PK/PD/Metabolite/Biomarker-Cohort).
5. Recommend intra-participant dose escalation allowing participants to be moved from a lower to a higher GSK3368715 dose, not exceeding the MTD if the DEC has declared the next dose cohort as safe
6. 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)
7. Increase the size of an expansion cohort or recommend to add additional expansion cohorts to further characterize the safety and efficacy profile of GSK3368715
8. Halt enrolment into any cohorts as deemed appropriate based on emerging clinical data at any time during the trial.

During Part 1 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. During Part 2 of the study, the DEC will meet approximately after every 10 participants in each expansion cohort have been on study for ≥ 2 cycles.

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

4.2. Scientific Rationale for Study Design

Given the high unmet medical need of relapsed/refractory advanced solid tumors and non-Hodgkin's lymphoma, this two-part Phase I study (207675) is proposed. This study evaluates the safety, tolerability, pharmacology, and preliminary clinical activity of GSK3368715. The study comprises a dose-escalation part to identify the MTD/

recommended expansion dose followed by two expansion cohorts to determine preliminary efficacy.

In Part 1, blood, serum and urine collections will be performed to characterize the pharmacokinetic and pharmacodynamic parameters of GSK3368715.

Cohort(s) of additional participants in Part 1, treated at or close to the expected MTD/RP2D, will be evaluated more extensively for metabolic and biomarker profiling. This cohort will provide samples for biomarker, pharmacodynamic, and metabolite assessment. Analysis of human samples will provide first-hand information on metabolism and disposition of GSK3368715 in humans. In addition to assessing known pharmacodynamic biomarkers, exploratory efforts will be conducted to evaluate the mechanism of action of GSK3368715, and discover novel pharmacodynamic and predictive biomarkers from blood, plasma, and tumor.

A subset of participants in Part 1, treated at or near the RP2D, will be evaluated more extensively to evaluate the effect of food on the pharmacokinetics of GSK3368715 (Section 4.1.1.1). This cohort will provide data that can be used to modify dosing instructions for participants in this and future studies (e.g., GSK3368715 may be taken without respect to food, or GSK3368715 must be taken on an empty stomach).

Once a RP2D dose of GSK3368715 has been identified that is safe, tolerable and demonstrates pharmacodynamic activity, enrolment into Part 2 may begin.

The intent of Part 2 is to evaluate MTAP as a potential selection biomarker in participants exposed to GSK3368715 at the RP2D. MTAP deficiency in tumor tissue will be evaluated as a potential biomarker to select participants for GSK3368715 study intervention and emerging data will be used to adaptively recruit participants based on MTAP status. to achieve approximately 50% of participants within each tumor type having an MTAP deletion.

4.3. Dose Justification

4.3.1. Starting Dose Justification

The starting dose for GSK3368715 has been selected based on preclinical toxicology, pharmacokinetic data from various species and pharmacodynamics (PD) and efficacy data from mouse xenograft tumor models (See IB for the latest information) [GlaxoSmithKline Document Number 2017N334333_02]. In addition, an integrated tumor exposure-PD response model was built to predict efficacious doses.

The Severely Toxic Dose in 10% rats (STD10) as per International Conference on Harmonization (ICH) S9 guidance was 150mg/kg/day for 28 days and the highest non-severely toxic dose (HNSTD) in the dog was 15mg/kg/day for 28 days (GlaxoSmithKline Document Number 2017N334333_02).

Using one tenth of the rat STD10 as per ICH S9 guidance, where STD10 is defined as 150 mg/kg/day administered daily for 4 weeks, translates to 146 mg using the human equivalent dose calculation (60 kg adult with a surface area of 1.62 m^2).

Using one sixth of the dog HNSTD as per ICH S9 guidance, where HNSTD is defined as 15 mg/kg/day administered daily for 4 weeks, translates to 81 mg using the human equivalent dose calculation (60 kg adult with a surface area of 1.62 m^2).

Minimally anticipated biologic effect level (MABEL): Mouse pre-clinical studies in the Toledo xenograft model revealed that tumor growth inhibition was associated with a minimum 30% increase in MMA in tumor tissues at doses of 10 mg/Kg/Day. Based on this, the MABEL exposures were defined as total AUC (0-24) of 1300 ng·hr/ml (free AUC [0-24] of 500 ng·hr/mL). For prediction of human dose which will reach MABEL exposure levels, the human pharmacokinetic parameters were predicted using preclinical PK IV data (mouse, rat and dog) and scaling to the human time and concentration scale using complex Dedrick plots with correction for maximum lifespan potential (Boxenbaum, 1983). The predicted human PK parameters are estimated to be 9.6 mL/min/Kg (Clearance), 25 L/Kg (Steady state volume of distribution), 48 hr (Half-Life) and 49% (Bioavailability). Accounting for higher free fraction in human (% unbound 64.2) relative to mouse (% unbound 35.7), projects human equivalent free MABEL exposures to be reached at 62 mg.

Potential therapeutic doses: An integrated tumor exposure-biomarker response model was utilized to describe the relationship between GSK3368715 tumor exposure and MMA increase in Toledo xenograft studies. Based on the model and predicted human PK, a projected human dose of 250 mg QD/110 mg BID will achieve a 95% increase in MMA induction; 99% increase is projected at doses around 900 mg QD and supports escalation upwards of 250 mg QD.

After considering the potential range of starting doses based on toxicology, pharmacology, and xenograft models, the proposed starting dose of 50 mg once daily was selected. Compared with total exposures observed in the most sensitive species, dogs at HNSTD, the starting dose provided 16- fold and 33-fold safety margins for the steady state AUC and Cmax, respectively.

4.3.2. Dose Justification for Food Effect Sub cohort

Food effect sub-study will be initiated at RP2D with tablets.

Preliminary physiologically based pharmacokinetic (PBPK) modeling suggests that GSK3368715 absorption is not limited by solubility or permeability, and is expected to be not as much affected by food. Further, PBPK modeling to-date and in vitro data from TinyTIM# suggest similar performance between capsules and tablets, and no substantial food effect.

#In-vitro model that mimics dynamic motility, volumes, secretion and digestion in the upper GI tract, designed by TNO/Triskelion [GlaxoSmithKline Document Number 2019N422334_01]

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 intervention 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 of the following criteria apply:

Age:

1. Participant must be ≥18 to years of age inclusive, at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2. Diagnosis of one of the following:

   Part 1 (Dose Escalation and food effect cohort):

   - Histologically- or cytological-confirmed diagnosis of solid tumor malignancy that is metastatic or non-resectable
   - Have received all standard treatment options or are no longer eligible for additional standard treatment options
   - Evaluable disease that may be measured directly by the size of the tumor or can be evaluated by other methods.
   - Availability of a biopsy of the tumor tissue obtained at any time from the initial diagnosis to study entry. Although a fresh biopsy, which is

obtained during screening, is preferred, archival tumor specimen is acceptable if it is not feasible to obtain a fresh biopsy.

For participants in the PK/PD cohort, a fresh biopsy and consent for one on treatment biopsy are required for enrollment.

Part 2 (Dose Expansion):

- **Cohort 2A & 2B:**
  - The availability of archival tumor tissue, or willingness to undergo a fresh biopsy to determine S-methyl-5'-thioadenosine phosphorylase (MTAP) status (any archival tumor specimen must have been obtained within 6 months prior to starting study drug unless approved by the study Medical Monitor). Local MTAP or *CDKN2A* results are acceptable for enrollment but must be confirmed through central laboratory testing.
- **Cohort 2A:**
  - Histologically- or cytological-confirmed diagnosis of Diffuse-large B-cell lymphoma (DLBCL)
  - Relapse or refractory disease after at least 1 but not more than 4 lines of prior therapy
  - At least 1 measurable site of disease according to the Lugano Classification. The site of disease must be greater than 1.5 cm in the long axis regardless of short axis measurement or greater than 1.0 cm in the short axis regardless of long axis measurement, and clearly measurable in 2 perpendicular dimensions.
- **Cohort 2B:**

  Pancreatic Cancer
  - Histologically or cytologically confirmed adenocarcinoma of the pancreas
  - Unresectable, locally advanced (Stage III), or metastatic (Stage IV) disease
  - Relapsed or refractory disease after at least 1 prior line of approved, systemic therapy
  - At least 1 measurable tumor lesion per RECIST 1.1 (Appendix 10)

  Non-small cell lung Cancer (NSCLC)
  - Histologically or cytologically confirmed NSCLC
  - Stage IV disease
  - Tested for presence of EML4-ALK rearrangement
  - Received at least 2 prior lines of approved, systemic therapy, of which 1 therapy has to be a platinum containing regimen.

    or

Failed a first-line platinum-containing regimen in combination with an anti-PD1 monocloncal antibody and refused a second-line regimen despite being informed about the different therapeutic options and their specific clinical benefit by the investigator; the content of this informed consent discussion including the therapeutic options reviewed by the investigator need to be documented and the participant needs to sign a specific consent form

- At least 1 measurable tumor lesion per RECIST 1.1.

Transitional cell carcinoma of the Urothelium

- Histologically or cytologically confirmed transitional cell carcinoma (TCC) of the urothelium (urinary bladder, urethra, ureter or renal pelvis) including mixed pathology with predominantly (i.e., > 50% of the histopathology sample) TCC with the exception of neuroendocrine or small cell carcinoma
- Unresectable, locally advanced (T4b) or metastatic (lymph node or visceral) disease
- Relapsed or refractory disease after at least 1 prior line of approved systemic therapy
- At least 1 measurable tumor lesion per RECIST 1.1.

3. Adequate organ function as defined by:

System	Laboratory Values
Hematologic	
Absolute neutrophil count (ANC)	≥1.5 X 10^9/L
Hemoglobin[a]	Solid malignancy: ≥9 g/dL Non-Hodgkin's Lymphoma: ≥8 g/dL
Platelets[a]	≥100 X 10^9/L
PT/INR and PTT	≤1.5 X upper limit of normal (ULN), unless participant is receiving systemic anticoagulation
Hepatic	
Albumin	≥2 g/dL
Total bilirubin	≤1.5 x ULN **NOTE**: Isolated bilirubin >1.5 X ULN is acceptable if: • bilirubin is fractionated and direct bilirubin <35% OR • participant has a diagnosis of Gilbert's syndrome
Alanine aminotransferase (ALT)	Part 1 and 2: ≤2.5 × ULN Part 2 ONLY: <5 x ULN is acceptable for participants with documented liver metastases/tumor infiltration
Renal	
Calculated creatinine clearance by Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation or measured from 24hr urine	≥ 50 mL/min

Cardiac	
Ejection fraction	≥Lower limit of normal (LLN) by echocardiogram (minimum of 50%) / MUGA
ECG:QTcF[b]	<450 ms

a. Participants that require transfusion or initiation of growth factor support in order to achieve necessary platelet and/or hemoglobin must maintain adequate values for at least 7 days without transfusion or while on growth factor in order to be eligible for participation

b. Baseline QTc interval using Fridericia's formula based on average of triplicate ECGs obtained over a brief recording period.

4. Eastern cooperative oncology group (ECOG) performance status of 0 or 1.
5. Able to swallow and retain orally-administered medication.

Sex

6. **Female Participants**: A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least one of the following conditions applies:

    - Is not a woman of childbearing potential (WOCBP)

      OR

    - Is a WOCBP and using a contraceptive method that is highly effective, with a failure rate of <1%, as described in Appendix 4 during the intervention period and for at least 120 days, corresponding to the time needed to eliminate any study intervention(s) (e.g., 5 terminal half-lives) after the last dose of study intervention. The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

    A WOCBP must have a negative highly sensitive pregnancy test (urine as required by local regulations) within 7 days before the first dose of study intervention.

    Additional requirements for pregnancy testing during and after study intervention are located in Appendix 2.

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

Male Participants: Male participants are eligible to participate if they agree to the following during the intervention period and for at least 100 days, corresponding to time needed to eliminate study intervention(s) (e.g., 5 terminal half-lives) plus 90 days after the last dose of study intervention:

Refrain from donating sperm

Plus either:

Be abstinent from heterosexual or homosexual intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent

OR

Must agree to use contraception/barrier as detailed below

- Agree to use a male condom and should also be advised of the benefit for a female partner to use a highly effective method of contraception as a condom may break or leak when having sexual intercourse with a woman of childbearing potential who is not currently pregnant
- Agree to use male condom when engaging in any activity that allows for passage of ejaculate to another person

Informed consent

7. 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

Prior or Concomitant Diseases:

1. History of malignancy other than the disease under study.

   EXCEPTION NOTE: Participants who have been disease-free for 5 years, or participants with a history of completely resected non-melanoma skin cancer or successfully treated in situ carcinoma are eligible. Participants with second malignancies that are indolent or definitively treated may be enrolled even if less than 5 years have elapsed since treatment. Consult GSK Medical Monitor if unsure whether second malignancies meet requirements specified above

2. Primary central nervous system (CNS) tumors, Glioblastoma multiforme (GBM), symptomatic or untreated leptomeningeal or brain metastases or spinal cord compression.

   EXCEPTION NOTE: Participants previously treated for these conditions that have had stable CNS disease (verified with consecutive imaging studies) for >1months, are asymptomatic and off corticosteroids, or are on stable dose of corticosteroids for at least 1 month prior to study Day 1 are permitted. Stability of brain metastases must be confirmed with imaging. Participant treated with gamma knife therapy can be enrolled 2 weeks post-procedure as long as there are no post-procedure complications/they are stable.

3. Any severe or uncontrolled systemic diseases (e.g., unstable or uncompensated respiratory, hepatic, renal, cardiac disease, or clinically significant bleeding episodes, or active infection).
4. Any serious and/or unstable pre-existing medical, psychiatric disorder, or other conditions that could interfere with participant's safety, obtaining informed consent or compliance to the study procedures, in the opinion of the Investigator.

5. Any clinically significant gastrointestinal (GI) abnormalities that may alter absorption such as malabsorption syndrome or major resection of the stomach and/or bowels.
6. History of known human immunodeficiency virus (HIV) infection or positive HIV test result at screening.
7. Presence of hepatitis B surface antigen (HBsAg) or positive hepatitis C antibody test result at screening to first dose of study intervention.

   NOTE: Participants with positive Hepatitis C antibody due to prior resolved disease can be enrolled only if a confirmatory negative Hepatitis C RNA polymerase chain reaction (PCR) is obtained.
8. Any of the following cardiac abnormalities:
   a) Uncontrolled high blood pressure.
   b) Any history of coronary artery disease, including acute coronary syndromes, myocardial infarction, unstable angina, and history of coronary angioplasty, or stenting
   c) Presence of a cardiac pacemaker or implanted defibrillator.
   d) AV-block (asymptomatic 2nd degree Type II or 3rd degree and any degree AV block if related to heart disease or if symptomatic), RBBB (right bundle branch block), LBBB (left bundle branch block), and any fasicular hemiblocks.
   e) A QRS interval at Screening or Baseline ≥110 msec.
   f) Patients with any symptomatic or sustained arrhythmias (past or present), including but not limited to:
      - Atrial fibrillation.
      - Atrial flutter
      - Ventricular tachycardia
      - Ventricular fibrillation
      - Supraventricular tachycardia
   g) Current or past congestive heart failure.
   h) Evidence of a left ventricular ejection fraction below the institutional lower limit of normal on Screening echocardiogram.
   i) Evidence of significant structural heart disease on echocardiography at Screening (including any valvular disease greater than “mild” in severity)
   j) Cardiac troponin > upper limit of the reference range at Screening.

Prior or Concomitant Anti-cancer Therapies

9. Treatment with any local or systemic anti-neoplastic therapy or investigational anti-cancer agent within 14 days or 4 half-lives, whichever is longer, up to a maximum wash-out period of 28 days prior to initiation of study drug administration

   EXCEPTION NOTE: Anti-androgen therapies for prostate cancer, such as bicalutamide, must be stopped 28 days prior to first dose of GSK3368715. Second-line hormone therapies such as enzalutamide or abiraterone should be stopped 14 days prior to enrolment. Participants with prostate cancer may remain on (i) luteinizing hormone-releasing hormone (LHRH) agonists or antagonists and/or (ii) low-dose prednisone or prednisolone (up to 10 mg/day).

Nitrosureas and mitomycin C must be stopped within 42 days prior to first dose of GSK3368715.

10. Allogeneic hematopoietic stem-cell transplantation
11. Toxicities from previous anti-cancer therapies have not resolved to baseline or NCI-Common terminology criteria for adverse events (CTCAE) v5 ≤ Grade 1 (except fatigue and alopecia [permissible at any grade] and peripheral neuropathy [which must be ≤ Grade 2]) at the time of starting study intervention.

Prior or Concomitant Therapies:

12. Major surgery (i.e. requiring general anesthesia) within 3 weeks before screening, or not fully recovered from major surgery, or major surgery planned during study participation

    EXCEPTION NOTE: Planned surgical procedures to be conducted under local anesthesia are allowed.

13. Prior organ transplantation
14. Current use of a prohibited medication or planned use of any forbidden medications during intervention with GSK3368715
15. History of sensitivity to any of the study medications, or components thereof or a history of drug or other allergy that, in the opinion of the investigator or Medical Monitor, contraindicates their participation.
16. Participant is considered high-risk for VTE as defined by either Khorana Score of ≥3 (see Appendix 13), or prior medical history of VTE. Note: Participants with Khorana score of 2 should be considered for prophylactic anticoagulation per current ASCO guidelines (Key, 2019) if deemed appropriate by the investigator.

5.3. Lifestyle Restrictions

5.3.1. Meals and Dietary Restrictions

On serial PK days (Day 1, Day 8 and Day 15), participants should fast from 8 hours prior to dose until 2 hours after dose. On all other days, GSK3368715 should be administered on an empty stomach at approximately the same time of day (± 4 h), with no food for 1 hour before and 2 hours after each dose. Requirements for fasting before and after dosing may be modified based on available PK, PD and safety data. The exact timing of the meals administered will be recorded on serial PK days.

On serial PK days, 8 and 15 and for two days prior to each serial PK day other than Day 1 (Days 6 and 7 and 13 and 14), participants should attempt to take GSK3368715 within a 1 hour window (i.e., 23-25 hours) after the last dose.

Participants will abstain from alcohol, tobacco, caffeine- or xanthine-containing products (eg, coffee, tea, cola drinks, and chocolate) for 24 hours before the start of dosing until after collection of the final PK and/or PD sample on Day16. In addition, participants should also abstain from ingesting these products prior to clinic visits on days scheduled for periodic PK and PD sample collection throughout the study.

Refrain from consumption of red wine, seville oranges, grapefruit or grapefruit juice for at least 24 hours before the start of study intervention until after the final dose.

For participants in the food effect sub-study, the administration of GSK3368715 on the ‘fed’/’fasted’ days will be performed as described in Section 4.1.1.1. For all other days, it will be administered as described above.

5.4. Screen Failures

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

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once. Rescreened participants should be assigned the same participant number as for the initial screening if rescreening for same arm of study. Please refer to the Study Reference Manual for more details.

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

The participants in each cohort will receive GSK3368715 orally, administered as either a capsule or tablet formulation (please refer to Section 1.2 and Section 1.3 for more detail).

During the DLT observation period, participants will only receive capsules, and may receive the tablet formulation if the participant continues on treatment at the end of Part 1.

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Table 7 Study intervention

ARM Name	GSK3368715
Intervention Name	N/A
Type	Drug
Dose Formulation	1. API in Hydroxypropyl Methylcellulose (HPMC) Capsule 2. Immediate release (IR) white film-coated tablet containing API and excipients
Unit Dose Strength(s)	1. Capsule: 25 mg, 100 mg, 250 mg as free-base drug substance 2. Tablet: 50 mg, 100 mg and 250 mg as the free-base drug substance
Dosage Level(s)	As required by protocol
Route of Administration	Oral
IMP and NIMP	IMP (GSK3368715)
Sourcing	Provided centrally by the Sponsor
Packaging and Labelling	Study intervention will be labelled as required as per country requirement
Current/Former Name(s) or Alias(es)	N/A

6.2. Dose Modification

Safety management guidelines, including dose modification algorithms, are provided. Please note, in cases where the investigator is directed to permanently discontinue study intervention, these instructions are mandatory as described in Section 7.

An overview of the available dose modification guidelines is presented in Appendix 12.

All AEs are to be graded according to NCI-CTCAE, version 5. All dose modifications and the reason(s) for the dose modification must be documented in the eCRF.

Investigators should refer to the IB for GSK3368715 [GlaxoSmithKline Document Number 2017N334333_02] and for additional information regarding the background of the drug and the management of other AEs or potential safety-related issues.

In case a dose modification is necessary, the dose level of one or both study interventions may be changed as determined by the investigator and sponsor/medical monitor.

6.3. Method of Intervention Assignment

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 of 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.

6.4. Blinding

This is an open-label study.

6.5. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
3. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
4. Further guidance and information for the final disposition of unused study intervention are provided in the SRM.

5. Under normal conditions of handling and administration, study intervention is not expected to pose significant safety risks to site staff. Precaution will be taken to avoid direct contact with the study intervention.
6. A Material Safety Data Sheet (MSDS) describing occupational hazards and recommended handling precautions will be provided to the investigator. In the case of unintentional occupational exposure notify the monitor, Medical Monitor and/or GSK study contact.

6.6. Intervention Compliance

At each visit, an evaluation of participant compliance with taken medication will be performed. The investigator will make every effort to bring non-compliant participants into compliance.

Compliance with GSK3368715 and other study interventions provided will be assessed through querying the participant during the site visits and documented in the source documents and eCRF.

A record of the number of GSK3368715 capsules and other study interventions dispensed to and taken by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention interruptions and/or dose reductions will also be recorded in the eCRF.

6.7. Concomitant Therapy

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 enrolment or receives while on study intervention and for 30 days after last dose 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.

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

Participants will be instructed to inform the investigator prior to starting any new medications from the time of first dose of study intervention until the end of the study (Final Study Visit).

A complete list of all prior anti-cancer therapies will be recorded in the eCRF.

If future changes are made to the list of permitted/prohibited medications, formal documentation will be provided by GSK and stored in the study file. The SRM will be

updated to include this information. Any such changes will be communicated to the investigative sites in the form of a letter.

The prophylactic use of low molecular weight heparin and oral anticoagulation using Factor Xa inhibitors such as Apixaban and Rivaroxaban is allowed on trial. Current ASCO 2019 Guidelines (Key, 2019) and the bleeding risk associated with above agents should be considered.

If a participant experiences a VTE and requires therapeutic anticoagulation, treatment should be initiated without delay following best medical practice, GSK3368715 should be held and the situation should be discussed with the GSK medical monitor (see Appendix 12, Table 14).

6.7.1. Prohibited Medications/Therapy

- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Radiotherapy (strictly palliative radiotherapy while on study treatment may be acceptable if discussed with and approved by the sponsor).
- Investigational interventions other than with GSK3368715.
- Anticoagulation with oral Vitamin K antagonists such as Warfarin.

6.7.2. Cautionary Medications

Co-administration of GSK3368715 and substrates of CYP2D6 should be avoided in order to prevent inadvertent over-exposure to these agents. GSK3368715 inhibits CYP2D6 in vitro (IC50 = 22.6 uM), indicating a potential for interaction between GSK3368715 and CYP2D6 substrates.

No *in vitro* CYP phenotyping data are available for GSK3368715. In the absence of these data, potent inhibitors or inducers of CYP3A4 isoenzymes should not be co-administered with GSK3368715.

6.8. Intervention After the End of the Study

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

Refer to SOA (Section 1.3) for follow-up assessments of participants who are to be followed for disease progression and/or survival after they permanently discontinue from study intervention.

6.9. Dose Delay

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. The procedures at the next scheduled visit

should be performed. Participants with dosing delays equivalent to 14 consecutive missed doses should discontinue study intervention(s) unless the treating investigator and Sponsor agree there is strong evidence supporting continued intervention.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

Participants will receive study intervention until one of the following events occur earlier: disease progression (as determined by Appendix 10), death or unacceptable toxicity, including meeting stopping criteria for liver chemistry or cardiac parameters defined in Section 7.1.1 and Section 7.1.2.

7.1. Discontinuation of Study intervention

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

- Deviation(s) from the protocol
- Request of the participant or proxy (withdrawal of consent by participant or proxy)
- Investigator's discretion
- Participant is lost to follow-up
- Study is closed or terminated.
- Criteria described in Section 6.9 (Dose Delay)
- Female participant who becomes pregnant while on study intervention
- Criteria for discontinuation of study intervention(s) as described in Section 6.2 (Dose Modification Guidelines) have been met
- Criteria described in Section 7.1.2 and Section 7.1.3 (QTc or QRS Stopping Criteria and LVEF Stopping Criteria) have been met
- Criteria described in Section 7.1.4 (Stopping Rules for Clinical Deterioration) have been met

If study intervention is permanently discontinued, the participant will remain in the study to be evaluated for safety and efficacy. See the SOA for data to be collected at the time of discontinuation of study intervention. The assessments required at the TDV should be completed within 30 days of the last dose of study intervention(s). The primary reason study intervention was permanently discontinued must be documented in the participant's medical records and electronic case report form (eCRF).

All participants who permanently discontinue study intervention(s) without disease progression will be followed for progression according to the protocol schedule until

- New anti-cancer therapy is initiated
- Disease progression
- Death, or
- Participant has been followed for 2 years after stopping intervention.

All participants who have disease progression will be followed for survival and new anti-cancer therapy (including radiotherapy). Survival follow-up will continue from the time of study drug discontinuation until the earliest of the following: 1.) death or 2.) a maximum time period of 2 years has passed after discontinuing study intervention or 3.) study is closed for further follow-up (expected when70% of participants in the last part of the study have progressed or died). If participants are unable or unwilling to attend clinic visits during follow-up, contact to assess survival may be made via another form of communication (e.g., phone, email, etc.).

If the participant voluntarily discontinues from intervention due to toxicity, ‘adverse event (AE)’ will be recorded as the primary reason for permanently discontinuation on the eCRF.

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

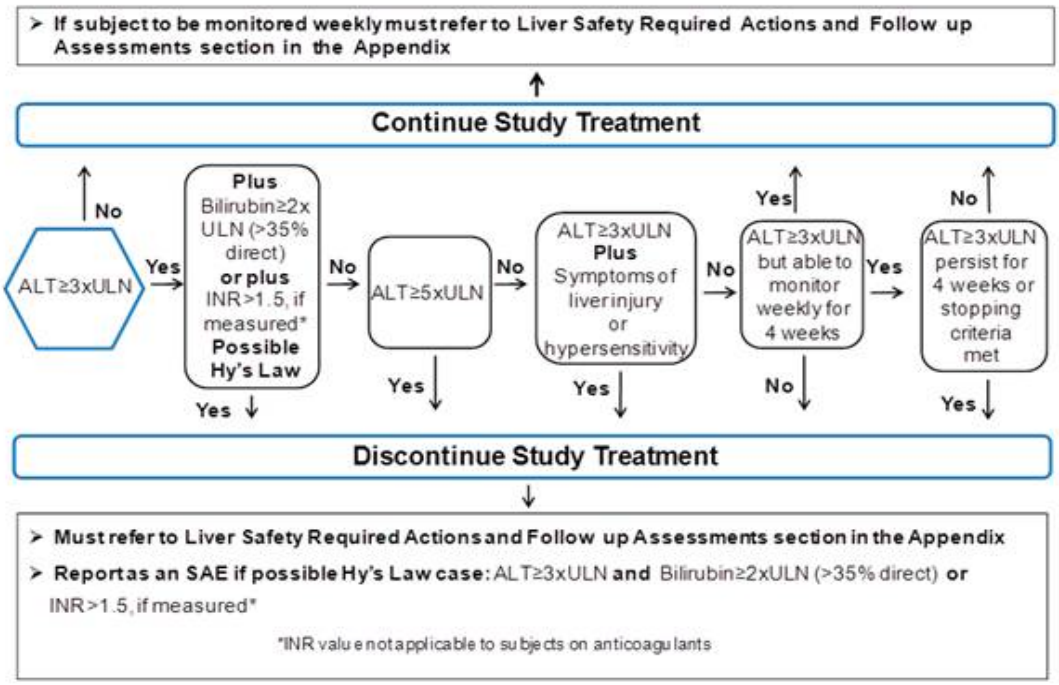
All participants who discontinue from study intervention will have safety assessments at the time of discontinuation and during post-study intervention follow-up as specified in Schedule of Activities Table (see Section 1.3).

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 the conditions outlined in Figure 3.

Figure 3 Liver Chemistry Stopping Criteria



Liver Safety Required Actions and Follow-up Assessments Section can be found in Appendix 6.

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:

- 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

Refer to Appendix 6 for full guidance.

7.1.2. QTc Stopping Criteria

For trial eligibility and discontinuation, ideally the same QT correction formula will be used for *all* participants within a single trial. However, GSK does recognize that because multiple sites from different countries may participate in a single trial, this may not always be possible since QT correction formulae pre-programmed by different manufacturers within ECG machines tend to vary. In these situations, the same QT correction formula must be used throughout the trial for an individual participant.

- QTcF > 500 msec

OR

- Change from baseline of QTc > 60 msec

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.

The QTc should be based on single or averaged QTcF values of triplicate electrocardiograms obtained over a brief (e.g., 5-10 minute) recording period.

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

7.1.3. QRS Interval Stopping Criterion

An increase in the QRS interval of > 20 ms from baseline.

7.1.4. PR Interval Stopping Criteria

An increase in the PR interval to >250 msec in participants without pre-existing AV-block.

Stopping Rules for Clinical Deterioration

In order to adequately assess the antitumor effect of epigenetic agents, participants experiencing apparent progression as defined by RECIST version 1.1 guidelines may continue to receive intervention until progression is confirmed at the next imaging assessment at least 4 weeks later as indicated by RECIST 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 intervention. Participants who had documented reduction in tumor size or a prolonged period of stable disease may be eligible for additional intervention with GSK3368715 at the time of relapse/progression if determined to be deriving clinical benefit in the opinion of the investigator and with sponsor approval.
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 intervention or managed by supportive care (e.g., bisphosphonates and/or bone directed radiotherapy, thoracentesis, or paracentesis for accumulating effusions), study intervention should be discontinued. The decision to stop intervention 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 include, but are not limited to the following:

- ECOG PS decrease of at least 2 points from baseline
- 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
- 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, or may be withdrawn at any time at the discretion of the investigator for safety, behavioural, compliance or administrative reasons.
- The participant will be permanently discontinued both from the study intervention and from the study at that time.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.
- At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA. Refer to the SoA (Section 1.3) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

7.3. Lost to Follow-Up

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

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, three 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.

7.4. Participant and Study Completion

A participant will be considered to have completed the study if they are evaluable with regard to the primary endpoint, and are no longer being followed for progression or survival. Specifically:

A participant enrolled in Part 1 will be considered to have completed the study if they are DLT-evaluable, i.e.:

- they complete screening assessments, at least 21 days of study intervention and the post-intervention follow-up visit, or
- they discontinue study intervention before Day 21 due to drug related toxicity. Participants who discontinue study intervention before day 21 or who received less than 75% of the intended dose in the first 21 days for reasons other than study drug related toxicity are not considered to have completed the study.

Participants enrolled in Part 2 will be considered to have completed the study if:

- they have completed at least 1 interpretable disease assessment

Participants who do not meet the above criteria and are no longer being followed for progression or survival are considered to have discontinued the study.

The End of Study eCRF should only be completed when a participant is no longer being followed.

The study may be considered completed for purposes of a final analysis when 70% of participants enrolled in Part 2 have progressed or died. If available, participants continuing on intervention at the time of final analysis may be offered the option to continue in a rollover trial.

8. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the SoA (Section 1.3 Table 1-Table 3). A brief description of the assessments is provided below. Further details on important assessments and any study-specific equipment are provided in Study Reference Manual.

- 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 (eg, 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, then 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 institutional review board (IRB)/ independent ethics committee (IEC) will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the informed consent form.
- No more than 500 mL of blood for the purposes of this study, will be collected over the first 12 weeks of the study. No more than 120 mL of blood will be collected at each dosing visit, thereafter. The total volume will depend on how long the participant remains on intervention. There may be additional blood collection performed for non-study reasons.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1. Efficacy

- Disease assessment modalities may include imaging (e.g., computed tomography [CT] scan, magnetic resonance imaging [MRI], bone scan, plain radiography) and physical examination (as indicated for palpable/superficial lesions).
- The baseline disease assessment will be completed within 4 weeks prior to the first dose of GSK3368715, then after 8 weeks of dosing (week 9 day 1) and every 8 weeks thereafter until the end of week 32 then every 16 weeks, until disease progression. See the SoA (Section 1.3 Table 2) for the schedule of assessments of anticancer activity.
- Assessments must be performed on a calendar schedule and should not be affected by dose interruptions/delays.
- For post-baseline assessments, a window of ±7 days is permitted to allow for flexible scheduling. If the last radiographic assessment was 8 weeks or more prior to the participant's withdrawal from study intervention and PD has not been documented, a disease assessment should be obtained at the time of withdrawal from the study intervention.
- Participants whose disease responds (either complete response [CR] or partial response [PR]) should have a confirmatory disease assessment performed at least 4 weeks after the date of assessment during which the response was

demonstrated. More frequent disease assessments may be performed at the discretion of the investigator.

- To ensure comparability between the baseline and subsequent assessments, the same method of assessment and the same technique will be used when assessing response.

8.1.1. Evaluation of Anti-Cancer Activity – Participants with Solid Tumors

Lesion assessment method and timing, evaluation of disease, disease progression and response criteria will be conducted according to RECIST (version 1.1) [Eisenhauer, 2009] as outlined below and in Appendix 10 of this protocol.

8.1.2. Evaluation of Anti-Cancer Therapy – Participants with Non-Hodgkin's Lymphoma

Response will be assessed by the investigator every 8 weeks, as outlined in the SoA (Section 1.3 Table 2), using standardized Lugano, as described in Appendix 10.

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Section 1.3).

8.2.1. Physical Examinations

- A full physical examination will be done at screening and will include, at a minimum, assessments of the Cardiovascular, Respiratory, Gastrointestinal and Neurological systems. Height and weight will also be measured and recorded.
- A brief physical examination will be done at all other timepoints and will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.2.2. Vital Signs

- Vital signs will be measured in a semi-supine position after 5 minutes rest and will include temperature, systolic and diastolic blood pressure, and pulse
- In the case of an abnormal first reading, three readings of blood pressure and/or pulse rate must be taken, whereby the first reading should be rejected and the second and third averaged to give the measurement to be recorded in the eCRF.
- Vital signs will be measured more frequently of warranted by the clinical condition of the participant.
- On days where vital signs are measured multiple times, temperature does not need to be repeated unless clinically indicated.

- If a participant develops a fever, refer to Appendix 12 for management guidelines.

8.2.3. Electrocardiograms

Triplicate 12-lead ECG will be obtained as outlined in the SoA (Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. Refer to Section 7.1.2 for QTc withdrawal criteria and additional QTc readings that may be necessary. In cases with equivocal findings a site cardiologist may aid in determining eligibility.

- At each time point at which triplicate ECG are required, three individual ECG tracings should be obtained as closely as possible in succession, but no more than 2 minutes apart. The full set of triplicates should be completed in less than 4 minutes.

8.2.4. Holter Monitoring

Digital Holter ECG data will be obtained from 12-lead continuous Holter monitoring device supplied by the Sponsor. ECG acquisition via the Holter monitoring device will be performed at planned time points indicated in the SoA (Section 1.3) and should be obtained prior to phlebotomy and vital sign time points.

Analysis of intervals and morphology from the continuous digital ECG data will be acquired and stored electronically for all on-intervention timepoints. The 24 hour screening Holter to determine eligibility will be manually over-read by an external central validated ECG laboratory. In cases with equivocal findings a site cardiologist may aid in determining eligibility.

8.2.5. Telemetry

To complement real-time ECG assessments, monitoring for potential adverse arrhythmias will be conducted utilizing continuous telemetry as outlined in the SOA initially for at least 24 hours for the first 10 participants at each dose level > 200mg. If clinically indicated, telemetry may be extended past 24 hours. Participating sites will have trained staff capable of monitoring and responding in real time to any potential cardiac adverse event detected by telemetry. In addition, emergency resuscitation equipment including appropriate pharmacological agents will also be immediately accessible.

8.2.6. Clinical Safety Laboratory Assessments

- Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.
- The investigator must review the laboratory report, document this review, and record any clinically 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.

Laboratory requisition forms must be completed and samples must be clearly labeled with the participant number, protocol number, site/center number, and visit date. Details for the preparation and shipment of samples will be provided by the laboratory and are detailed in the SRM. Reference ranges for all safety parameters will be provided to the site by the laboratory responsible for the assessments.

If additional non-protocol specified laboratory assessments are performed at the institution's local laboratory and result in a change in participant management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification) the results must be recorded in the eCRF.

Refer to the SRM for appropriate processing and handling of samples to avoid duplicate and/or additional blood draws.

8.3. Adverse Events and Serious Adverse Events

The definitions of an AE or SAE can be found in Appendix 4.

AEs will be coded using the standard MedDRA and grouped by system organ class. AEs will be graded by the investigator according to the National Cancer Institute- Common Toxicity Criteria for Adverse Events (NCI-CTCAE), (version 5).

DLTs will be listed for each participant and summarized by dose cohort according to International Data Standards Library (IDSL) standards.

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or the study, or that caused the participant to discontinue the study intervention(s) (see Appendix 3).

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

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

- All AEs will be collected from the start of intervention until the follow-up visit at the time points specified in the SoA (Section 1.3).
- Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the eCRF 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.
- Any SAEs assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product will be recorded from the time a participant consents to participate in a study up to 90 days after the last dose of study intervention(s). if another anti-cancer agent is started during this time, SAEs should be recorded until 30 days after the last dose, or initiation of other anti-cancer agent (whichever is later).
- Investigators are not obligated to actively seek AEs or SAEs in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.
- 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.

8.3.2. Method of Detecting AEs and SAEs

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

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, 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.

8.4. 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, IRB/IEC, and investigators.

- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information e g, summary or listing of SAE) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

8.4.1. Pregnancy

- Details of all pregnancies in female participants will be collected after the start of study intervention and until 150 days after the last dose.
- 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 (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.4.2. Cardiovascular and Death Events

For any cardiovascular events 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 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.

A CV event is defined as:

- 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

8.4.3. 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 a 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 intervention with study intervention(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 intervention with study intervention(s).

8.5. Intervention of Overdose

For this study, any dose of GSK3368715 greater than the daily dose of study intervention within a 24-hour time period [± 4 hours] will be considered an overdose.

There is no specific antidote for overdose with GSK3368715. 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.

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

1. Contact the Medical Monitor immediately.
2. Closely monitor the participant for AE/SAE and laboratory abnormalities until GSK3368715 can no longer be detected systemically (at least 28 days).
3. Obtain a plasma sample for PK analysis as soon as possible from the date of the last dose of study intervention if requested by the Medical Monitor (determined on a case-by-case basis).
4. Document the quantity of the excess dose as well as the duration of the overdosing in the CRF.

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

8.6. Pharmacokinetics

All participants enrolled in Part 1 (dose escalation/food effect) will receive a single dose on Day 1 and then begin continuous dosing after collection of the 72 hour PK sample. The timing of the PK samples may be altered and/or additional PK samples may be obtained at additional points to ensure thorough monitoring.

For details of PK sample collection, please refer to Section 1, Table 2.

Day 1: participants will be administered GSK3368715 as a single oral dose followed by a 72 hour intervention-free period to evaluate PK. PK samples following Day 1 dose will be collected at Pre-dose, 15 ± 5 min, 30 ±5 min, 1h ± 5 min, 1.5h ± 5 min, 2h ± 10 min, 3h ± 10 min, 4h ± 10 min, 6h ± 30 min, 8h ± 30 min, 12 ±2h, 24 ±2h, 48 ± 2h, 72 ± 2 hrs post-dose.

Day 8: PK samples will be collected at Pre-dose, 1.0h± 5 min, and 4h ± 10 min post-dose.

Day 15: PK samples will be collected at Pre-dose, 30 ±5 min, 1h ± 5 min, 2h ± 10 min, 3h ± 10 min, 4h ± 10 min, 6h ± 30 min, 8h ± 30 min, 12 ±2h, and 24 ±2h (prior to the next dose) post-dose.

PK samples on other visit days should be collected pre-dose only. All pre-dose PK samples at each visit should be collected within 1 hour prior to dose administration.

For details of PK sample collection for the PK/PD cohort in Part 1, please refer to Section 1.3, Table 3.

For details of PK sample collection during the food effect cohort in Part 1, please refer to Section 1.3, Table 4.

Meal times will be recorded on all PK collection days for Part 1 (dose escalation and PK/PD cohort) and on the dosing days (Days 1 and 5) in the food effect cohort.

Whole blood samples of approximately 2 mL will be collected for measurement of GSK3368715 and its metabolites as specified in the SoA. Blood may be collected at additional time points during the study if warranted and agreed upon between the investigator and the sponsor. Instructions for the collection and handling of biological samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded. Details of PK blood sample collection, processing, storage and shipping, procedures will be provided in study reference manual (SRM).

Urine samples for quantitative analysis of GSK3368715 will be collected after single dose and at steady state. The actual date, time of volume of each urine sample collection will be recorded. The urine samples may also be analysed for compound-related metabolites and the results will be reported under a separate DMPK protocol.

Quantitative analysis of GSK3368715 from tumor samples collected pre-dose and on-intervention from a limited number of participants will be performed as indicated in the SoA (Section 1.3).

8.7. Pharmacodynamics

8.7.1. Whole Blood

Whole blood samples will be collected for measurement of ADMA-hnRNP-A1 in peripheral blood mononuclear cells (PBMCs) and circulating free ADMA, SDMA and/or MMA levels in plasma as indicated in the SoA.

8.7.2. Tumor Biopsy

Tumor samples will be collected pre-dose and on-intervention from a limited number of participants for measurement of ADMA-hnRNP-A1, gene expression and immune markers such as, but not limited to, CD8 as indicated in the SoA (Section 1.3).

8.7.3. Tumor Biopsy Collection/Surgical Procedures

Biopsies collected during the study will only occur after participant consent and at dose levels deemed relevant in terms of safety and efficacy. Suitable participants will be identified by investigator and deemed acceptable by Medical Monitor. Fresh pre-treatment and on intervention biopsies are required for participants in PK/PD cohorts and optional for all other participants. During the study, it is expected that fresh biopsies will be provided pre-dose (within 14 days of the first dose), and at steady state (anticipated to be between Day 15 and Day 20) following GSK3368715 intervention. Additional optional timepoints include end of study and remission, especially if there is a question of residual viable tumor. No more than 4 fresh biopsies will be collected per participant as part of this study. Any fresh on-intervention biopsy should be accompanied by a plasma sample for PK analysis collected as close as possible to the time of biopsy (preferably within 1 h)

Participants undergoing fresh biopsies must have a platelet count of $\geq$75,000/mm^3 and a PT, international normalized ratio (INR) and aPTT that are within normal limits and taken within 48 hours prior to the post-dose biopsy or any other planned surgical procedure. Further details regarding sample type and processing will be provided in the SRM.

8.8. Genetics

Information regarding genetic research is included in Appendix 5.

A 6 mL blood sample for DNA isolation will be collected from participants who have consented to participate in the genetics analysis component of the study. Participation is optional. Participants who do not wish to participate in the genetic research may still participate in the study.

In the event of DNA extraction failure, a replacement genetic blood sample may be requested from the participant. Signed informed consent will be required to obtain a replacement sample unless it was included in the original consent.

Details on processes for collection and shipment and destruction of these samples can be found in SRM.

8.9. Biomarkers and Translational Research

8.9.1. Samples

After completion of the clinical trial and/or during the conduct of the study, investigations may be performed on samples collected during the trial to detect factors or profiles that correlate with response to intervention with GSK3368715. Performance of these investigations may be conditional on the results of the clinical trial and samples will be selected for analysis on the basis of the clinical outcome.

Samples may be tested for immunophenotyping to evaluate the association with efficacy in response to intervention with GSK3368715. Additionally, comparative examination of post-dosing profiles in conjunction with pre-dosing profiles may yield known and novel candidate biomarkers/profiles and new insights which relate to the action of GSK3368715.

All samples will be retained for the length of time described in participant ICFs after the last participant completes the trial.

Novel candidate biomarkers and subsequently discovered biomarkers of biological response associated with lymphoma and solid tumors and/or the action of GSK3368715 may be identified by application of:

- DNA, RNA and protein analysis of tumor tissue.
- DNA, RNA and protein analysis of PBMCs.
- Circulating protein analysis of plasma.
- Immunophenotyping of PBMCs and/or tumor tissues.
- Coagulation markers from plasma and serum samples

Blood samples will be collected according to the SoA (Section 1.3). One or more timepoints could be removed with emerging data.

8.9.2. Exploratory Tumor Biomarker Analysis

To further characterize the participant population, DNA, RNA and/or protein measurements may be utilized to identify predictors of sensitivity or resistance to GSK3368715 utilizing baseline tissue (archival tissue or a recent biopsy) and in tissue obtained at disease progression.

8.9.3. Circulating Protein Analysis

Blood-based markers have the important advantage that specimens are readily available, simple to prepare and store, and can be obtained prior to and during intervention. This allows for the assessment of predictive markers based on the baseline evaluation as well as markers of activity and resistance based on changes that occur during and/or after intervention. Additionally, levels of protein in plasma samples may be analyzed to better understand modulation of secretory proteins from the tumor or the immune system in response to intervention with GSK3368715 and how this correlates with efficacy. For instance, plasma samples collected at the time points provided in the SoA may be analyzed for Interferon gamma (IFN-gamma) and Tumor Necrosis Factor (TNF-alpha) signatures by investigating a panel of pro-inflammatory cytokines, immuno-regulatory factors and chemokines.

8.9.4. MTAP testing

A requirement for inclusion in the study is the availability of archival tumor tissue, or willingness to undergo a fresh biopsy to determine MTAP status.

In part 1, MTAP testing will be performed retrospectively.

In Part 2, prospective MTAP testing is required to confirm MTAP deficiency for enrolment unless local MTAP or *CDKN2A* results are available. In this latter situation, central MTAP testing will be used to confirm MTAP deficiency.

Additionally, SDMA IHC may be conducted to correlate MTAP expression level and SDMA level with response.
Screen failure tissue, used for central testing will be retained. This tissue may be used in the validation of potential diagnostic assays to detect MTAP.

8.9.5. Coagulation markers

Markers of hemostasis will be assessed and monitored over time to better understand the potential mechanism leading to venous thromboembolic (VTE) events. Analytes of interest may include, but not limited to, D-dimer, fibrinogen, soluble P-selectin and several factors from the extrinsic and intrinsic coagulation pathways, such as factors II, V, VII, VIII, IX, X, XI and XI and von Willebrand Factor..

8.10. Patient Reported Outcomes (PRO)

8.10.1. Qualitative Telephone Interviews

To further evaluate disease and intervention related symptoms and associated impacts on function and health-related quality of life, participants in Part 2 only, will participate in a qualitative interview conducted via telephone. The interview will be conducted by a trained interviewer in the participant’s native language and will be audio recorded for transcription and analysis.

The telephone interview is to be completed within 21 days following completion of the week 8 disease assessment and following the intervention discontinuation visit in Part 2 of the study. Participants who have the intervention discontinuation visit (TDV) within 30 days of the week 8 interview are not required to repeat the interview.

9. STATISTICAL CONSIDERATIONS

9.1. Hypotheses

9.1.1. Dose Escalation

With respect to the primary objectives and endpoints, no specific statistical hypotheses are being tested in Part 1. The primary focus will be on determining the RP2D for further exploration, based upon the safety, PK, food effect on PK and efficacy profiles of GSK3368715.

9.1.2. Dose Expansion

The primary goal of Part 2 is to evaluate clinical activity in each disease specific cohort for GSK3368715 for MTAP- subgroup and MTAP+ subgroup separately.

All evaluations in Part 2 are designed to exclude a 10% response rate representing best available therapy in favour of a 30% response rate.

9.2. Sample Size Determination

The sample size for each part of the trial was chosen to adequately characterize the safety, clinical activity, PK, and pharmacodynamic marker data based on the objectives of each part of the study.

Part 1 will enroll approximately 60 participants. Dose escalation and de-escalation decisions will be guided by an N-CRM model. In Part 1 where an N-CRM design is utilized it is assumed that approximately 50 participants will complete the DLT evaluation period. Approximately 10 participants will be enrolled at a dose or doses near the MTD/RP2D in each PK/PD/Biomarker cohort. At least twelve (12) participants will be enrolled in the food effect sub cohort as per the minimum sample size recommendation from FDA food effect guidance. For both Cmax and AUClast, a total sample size of 12 patients achieves 80% power at a 10% significance level when the actual ratio of the means in the presence or absence of food is 1.0, if the coefficient of variation (COV) on the original, unlogged scale is 0.206, and the equivalence limits of the mean ratio are 0.80 and 1.25; if the COV on the original, unlogged scale is 0.334, the equivalence limits of the mean ratio will be 0.70 and 1.428 to achieve the same level of power.

In Part 2, a maximum of 36 participants will be enrolled in the DLBCL cohort and up to 35 participants will be enrolled in each of the solid tumor cohorts. If all cohorts enroll the maximum number of participants, this will result in 141 participants in total.

Additional tumor-specific cohort(s) and combinations may be added by protocol amendment, based upon emerging pre-clinical data, or clinical data from the dose-escalation portion of the study.

9.2.1. Dose Escalation

N-CRM design is a type of Bayesian adaptive dose-escalation approach. The design classifies the DLT rate into four categories and makes dose recommendations based on posterior distribution of the four categories:

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

At the end of DLT observation period for each dose level, the posterior distribution of DLT rate will be summarized by the posterior probability of the DLT rate falling into the interval of under-dosing, target toxicity, excessive toxicity, and unacceptable toxicity respectively. The recommended dose is the one that maximizes the probability of target toxicity while controlling the probability of excessive or unacceptable toxicity no more than 25%.

9.2.1.1. Operating characteristics of the safety stopping rule for VTE events in dose escalation

Simulations were used to evaluate the design performance of the safety stopping rules planned for the safety evaluation of VTE events during the dose escalation phase (Part 1) of this study. In these simulations, we simulate 100,000 independent trials and evaluate the performance of the model on average. In each simulation, a cohort is enrolled until either 2 or more VTE events have been observed among 6 or fewer participants or 3 or more VTE events have been observed among 7-10 participants.

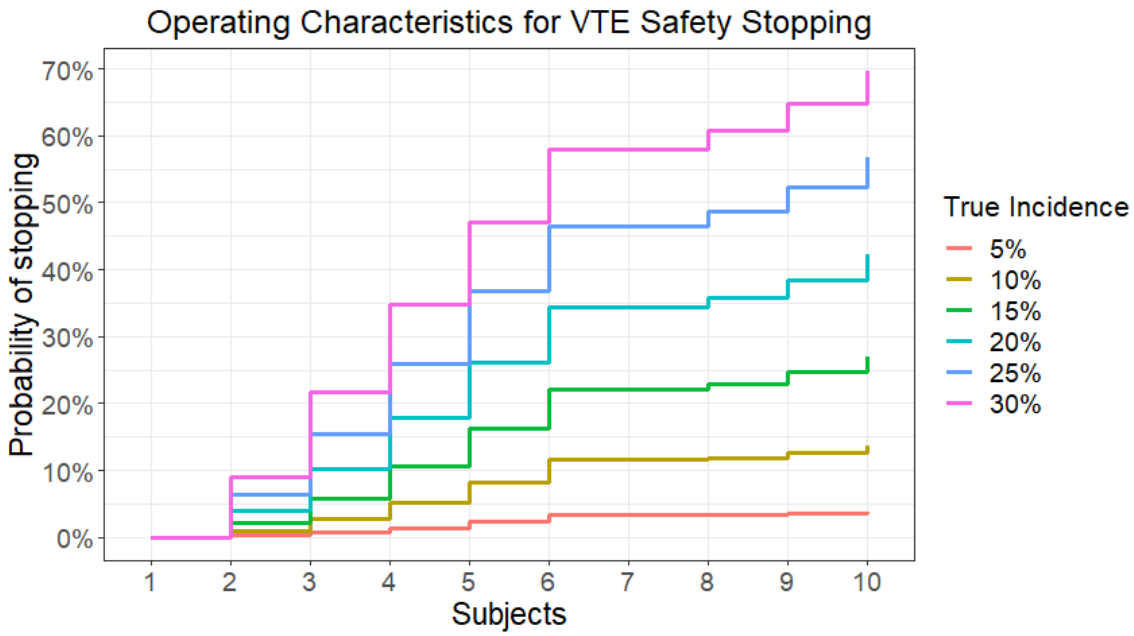
Table 8 details the scenarios evaluated as well as the average number of participants dosed in each cohort, and the percentage of simulated trials that completed that dose level. Figure 4 graphically represents the operating characteristics of the safety stopping rules for each cohort. Each line of the plot represents a different true VTE incidence rate detailed in Table 8. The scenarios considered a range from a true VTE incidence rate of 5% to a true VTE incidence rate of 30%. Note that these simulations only take VTE events into consideration, and this VTE safety stopping rule will be evaluated in addition to the traditional DLT rules within the dose escalation framework detailed in Section 4.1.1.

In low VTE incidence scenarios, the cohorts are more likely to fully recruit without stopping early for safety evaluation of the VTE rate. For example, if the true population VTE incidence rate is 5%, only 3.8% of the simulations stopped early for safety, however, if the true population VTE incidence rate is 30%, 69.5% of our simulations stopped early for safety.

Table 8 Simulation scenarios and probability of stopping for VTE safety stopping rule across various true VTE incidence rates

True VTE incidence	% of trials that stopped early for safety
5%	3.8
10%	13.6
15%	26.9
20%	42.1
25%	56.8
30%	69.5

Figure 4 Operating characteristics for the VTE safety stopping criteria



9.2.2. Dose Expansion

Part 2A DLBCL Cohort

ORR will be analyzed using a Bayesian hierarchical model that allows information borrowing between MTAP proficient and MTAP deficient subgroups within the DLBLC cohort. An MTAP defined subgroup will be considered as effective at the end of study if the posterior probability of ORR>10% is more than 85%. In this design, up to 30 participants will be enrolled into each MTAP defined subgroup and up to 36 will be

enrolled for the entire cohort. The simulation results assuming 50:50 ratio between MTAP proficient participants and MTAP deficient participants are displayed in Table 9.

Assume π_g = Pr(*response* | intervention, *group g*) denote the probability of response for group g participants, where group g represents MTAP proficient subgroup or MTAP deficient subgroup, and π = Pr(*response* | intervention) denote the probability of response for the entire cohort. Let $\theta_g + R_g$ be the logit of the group g response rate, $\theta_{AC} + R_g$ be the logit of the cohort response rate, i.e.,

$$\theta_g + R_g = \log\left(\frac{\pi_g}{1-\pi_g}\right).$$

and

$$\theta_{AC} + R_g = \log\left(\frac{\pi}{1-\pi}\right).$$

The hierarchical model assumes

$$\theta_g \sim N(\mu, \tau^2),$$

The prior distributions for μ, τ^2 *and* θ_{AC} are defined as follows:

$$\mu \sim N(-2.2, 6.9),$$
$$\tau^2 \sim IG(1, 47.61),$$
$$\theta_{AC} \sim N(-2.2, 6.9).$$

where *IG(α, β)* is the inverse gamma distribution defined by:

$$f(x|\alpha,\beta) = \frac{\beta^{\alpha} e^{-\beta/x}}{x^{\alpha+1}\Gamma(\alpha)}.$$

These choices of α and β correspond to a mean weight parameterization with mean 6.9 and weight 2. The prior for μ *and* θ_{AC} centers the response rate at 10% (the assumed underlying control rate).

Table 9 Design Characteristics for Bayesian Hierarchical Design for Part 2A DLBCL Cohorts

Scenarios for ORR	Proportion of MTAP- group meeting success criteria	Proportion of MTAP+ group meeting success criteria
0.3 in MTAP-; 0.3 in MTAP+	81.3%	81.7%
0.1 in MTAP-; 0.1 in MTAP+	8.3%	8.2%
0.3 in MTAP-; 0.1 in MTAP+	80.4%	10.3%

*The results are based on 5000 simulations with interim futility analysis starting after at least five participants in each subgroup and being done every 12 weeks.

Part 2B Solid Tumor Cohorts

The primary endpoint of ORR will be assessed for each of the two MTAP defined subgroups (MTAP proficient and MTAP deficient) within each of the three solid tumor cohorts in Part 2B. The primary analysis of ORR for each tumor cohort and MTAP defined subgroup is based on a Bayesian hierarchical model. The Bayesian hierarchical model will allow information borrowing across the three different cohorts as well as between MTAP proficient and MTAP deficient subgroups. The models focuses more on the MTAP- subgroups than MTAP+ subgroups. It borrows more across MTAP- subgroups compared to MTAP+ subgroups when treatment works across MTAP- subgroups and MTAP+ subgroups. An MTAP defined subgroup within one cohort will be considered as effective at the end of study if the posterior probability of ORR>10% is more than 94%. Up to 35 participants will be enrolled into one disease specific cohort.

The simulation results under the scenario of 50:50 ratio between MTAP proficient participants and MTAP deficient participants are displayed in Table 10. The design has been simulated under nine scenarios for the true distribution of ORR effects across tumor cohort and MTAP defined subgroups. The probability of declaring effective for each subgroup within each disease specific cohort is provided. Additionally, the proportion of trials that correctly detect all effective subgroups (ignoring the design decisions for any ineffective subgroups) is provided.

Table 10 Design Characteristics for Bayesian Hierarchical Design for Part 2B Solid Tumor Cohorts

	Pancreatic		NSCLC		Bladder	
	ORR in truth					
	MTAP-	MTAP+	MTAP-	MTAP+	MTAP-	MTAP+
All Null	10%	10%	10%	10%	10%	10%
All effective	30%	30%	30%	30%	30%	30%
2 Eff in all comers	30%	30%	30%	30%	10%	10%
1 Eff in all comers	30%	30%	10%	10%	10%	10%
All Eff in MTAP-	30%	10%	30%	10%	30%	10%
2 Eff in MTAP-	30%	10%	30%	10%	10%	10%
1 Eff in MTAP-	30%	10%	10%	10%	10%	10%
1 Eff in all comers, 2 Eff in MTAP-	30%	30%	30%	10%	30%	10%
1 Eff in all comers, 1 Eff in MTAP-	30%	30%	30%	10%	10%	10%

	Pancreatic		**NSCLC**		**Bladder**	
	Proportion of trials declaring efficacy (Power or Type I error)					
All Null	0.015	0.021	0.025	0.031	0.023	0.031
All effective	0.904	0.838	0.914	0.831	0.913	0.831
2 Eff in all comers	0.817	0.758	0.812	0.783	0.117	0.074
1 Eff in all comers	0.631	0.688	0.066	0.051	0.068	0.055
All Eff in MTAP-	0.903	0.032	0.890	0.026	0.890	0.033
2 Eff in MTAP-	0.737	0.028	0.738	0.042	0.209	0.022
1 Eff in MTAP-	0.571	0.047	0.093	0.016	0.090	0.021
1 Eff in all comers, 2 Eff in MTAP-	0.934	0.595	0.851	0.067	0.857	0.072
1 Eff in all comers, 1 Eff in MTAP-	0.842	0.639	0.730	0.090	0.184	0.040
	Proportion of trials picking all the effective subgroups correctly					
All Null	NA					
All effective	0.535					
2 Eff in all comers	0.472					
1 Eff in all comers	0.459					
All Eff in MTAP-	0.777					
2 Eff in MTAP-	0.614					
1 Eff in MTAP-	0.571					
1 Eff in all comers, 2 Eff in MTAP-	0.435					
1 Eff in all comers, 1 Eff in MTAP-	0.440					

9.2.3. Sample Size Sensitivity

No analysis of sample size sensitivity was performed.

9.2.4. Sample Size Re-estimation or Adjustment

Sample size re-estimation is not planned for this study.

9.3. Analysis Populations

The **All-Treated Population** is defined as all participants who receive at least one dose of GSK3368715.

All Evaluable Population is defined as the study population used for decision-making at the interim futility analysis. Participants who have had Week 24 disease assessments, have progressed or died, or permanently discontinued from the study intervention will be included in this population.

The **PK Population** will consist of all participants from the All-Treated Population for whom a PK sample is obtained and analyzed.

Additional analysis populations may be defined in the Reporting and Analysis Plan (RAP).

9.4. Interim Analysis

9.4.1. Dose escalation and safety analyses

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

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

Further details regarding such analyses will be provided in the Reporting and Analysis Plan (RAP).

9.4.2. Dose Expansion Cohorts

9.4.2.1. Efficacy Analyses

Part 2A DLBCL Cohort

For Part 2A DLBCL cohort, the first interim analysis will be performed when at least 10 participants become evaluable in each of the MTAP defined subgroup. Data from both subgroups will be included in the analysis to form the Bayesian hierarchical model. For each MTAP defined subgroup, the therapeutic effect will be declared insufficient and enrolment will be terminated if the posterior probability of ORR > 10% is sufficiently low (<20%) based on the hierarchical model. The interim futility analysis will be performed every 2-3 months depending on enrolment rate with minimum of additional five evaluable participants for the cohort. If only one subgroup is stopped early due to futility, the other subgroup will continue enrolment with the constraint of maximum of 30 participants for one subgroup and maximum of 36 participants for the entire cohort.

Part 2B Solid Tumor Cohorts

For Part 2B solid tumor cohorts, the first interim futility analysis will be performed when at least five participants become evaluable from MTAP proficient subgroup within any cohort. Data from all three cohorts will be included in the analysis to form the Bayesian hierarchical model.

For each MTAP+ subgroup within an individual expansion cohort, the therapeutic effect will be declared insufficient and enrolment will be terminated to MTAP+ participants if there are at least 5 MTAP+ participants within that cohort and the posterior probability of ORR > 10% is sufficiently low (<20%) based on the hierarchical model. That is,

$$P(\pi_{j,MTAP+} > 10\% \mid \text{current data}) < 20\%, \text{ for the j-th cohort}$$

For each individual expansion cohort, the therapeutic effect will be declared insufficient and enrolment will be terminated to all participants (regardless of MTAP status) if at least 5 MTAP+ and 5 MTAP- participants within that cohort have ORR data and the posterior

probability that the ORR is greater than 10% is sufficiently low (<20%) based on the hierarchical model. That is,

$$P(\pi_{j,MTAP+} > 10\% \mid \text{current data}) < 20\%, \text{ for the j-th cohort AND}$$

$$P(\pi_{j,MTAP-} > 10\% \mid \text{current data}) < 20\%, \text{ for the j-th cohort}$$

The interim futility analysis will be performed every 2-3 months depending on enrolment with minimum additional five evaluable participants across all cohorts.

All evaluable population will be used for the interim futility analyses. Within each design, the cohort/subgroup may be stopped early for futility but not for efficacy.

The final decision to close a cohort or the study based on futility will be made by the Sponsor, taking into consideration the results of the futility analyses and the entirety of the available data.

9.5. Final Analysis

The final analyses will be conducted when the study is completed. Data from the dose escalation and expansion cohort will be combined as appropriate.

9.6. Key Elements of Analysis Plan

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

All data up to the time of study completion/withdrawal from study will be included in the analysis, regardless of duration of intervention and duration of follow-up.

Demographic and baseline characteristics will be summarized.

Unless otherwise specified, Part 1 will be summarized by dose, Part 2 will be summarized by disease type and MTAP status if applicable. Participants enrolled in Part 1 dose escalation and treated at expansion cohort dose will be included in the analysis for Part 2 provided that the participant has the same tumor type as the expansion cohort.

9.6.1. Efficacy Analyses

Anti-tumor activities will be evaluated based on the response criteria specific to the disease type.

Primary Efficacy Endpoint - ORR
The overall response (ORR) rate is defined as

- Solid tumor: the percentage of participants with a confirmed complete response (CR) or a partial response at any time as per RECIST 1.1 (Appendix 10).

- DLBCL: the percentage of participants with a confirmed complete response (CR) or a partial response (PR) based on Lugano Criteria (See Appendix 10).

Participants with unknown or missing response will be treated as non-responders, i.e. these participants will be included in the denominator when calculating the percentage. The analysis of ORR will only be performed for participants with measurable disease. The estimate of ORR along with 95% exact confidence interval (CI) will be provided. The interim futility analyses for the dose expansion cohorts will be based on the All Evaluable population and final efficacy analysis will be based on the All-Treated Population.

Progression-Free Survival (PFS) is defined as the time from the first dose of study intervention to disease progression or death due to any cause, whichever occurs earlier. Participants who have not progressed or died at the time of the PFS analysis, will be censored at the date of last adequate disease assessment. In addition, participants with an extended time without adequate assessment or who start a new anti-cancer therapy prior to a PFS event will be censored at the date of last adequate disease assessment (e.g. assessment where visit level response is CR, PR, or stable disease [SD]) prior to the extended time without adequate assessment or initiation of new anti-cancer therapy, respectively. Further details on rules for censoring will be provided in the RAP. PFS will be summarized in Part 2 using Kaplan-Meier quantile estimates along with 95% CIs, if data warrant.

Duration of Response (DOR) is defined as the time from the onset of response to disease progression or death due to any cause, whichever occurs earlier in participants who have achieved a response of CR or PR. The same censoring rules as for PFS will be used. DOR will be summarized in Part 2 using Kaplan-Meier quantile estimates along with 95% CIs, if data warrant.

Time to Response (TTR) is defined as the time from first dose to first evidence of response for participants achieving a CR or PR. If data warrant, TTR will be summarized descriptively using median and quartiles.

Overall Survival (OS), is defined as the time from the first dose of study intervention to the death due to any cause. Participants who're alive at the time of OS analysis will be censored at the last date of known contact. If data warrant, OS will be summarized in Part 2 using Kaplan-Meier quantile estimates along with 95% CIs, if data warrant.

9.6.2. Safety Analyses

The All-Treated Population will be used for the analysis of safety data.

9.6.2.1. Extent of exposure

The intervention exposure will be summarized with intervention duration and dose intensity (daily dose for oral daily dosing) as well as the dose modifications including dose reductions, dose interruptions/delays and dose escalations. Details will be specified in the RAP.

9.6.2.2. Adverse Events

AEs will be coded using the standard MedDRA and grouped by system organ class. AEs will be graded by the investigator according to the NCI-CTCAE v5.

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

DLTs will be listed and summarized by dose cohort for Part 1.

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

9.6.2.3. Clinical Laboratory Evaluations

Hematology and clinical chemistry data will be summarized using frequencies and proportions according to NCI-CTCAE v5. Laboratory test results that do not have an associated NCI-CTCAE criterion will be summarized based on normal ranges. Summaries by visit will include data from scheduled assessments only, and all data will be reported according to the nominal visit date for which it was recorded (i.e., no visit windows will be applied). Unscheduled data will be included in 'worse case post-baseline' summaries which will capture a worst case across all scheduled and unscheduled visits after the first dose of study intervention. Further details will be provided in the RAP.

9.6.2.4. Other Safety Measures

Data for vital signs, ECGs, and ECHOs and/or MUGA scans will be summarized based on predetermined criteria identified to be of potential clinical concern. Further details will be provided in the RAP.

9.6.3. Pharmacokinetic Analyses

9.6.3.1. Pharmacokinetic Parameters

Pharmacokinetic (PK) analysis of GSK3368715 (and its metabolite[s]), concentration-time data will be conducted by non-compartmental methods under the direction of CPMS, CPEM, GSK. Calculations will be based on the actual sampling times recorded during the study. The following PK parameters will be determined if data permit:

- maximum observed plasma concentration (Cmax)
- time to Cmax (tmax)
- area under the curve over a dosing interval (AUC(0-t), AUC(0-∞) and AUC(0-τ)
- trough concentration (Cτ)

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

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

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

9.6.3.2. Statistical analysis of Pharmacokinetic data

GSK3368715 plasma concentration-time data will be listed for each participant and summarized using descriptive statistics (n, mean, SD, median, minimum and maximum) by planned relative assessment time. PK parameters will be summarized using mean, standard deviation, median, minimum, maximum, and the standard deviation and geometric mean of log-transformed parameters.

Cmax and AUC (AUC(0-∞), single dose; and AUC(0-τ), steady state) will be plotted as a function of the dose administered. If more than 2 dose cohorts are required to reach MTD (or the recommended dose based on available safety, PK and response data), dose proportionality of AUC and Cmax for GSK3368715 following single dose administration and AUC(0-τ) and Cmax following repeat dose administration will be assessed graphically and using the power model as described below:

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

where a is the intercept and b is the slope.

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

A nonlinear mixed effects model may be used to determine population pharmacokinetic parameters and identify important covariates (e.g., age, weight, or disease related covariates) and for PK/PD analysis. Further details of population PK and PK/PD analysis will be described in the separate RAP; results of such an analysis may be included in a report separate from the clinical study report.

9.6.3.2.1. Food Effect Sub-Study

Pharmacokinetic (PK) parameters AUC(0-∞), AUC(0-t) and Cmax will be log-transformed and analyzed separately using a mixed-effects model with fixed-effect term for fed status (fed or fasted), and participant as a random effect. Point estimates and their associated 90% CIs will be constructed for the differences between fed and in fasted state. The point estimates and their associated 90% CIs will be then back transformed to provide point estimates and 90% CIs for the ratios of fed/fasted. Non-parametric methods such as the

Hodges and Lehmann estimator will be used to estimate the median differences between the fed treatments and the fasted state treatments for tmax and t½. An associated 90% CI for the median differences will be constructed.

Based on the US FDA guidance on food-effect bioavailability studies, the absence of a food-effect will be established if the 90% CI of the ratio for Cmax and AUC, based on log-transformed data, is within the 80 to 125% equivalence limit. Recommendation on the clinical significance of the effect of food will be based on the magnitude of the change and our understanding of the exposure-clinical response relationship. For the evaluation of food effect, tmax at fed and fasted status will be presented by participant and dose cohort in tabular and graphical form.

9.6.4. Pharmacokinetic/Pharmacodynamic Analyses

Observed or predicted concentrations will be combined with safety, efficacy, and other pharmacodynamic measures of interest to examine potential exposure response relationships.

Other quantitative safety parameters and biomarkers of interest will be plotted graphically against summary exposure measures (e.g., Cmax, Cτ, and Cav). Where evidence of a signal is seen, linear and non-linear mixed effect models will be fitted to the data to estimate PK/PD parameters of interest; slope, baseline (E0), concentration for 50% of maximum effect (EC50) and maximum effect (Emax).

9.6.5. Other Analyses

9.6.5.1. Translational Research Analyses

The results of translational research investigations will be reported separately from the main clinical study report (CSR). All endpoints of interest from all comparisons will be descriptively and/or graphically summarized as appropriate to the data.

Further details on the translational research analyses will be addressed in the translational research RAP.

9.6.5.2. Pharmacogenetic Analyses

Further details on pharmacogenetic (PGx) analyses will be addressed in the PGx RAP.

10. APPENDICES

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

10.1.1. Regulatory and Ethical Considerations

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

10.1.2. Financial Disclosure

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

10.1.3. Informed Consent Process

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

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

10.1.4. Data Protection

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

10.1.5. Publication Policy

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

10.1.6. Dissemination of Clinical Study Data

- Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the CSR. 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.
- GSK will provide the investigator with the randomization codes for their site only after completion of the full statistical analysis.
- The procedures and timing for public disclosure of the results summary and for development of a manuscript for publication will be in accordance with GSK Policy.

10.1.7. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, 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, pertaining to the conduct of this study must be retained by the investigator for 25 years from the issue of the final clinical study report (CSR)/ equivalent summary unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.1.8. Source Documents

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

10.1.9. 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

10.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 11 will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.
- Pregnancy Testing

  Refer to Section 5.1 Inclusion Criteria for screening pregnancy criteria.
- Pregnancy testing (urine or serum as required by local regulations) should be conducted at monthly intervals during intervention

Table 11 Protocol-Required Safety Laboratory Assessments

<table>
<tr><th>Laboratory Assessments</th><th colspan="4">Parameters</th></tr>
<tr><td>Hematology</td><td>Platelet Count
RBC Count
Hemoglobin
Hematocrit</td><td colspan="2">RBC Indices:
MCV
MCH
%Reticulocytes</td><td>WBC count with Differential:
Neutrophils
Lymphocytes
Monocytes
Eosinophils
Basophils</td></tr>
<tr><td rowspan="4">Clinical Chemistry[1]</td><td>BUN</td><td>Potassium</td><td>AST (SGOT)</td><td>Total and direct bilirubin</td></tr>
<tr><td>Creatinine</td><td>Sodium</td><td>ALT (SGPT)</td><td>Total Protein</td></tr>
<tr><td>Glucose</td><td>Calcium</td><td>Alkaline phosphatase</td><td>Albumin</td></tr>
<tr><td>Lipase</td><td>Amylase</td><td></td><td></td></tr>
<tr><td>Coagulation</td><td colspan="4">PTT, PT/INR</td></tr>
<tr><td>Routine Urinalysis</td><td colspan="4">• Specific gravity
• pH, glucose, protein, blood, and ketones by dipstick
• Microscopic examination (if blood or protein is abnormal)</td></tr>
<tr><td>Other Screening Tests</td><td colspan="4">• Highly sensitive serum or urine Beta human chorionic gonadotropin (βhCG) pregnancy test (as needed for women of childbearing potential)[2]
• Serology (HIV antibody, HBsAg, and hepatitis C virus antibody)
• Cardiac Troponin I or TroponinT (local standard, no point-of-care assay)
The results of each test must be entered into the CRF.</td></tr>
</table>

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; βhCG = beta-human chorionic gonadotropin; BUN = blood urea nitrogen; HBsAg = Hepatitis B surface antigen; MCH = mean corpuscle haemoglobin; MCV = mean corpuscle volume; RBC = red blood cells; SGOT = serum glutamic-oxaloacetic transaminase; SGPT = serum glutamic-pyruvic transaminase; WBC = white blood cells

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 and Appendix 7 All events of ALT ≥3 × upper limit of normal (ULN) and bilirubin ≥2 × ULN (>35% direct bilirubin) or ALT ≥3 × ULN and international normalized ratio (INR) >1.5, if INR measured, which may indicate severe liver injury (possible Hy's Law), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis).
2. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.

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

10.3.1. Definition of AE

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

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

Events 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 (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.

Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, 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:

a. Results in death

b. Is life-threatening

The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or intervention that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AE. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" ocurred or was necessary, the AE should be considered serious.

Hospitalization for elective intervention of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in persistent disability/incapacity

The term disability means a substantial disruption of a person's ability to conduct normal life functions.

This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. 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 intervention 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.

10.3.3. Definition of Cardiovascular Events

Cardiovascular Events (CV) Definition:

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

Myocardial infarction/unstable angina

Congestive heart failure

Arrhythmias

Valvulopathy

Pulmonary hypertension

Cerebrovascular events/stroke and transient ischemic attack

Peripheral arterial thromboembolism

Deep venous thrombosis/pulmonary embolism

- Revascularization

10.3.4. Recording AE and SAE

AE and SAE Recording

When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.

The investigator will then record all relevant AE/SAE information in the CRF.

It is **not** acceptable for the investigator to send photocopies of the participant's medical records to GSK in lieu of completion of the GSK /AE/SAE CRF page.

There may be instances when copies of medical records for certain cases are requested by GSK. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to GSK.

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

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to one of the following categories:

Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.

Moderate: An event that causes sufficiently discomfort and interferes with normal everyday activities.

Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AE and SAE can be assessed as severe.

> An event is defined as 'serious' when it meets at least one of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.

A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

The investigator will use clinical judgment to determine the relationship.

Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.

The investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.

For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to** GSK**.**

The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

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

Follow-up of AE and SAE
The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by GSK to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. If a participant dies during participation in the study or during a recognized follow-up period, the investigator may be asked to 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.

10.3.5. Reporting of SAE to GSK

SAE Reporting to GSK via Electronic Data Collection Tool
The primary mechanism for reporting SAE to GSK will be the electronic data collection tool. If the electronic system is unavailable, then the site will use the paper SAE data collection tool as outlined in the SRM 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. The investigator or medically-qualified sub-investigator must show evidence within the eCRF (e.g., check review box, signature, etc.) of review and verification of the relationship of each SAE to IP/study participation (causality) within 72 hours of SAE entry into the eCRF. 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 to the medical monitor by telephone. Contacts for SAE reporting can be found in the SRM.

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

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

10.4.1. Definitions

Woman of Childbearing Potential (WOCBP)

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

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with ONE of the following:

- Documented hysterectomy
- Documented bilateral salpingectomy
- Documented bilateral oophorectomy

Note: Documentation can come from the site personnel's: review of 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, a single FSH measurement is insufficient.
- Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrolment.

10.4.2. Contraception Guidance

Male participants

Male participants with female partners of childbearing potential are eligible to participate if they agree to ONE of the following while on study intervention and for 100 days after the last dose

- Are abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent.
- Agree to use a male condom plus an additional method of contraception with a failure rate of <1% per year as described below when having penile-vaginal intercourse with a woman of childbearing potential.

Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration while on study intervention and for 100 days after the last dose

- In addition male participants must refrain from donating sperm for duration of study and for 100 days after last dose.

Female participants

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in the Table below.

Highly Effective Contraceptive Methods

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
Highly Effective Methods[b] That Have Low User Dependency
Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c]
Intrauterine device (IUD)
Intrauterine hormone-releasing system (IUS)[c]
Bilateral tubal occlusion
Vasectomized partner *Note: Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.*
Highly Effective Methods[b] That Are User Dependent
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c] oral intravaginal transdermal injectable
Progestogen-only hormone contraception associated with inhibition of ovulation[c] oral injectable
Sexual abstinence *Note: Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant*

Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies. Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly. Note: Periodic abstinence (calendar, sympto-thermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception for this study. Male condom and female condom should not be used together (due to risk of failure with friction)

Pregnancy Testing

WOCBP should only be included after a confirmed menstrual period and a negative highly sensitive serum pregnancy test

Additional pregnancy testing should be performed at monthly intervals during the intervention period and at 150 days after the last dose of study intervention and as required locally.

Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected.

10.4.3. Collection of Pregnancy Information

Male participants with partners who become pregnant

Investigator will attempt to collect pregnancy information on any male participant's female partner of a male study participant who becomes pregnant while participating in this study. This applies only to participants who receive study intervention.

After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to GSK within 24 hours of learning of the partner's pregnancy.

Partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to GSK

Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for procedure.

Female Participants who become pregnant

Investigator will collect pregnancy information on any female participant, who becomes pregnant while participating in this study.

Information will be recorded on the appropriate form and submitted to GSK within 24 hours of learning of a participant's pregnancy.

Participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on participant and neonate, which will be forwarded to GSK Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.

Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.

A spontaneous abortion is always considered to be an SAE and will be reported as such.

Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study intervention by the investigator, will be reported to GSK as described in Appendix 3. 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

10.5. Appendix 5: Genetics

USE/ANALYSIS OF DNA

Genetic variation may impact a participant's response to therapy, susceptibility, severity and progression of disease. Variable response to therapy may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis

DNA samples will be used for research related to GSK3368715 or advanced solid tumors or DLBCL and related diseases. They may also be used to develop tests/assays including diagnostic tests related to GSK3368715 or study interventions of this drug class, and advanced solid tumors or DLBCL Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome [or analysis of the entire genome] (as appropriate)

DNA samples will be analyzed if it is hypothesized that this may help further understand the clinical data.

DNA samples will be analyzed by using appropriate descriptive and/or statistical analysis methods. A detailed description of any planned analyses will be documented in a RAP prior to initiation of the analysis. The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to GSK3368715 or study interventions of this class. The results of genetic analyses may be reported in the CSR or in a separate study summary.

The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.

The samples will be retained while research on GSK3368715 (or study interventions of this class) or advanced solid tumors or DLBCL continues but no longer than 15 years after the last participant last visit or other period as per local requirements.

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

Phase I liver chemistry stopping and increased monitoring criteria have been designed to assure participant safety and evaluate liver event etiology (in alignment with the FDA premarketing clinical liver safety guidance). http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf.

Phase I liver chemistry stopping criteria and required follow up assessments

Liver Chemistry Stopping Criteria – Liver Stopping Event **Participant with entry criteria ALT≤ 2.5 x ULN**	
ALT-absolute	ALT ≥ 5xULN
ALT Increase	ALT ≥ 3xULN persists for ≥4 weeks
Bilirubin[1, 2]	ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin)
INR[2]	ALT ≥ 3xULN **and** INR>1.5, if INR measured
Cannot Monitor	ALT ≥ 3xULN **and** cannot be monitored weekly for 4 weeks
Symptomatic[3]	ALT ≥ 3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity
Liver Chemistry Stopping Criteria – Liver Stopping Event **Including participants with documented liver metastases/tumor infiltration at baseline AND entry criteria ALT>2.5 x ULN but ≤5 x ULN**	
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, if INR measured
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 intervention • Report the event to GSK **within 24 hours** • Complete the liver event CRF and complete an SAE data collection tool if the event also meets the criteria for an SAE[2] • Perform liver event follow up assessments • Monitor the participant until liver chemistries resolve, stabilize, or return to within baseline (see **MONITORING** below) • **Do not restart/rechallenge** participant with study intervention 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 intervention 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 perform liver event follow up assessments within **24 hrs** • Monitor participants twice weekly until liver chemistries resolve, stabilize or return to within baseline • A specialist or hepatology consultation is recommended **For All other criteria:** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24-96 hrs** • Monitor participants weekly until liver chemistries resolve, stabilize or return to within baseline	• Viral hepatitis serology[4] • Only in those with underlying chronic hepatitis B at study entry (identified by positive hepatitis B surface antigen) quantitative hepatitis B DNA and hepatitis delta antibody[5]. • Blood sample for pharmacokinetic (PK) analysis, obtained 24-72h after last dose[6] • Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH). • Fractionate bilirubin, if total bilirubin≥2xULN • Obtain complete blood count with differential to assess eosinophilia • Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form • Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications • Record alcohol use on the liver event alcohol intake case report form **For bilirubin or INR criteria:** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG or gamma globulins). • Serum acetaminophen adduct HPLC assay (quantifies potential acetaminophen contribution to liver injury in participants with definite or likely acetaminophen use in the preceding week [James, 2009]). **NOTE: not required in China** • Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy CRF forms.

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

Phase I Oncology liver chemistry increased monitoring criteria with continued therapy

Liver Chemistry Increased Monitoring Criteria – Liver Monitoring Event	
Criteria	**Actions**
Participant <u>with</u> entry criteria ALT≤2.5x ULN ALT ≥3xULN **but** <5xULN **and** bilirubin <2xULN, **without** symptoms believed to be related to liver injury or hypersensitivity **and** who can be monitored weekly for 4 weeks **Participant <u>with documented</u> liver metastases/tumor infiltration at baseline AND entry criteria ALT>2.5 x ULN but ≤5 x ULN** ALT ≥3x ULN and 1.5x baseline value **but** ALT <5x ULN and 2x baseline value **and** bilirubin <2xULN**, without** symptoms believed to be related to liver injury, or hypersensitivity **and** who can be monitored weekly for 4 weeks	• Notify the GSK medical monitor **within 24 hours** of learning of the abnormality to discuss participant safety. • Participant can continue study intervention • Participant must return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) until they resolve, stabilise or return to within baseline • If at any time participant meets the liver chemistry stopping criteria, proceed as described above **For participants with entry criteria ALT≤2.5 x ULN** • If, after 4 weeks of monitoring, ALT <3xULN and bilirubin <2xULN, monitor participants twice monthly until liver chemistries normalize or return to within baseline. **For participants with documented liver metastases/tumor infiltration at baseline AND entry criteria ALT>2.5 x ULN but ≤5 x ULN** • If, after 4 weeks of monitoring, ALT <3xULN and <1.5x baseline value, and bilirubin <2xULN, monitor participants twice monthly until liver chemistries normalize or return to within baseline

References

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

10.7. Appendix 7: Medical Device Incidents: Definition and Procedures for Recording, Evaluating, Follow-up, and Reporting

There are no medical devices used in this protocol.

10.8. Appendix 8 Country Specific Requirements

No country specific requirements are required.

10.9. Appendix 9: Abbreviations and Trademarks

ADMA	Asymmetric dimethylation of arginine
AE(s)	Adverse Event(s)
AESI	Adverse Event of Special Interest
ALT	Alanine Aminotransferease
AML	Acute Myeloid Leukemia
AST	Aspartate Aminotransferase
AUC	Area under the concentration-time curve
BSC	Best Supportive Care
CDKN2A	Cyclin Dependent Kinase Inhibitor 2A
CI	Confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CNS	Central nervous system
C_{max}	Maximum observed concentration
C_{min}	Minimum observed concentration
CONSORT	Consolidated Standards of Reporting Trials
CR	Complete Response
CRF	Case report form
CSR	Clinical Study Report
C_{tau}	Trough concentration
CT	Computerized Axial Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of Variance
CYP	Cytochrome
DCSI	Development core safety information
DEC	Dose Escalation Committee
DLBCL	Diffuse large B-cell lymphoma
DOR	Duration of response
DRE	Disease-related events
DILI	Drug Induced Liver Injury
DLT	Dose-Limiting Toxicity
DMPK	Drug Metabolism and Pharmacokinetics
DNA	Deoxyribonucleic acid
EC	Ethics Committee
ECG(s)	Electrocardiogram(s)
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EOT	End of Treatment
FACTS	Fixed and Adaptive Clinical Trial Simulator
FTIH	First Time In Humans
GALT	Galactose-1-phosphate uridylyltransferase
GCP	Good Clinical Practice
GI	Gastrointestinal

GLP	Good Laboratory Practices
GSK	GlaxoSmithKline
HBsAg	Hepatitis B Surface Antigen
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
Hgb	Hemoglobin
HIV	Human Immunodeficiency Virus
h/hr	Hour(s)
HIPPA	Health Insurance Portability and Accountability Act
HLA	Human Leukocyte Antigen
HNSTD	Highest Non- Severely Toxic Dose
HPLC	High-Performance Liquid Chromatography
HRT	Hormone Replacement Therapy
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
IDSL	International Data Standards
IEC	Independent Ethics Committee
IFN	Interferon
IND	Investigational New Drug
INR	International Normalization Ratio
IRB	Institutional Review Board
IU	International Unit
IV	Intravenous
Ka	Absorption rate
kg	Kilogram
L	Liter
LFTs	Liver Function Tests
LHRH	Leutinizing hormone- releasing hormone
LLN	Lower Limit of Normal
ln	Naperian (natural) logarithm
LSLV	Last Participant's Last Visit
LVEF	Left Ventricular Ejection Fraction
uM	Micromole
MABEL	Minimum Anticipated Biological Effect Level
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MDS	Myelodysplastic syndromes
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligrams
mL	Milliliter
MMA	Monomethylarginine
MPV	Mean Platelet Volume
MRI	Magnetic Resonance Imaging

MSDS	Material Safety Data Sheet
msec	Milliseconds
MTA	2-methylthioadenosine
MTAP	Methylthioadenosine phosphorylase
MTD	Maximum Tolerated Dose
MUGA	Multigated (radionuclide) angiogram
NCAS	Non-clinical assessment of safety
NCI-CTCAE	National Cancer Institute - Common Terminology Criteria for Adverse Events
N-CRM	The Neuenschwander -Continuous Reassessment Method
ng	Nanogram
NHL	Non-Hodgkins Lymphoma
nM	Nanomole
NOAEL	No Observed Adverse Effect Level
NSCLC	Non-small Cell Lung Cancer
NYHA	New York Heart Association
ORR	Overall response rate
OS	Overall survival
PBMC	Peripheral Blood Mononuclear Cells
PCI	Potential Clinical Importance
PCR	Polymerase Chain Reaction
PD	Progressive Disease or Pharmacodynamic
PFS	Progression Free Survival
PI	Principal Investigator
PK	Pharmacokinetic
PR	Partial Response
PRMT	Protein Arginine Methyl Transferase
PRO	Patient Reported Outcomes
RAP	Reporting and Analysis Plan
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	Recommended Phase 2 Dose
QTc	Corrected QT interval duration
QTcF	QT interval corrected for heart rate by Fridericia’s formula
RBC	Red Blood Cells
RNA	Ribonucleic acid
RP2D	Recommended Phase 2 Dose
SAE	Serious Adverse Event(s)
SAM	S-adenosyl methionine
SD	Standard Deviation
SDMA	Symmetric dimethylated arginine
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SRM	Study Reference Manual
SRT	Safety Review Team
SUSAR	Suspected unexpected serious adverse reactions
TCC	Transitional Cell Carcinoma

TCR	T-cell Receptor
TDV	Treatment (Intervention) Discontinuation Visit
Tmax	Time to reach maximum concentration
TNF	Tumor Necrosis Factor
TTR	Time to Reponse
ULN	Upper Limit of Normal
US/USA	United States/United States of America
VTE	Venous thromboembolism
WBC	White Blood Cells
WHO	World Health Organization
WOCPB	Woman of Childbearing Potential

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10.10. Appendix 10. Guidelines for Assessment of Disease, Disease Progression and Response Criteria

10.10.1. Response Criteria for Solid Tumors (RECIST version 1.1 [Eisenhauer, 2009]

10.10.1.1. Assessment 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 should 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 should 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 5mm contiguous slices is recommended.** Minimum size of a measurable baseline lesion should 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 should 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.

Bone Scan (typically bone scintigraphy): If a bone scan is performed and a new lesion(s) is equivocal, then correlative imaging (i.e.X-ray, CT, or MRI) is required to demonstrate malignant characteristics of the lesion(s).

Note: PET [FDG or fluoride] may be used in lieu of a standard bone scan providing coverage allows interrogation of all likely sites of bone disease and PET is performed at all assessments.

10.10.1.2. Guidelines for Evaluation of Disease

10.10.1.2.1. 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.

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

Measurable disease: The presence of at least one 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.

10.10.1.3. Baseline Documentation of Target and Non-target Lesions

- All baseline lesion assessments must be performed within 28 days of randomization.
- Lymph nodes that have a short axis of <10mm are considered non-pathological and should not be recorded or followed.
- Pathological lymph nodes with <15mm and but ≥10mm short axis are considered non-measurable.
- Pathological lymph nodes with ≥15mm 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 on the basis of 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 should 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 should 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) should be identified as non-target and should also be recorded at baseline. Non-target lesions will be group by organ. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

10.10.1.4. Response Criteria

10.10.1.4.1. Evaluation of target lesions

Definitions for assessment of response for target lesions are as follows:

- Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes must be <10mm in the short axis.
- Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as a reference, the baseline sum of the diameters (e.g. percent change from baseline).
- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease.

- Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as a reference, the smallest sum of diameters recorded since the intervention started (e.g. percent change from nadir, where nadir is defined as the smallest sum of diameters recorded since intervention start). In addition, the sum must have an absolute increase from nadir of 5mm.
- Not Applicable (NA): No target lesions at baseline.
- Not Evaluable (NE): Cannot be classified by one of the four preceding definitions.

Note:

- If lymph nodes are documented as target lesions the short axis is added into the sum of the diameters (e.g. sum of diameters is the sum of the longest diameters for non-nodal lesions and the short axis for nodal lesions). When lymph nodes decrease to non-pathological size (short axis <10mm) they should still have a measurement reported in order not to overstate progression.
- If at a given assessment time point all target lesions identified at baseline are not assessed, sum of the diameters cannot be calculated for purposes of assessing CR, PR, or SD, or for use as the nadir for future assessments. However, the sum of the diameters of the assessed lesions and the percent change from nadir should be calculated to ensure that progression has not been documented. If an assessment of PD cannot be made, the response assessment should be NE.
- All lesions (nodal and non-nodal) should have their measurements recorded even when very small (e.g. 2 mm). If lesions are present but too small to measure, 5 mm should be recorded and should contribute to the sum of the diameters, unless it is likely that the lesion has disappeared in which case 0 mm should be reported.
- If a lesion disappears and reappears at a subsequent time point it should continue to be measured. The response at the time when the lesion reappears will depend upon the status of the other lesions. For example, if the disease had reached a CR status then PD would be documented at the time of reappearance. However, if the response status was PR or SD, the diameter of the reappearing lesion should be added to the remaining diameters and response determined based on percent change from baseline and percent change from nadir.

10.10.1.4.2. Evaluation of non-target lesions

Definitions for assessment of response for non-target lesions are as follows:

- Complete Response (CR): The disappearance of all non-target lesions. All lymph nodes identified as a site of disease at baseline must be non-pathological (e.g. <10 mm short axis).
- Non-CR/Non-PD: The persistence of 1 or more non-target lesion(s) or lymph nodes identified as a site of disease at baseline ≥ 10 mm short axis.
- Progressive Disease (PD): Unequivocal progression of existing non-target lesions.
- Not Applicable (NA): No non-target lesions at baseline.
- Not Evaluable (NE): Cannot be classified by one of the four preceding definitions.

Note:

- In the presence of measurable disease, progression on the basis of solely non-target disease requires substantial worsening such that even in the presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy.
- In the presence of non-measurable only disease, consideration should be given to whether or not the increase in overall disease burden is comparable in magnitude to the increase that would be required to declare PD for measurable disease.
- Sites of non-target lesions, which are not assessed at a particular timepoint based on the assessment schedule, should be excluded from the response determination (e.g. non-target response does not have to be "Not Evaluable").

10.10.1.4.3. New lesions

New malignancies denoting disease progression must be unequivocal. Lesions identified in follow-up in an anatomical location not scanned at baseline are considered new lesions.

Any equivocal new lesions should continue to be followed. Intervention can continue at the discretion of the investigator until the next scheduled assessment. If at the next assessment the new lesion is considered to be unequivocal, progression should be documented.

10.10.1.4.4. Evaluation of overall response

Table 12 presents the overall response at an individual time point for all possible combinations of tumor responses in target and non-target lesions with or without the appearance of new lesions for participants with measurable disease at baseline.

Table 12 Evaluation of Overall Response for Participants with Measurable Disease at Baseline

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR or NA	No	CR
CR	Non-CR/Non-PD or NE	No	PR
PR	Non-PD or NA or NE	No	PR
SD	Non-PD or NA or NE	No	SD
NE	Non-PD or NA or NE	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR=complete response, PR = partial response, SD=stable disease, PD=progressive disease, NA= Not applicable, and NE=Not Evaluable

Table 13 presents the overall response at an individual time point for all possible combinations of tumor responses in non-target lesions with or without the appearance of new lesions for participants with non-measurable only disease at baseline.

Table 13 Evaluation of Overall Response for Participants with Non-Measurable Only Disease at Baseline

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non CR/Non PD	No	Non CR/Non PD
NE	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD
CR=complete response, PD=progressive disease, and NE=Not Evaluable		

Note: Participants with a global deterioration of health status requiring discontinuation of intervention without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration." Objective response status is determined by evaluations of disease burden. Every effort should be made to document the objective progression even after discontinuation of intervention.

In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of CR depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the CR.

10.10.1.4.5. Evaluation of best overall response

The best overall response is the best response recorded from the start of the intervention until disease progression/recurrence and will be determined programmatically by GSK based on the investigators assessment of response at each time point.

- To be assigned a status of SD, follow-up disease assessment must have met the SD criteria at least once after first dose at a minimum interval of 49 days (based on the expected 56 ± 7day window).
- If the minimum time for SD is not met, best response will depend on the subsequent assessments. For example if an assessment of PD follows the assessment of SD and SD does not meet the minimum time requirement the best response will be PD. Alternatively, participants lost to follow-up after an SD assessment not meeting the minimum time criteria will be considered not evaluable.

10.10.1.4.6. Confirmation Criteria:

- To be assigned a status of PR or CR, a confirmatory disease assessment should be performed no less than 4 weeks (28 days) after the criteria for response are first met.

10.10.2. Evaluation, Staging and Response Assessments for Non-Hodgkin's Lymphoma: The Lugano Classification (according to Cheson, 2014)

Evaluation, staging, and response criteria are summarized in 3 tables below.

Criteria for Involvement of Site

Tissue Site	Clinical	FDG Avidity	Test	Positive Finding
Lymph nodes	Palpable	FDG-avid histologies	PET-CT	Increased FDG uptake
		Non avid disease	CT	Unexplained node enlargement
Spleen	Palpable	FDG-avid histologies	PET-CT	Diffuse uptake, solitary mass, miliary lesions, nodules
		Non avid disease	CT	> 13 cm in vertical length, mass, nodules
Liver	Palpable	FDG-avid histologies	PET-CT	Diffuse uptake, mass
		Non avid disease	CT	Nodules
CNS	Signs, symptoms		CT	Mass lesion(s)
			MRI	Leptomeningeal infiltration, mass lesions
			CSF assessment	Cytology, flow cytometry
Other (eg, skin, lung, GI tract, bone, bone marrow)	Site dependent		PET-CT[a], biopsy	Lymphoma involvement

Abbreviations: CSF, cerebrospinal fluid; CT, computed tomography; FDG, fluorodeoxyglucose; MRI, magnetic resonance imaging; PET, positron emission tomography.
a: PET-CT is adequate for determination of bone marrow involvement and can be considered highly suggestive for involvement of other extralymphatic sites. Biopsy confirmation of those sites can be considered if necessary.

Staging System for Primary Nodal Lymphomas

Stage	Involvement	Extranodal (E) Status
Limited		
I	One node or a group of adjacent nodes	Single extranodal lesions without nodal involvement
II	Two or more nodal groups on the same side of the diaphragm	Stage I or II by nodal extent with limited contiguous extranodal involvement
II bulky[a]	II as above with "bulky" disease	Not applicable
Advanced		
III	Nodes on both sides of the diaphragm; nodes above the diaphragm with spleen involvement	Not applicable
IV	Additional noncontiguous extralymphatic involvement	Not applicable

NOTE. Extent of disease is determined by positron emission tomography–computed tomography for avid lymphomas and computed tomography for nonavid histologies. Tonsils, Waldeyer's ring, and spleen are considered nodal tissue.
a: Whether stage II bulky disease is treated as limited or advanced disease may be determined by histology and a number of prognostic factors.

Criteria for Response Assessment of Non-Hodgkin's Lymphoma

Response	Site	PET-CT-Based Response	CT-Based Response
Complete	Lymph nodes and extralymphatic sites	Complete metabolic response	Complete radiologic response (all of the following)
		Score 1, 2, or 3[a] with or without a residual mass on 5PS[2] It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (eg, with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake	Target nodes/nodal masses must regress to ≤ 1.5 cm in LDi No extralymphatic sites of disease
	Non measured lesion	Not applicable	Absent
	Organ enlargement	Not applicable	Regress to normal
	New lesions	None	None
	Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if determinate, IHC negative
Partial	Lymph nodes and extralymphatic sites	Partial metabolic response	Partial remission (all of the following)
		Score 4 or 5[b] with reduced uptake compared with baseline and residual mass(es) of any size At interim, these findings suggest responding disease At end of intervention, these findings indicate residual disease	≥ 50% decrease in SPD of up to 6 target measurable nodes and extranodal sites When a lesion is too small to measure on CT, assign 5 mm × 5 mm as the default value When no longer visible, 0 × 0 mm For a node > 5 mm × 5 mm, but smaller than normal, use actual measurement for calculation
	Nonmeasured lesion	Not applicable	Absent/normal, regressed, but no increase
	Organ enlargement	Not applicable	Spleen must have regressed by > 50% in length beyond normal
	New lesions	None	None

Response	Site	PET-CT-Based Response	CT-Based Response
	Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan	Not applicable
No response or stable disease	Lymph nodes and extralymphatic sites	No metabolic response	Stable disease
		Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of intervention	< 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
	Non measured lesion	Not applicable	No increase consistent with progression
	Organ enlargement	Not applicable	No increase consistent with progression
	New lesions	None	None
	Bone marrow	No change from baseline	Not applicable
Progressive disease	Individual target nodes/nodal masses Extranodal lesions	Progressive metabolic disease Score 4 or 5 with an increase in intensity of uptake from baseline and/or New FDG-avid foci consistent with lymphoma at interim or end-of-intervention assessment	Progressive disease requires at least 1 of the following: PPD progression: An individual node/lesion must be abnormal with: LDi > 1.5 cm and Increase by ≥ 50% from PPD nadir and An increase in LDi or SDi from nadir. 0.5 cm for lesions ≤ 2 cm 1.0 cm for lesions > 2 cm In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (eg, a 15-cm spleen must increase to > 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline New or recurrent splenomegaly
	Non measured lesions	None	New or clear progression of preexisting nonmeasured lesions
	New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (eg, infection, inflammation). If uncertain regarding etiology of new	Regrowth of previously resolved lesions A new node > 1.5 cm in any axis

Response	Site	PET-CT-Based Response	CT-Based Response
		lesions, biopsy or interval scan may be considered	A new extranodal site > 1.0 cm in any axis; if < 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma
	Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

Abbreviations: 5PS, 5-point scale; CT, computed tomography; FDG, fluorodeoxyglucose; IHC, immunohistochemistry; LDi, longest transverse diameter of a lesion; MRI, magnetic resonance imaging; PET, positron emission tomography; PPD, cross product of the LDi and perpendicular diameter; SDi, shortest axis perpendicular to the LDi; SPD, sum of the product of the perpendicular diameters for multiple lesions.

a: A score of 3 in many patients indicates a good prognosis with standard intervention, especially if at the time of an interim scan. However, in trials involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid underintervention). Measured dominant lesions: Up to six of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in two diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (eg, liver, spleen, kidneys, lungs), GI involvement, cutaneous lesions, or those noted on palpation. Nonmeasured lesions: Any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging. In Waldeyer's ring or in extranodal sites (eg, GI tract, liver, bone marrow), FDG uptake may be greater than in the mediastinum with complete metabolic response, but should be no higher than surrounding normal physiologic uptake (eg, with marrow activation as a result of chemotherapy or myeloid growth factors).

b: PET 5PS: CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.

10.11. Appendix 11. ECOG Performance Status

Grade	Descriptions
CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.	

1. Oken, 1982.

10.12. Appendix 12: Guidelines for Management of Toxicity

The following dose modification criteria should provide guidance for, but not act as a replacement for sound clinical judgment. The investigator should use clinical judgment to determine which drug may be contributing to the toxicity necessitating dose adjustment, and make the appropriate change for that drug. Dose modifications should be made after discussion with the GSK medical monitor.

10.12.1. Management of Selected Toxicities

Table 14 Dose Adjustment/Stopping Safety Criteria

Toxicity	Dose Adjustment/ Stopping Criteria	Management Guidelines
Thrombocytopenia	Grade 1 & 2	Continue dosing at same dose level with weekly or more frequent monitoring as necessary
	Grade 3	• Hold GSK3368715 until resolved to Grade ≤ 1 within ≤ 14 days • Monitor complete blood count (CBC) at least twice a week • Discuss with GSK Medical Monitor • Re-start GSK3368715 at a reduced dose • Discontinue GSK3368715 if not resolved to Grade ≤ 1 within ≤ 14 days
	Grade 4	• Discontinue GSK3368715 • Monitor CBC every 2-3 days.
Anemia	Grades 1 & 2	Continue dosing at same dose level with weekly or more frequent monitoring as necessary
	Grade 3	• Hold GSK3368715 until resolved to Grade ≤ 1 within ≤ 14 days. • Transfuse and treat as necessary. • Monitor CBC at least twice a week. • Discuss with GSK Medical Monitor. • Re-start GSK3368715 at a reduced dose. • Discontinue GSK3368715 if not resolved to Grade ≤ 1 within ≤ 14 days.
	Grade 4	• Discontinue GSK3368715. • Transfuse and treat as necessary. • Monitor CBC every 2-3 days.
PR Interval	An increase in the PR Interval to >250 msec	• This interval should be based on the average of the triplicate ECGs • Discontinue GSK3368715 • Contact the medical monitor • Maintain proper electrolytes similar to recommendations for QTcF

Toxicity	Dose Adjustment/ Stopping Criteria	Management Guidelines
QRS Interval	An increase of >20% from baseline	• This interval should be based on the average of the triplicate ECGs • Discontinue GSK3368715 • Contact the medical monitor • Maintain proper electrolytes similar to recommendations for QTcF

QTcF	If >30msec and < 60 msec change from baseline AND manual QTcF <500 msec (average of three ECGs over at least 15 minutes)	• Continue current dose of GSK3368715
		  • Supplement electrolytes, particularly potassium and magnesium, to recommended levels:
		  (1) Maintain serum potassium > 4 mol/L
		  (2) Maintain serum magnesium levels >0.85 mmol/L
		  • Discontinue any concomitant medications with potential for QTcF prolongation.
		  • Consider 24 hour or longer telemetry monitoring if clinically indicated.

	If ≥ 60 msec change from baseline occurs OR QTcF ≥500 msec (average of three ECGs over at least 15 minutes)	Discontinue GSK3368715 and notify the GSK Medical Monitor.
Liver		Refer to procedures outlined in Section 7.1.1 Liver Safety Required Actions and Follow up Assessments
Diarrhea	Grade 1	Initiate supportive care including loperamide.
	Grade 2	• Initiate supportive care including loperamide. • Consider hold of GSK3368715 • Discuss with GSK Medical Monitor.
	Grade 3	• Treat as above plus consider intravenous (IV) hydration, hospital admission and prophylactic antibiotics as appropriate. • Hold GSK3368715 • Discuss with GSK Medical Monitor. • Re-start GSK3368715 at a reduced dose • Discontinue GSK3368715 if not resolved to Grade ≤1 within ≤14 days
	Grade 4	• Above plus consider intravenous (IV) hydration, hospital admission and prophylactic antibiotics as appropriate. • Discontinue GSK3368715

Toxicity	Dose Adjustment/ Stopping Criteria	Management Guidelines
Nausea/Vomiting	Grade 1	• Initiate supportive care with antiemetics as necessary.
	Grade 2	• Initiate supportive care with antiemetics as necessary • Consider hold of GSK3368715 until resolved to Grade ≤ 1 within ≤ 14 days • Discuss with GSK medical monitor
	Grade 3	• Supportive care as above, plus consider intravenous (IV) hydration, hospital admission and IV nutrition as appropriate. • Hold GSK3368715 until resolved to Grade ≤ 1 within ≤ 14 days • Discuss with GSK Medical Monitor. • Re-start GSK3368715 at same dose if resolved within ≤ 2 days • Re-start GSK3368715 at reduced dose if resolved > 2 days • Discontinue GSK3368715 if not resolved to Grade ≤ 1 within ≤ 14 days
	Grade 4	• Supportive care as above, plus consider intravenous (IV) hydration, hospital admission and IV nutrition as appropriate • Discontinue GSK3368715 if lasting >2 days despite supportive care
All Other Toxicity*	Grade 1	• Continue dosing with no change
	Grade 2	• Continue dosing with no change OR • Hold GSK3368715 for up to 1 week for toxicity to be < Grade 2, then continue at the same dose (dose reduction is required if the grade 2 toxicity is considered a DLT)
	Grade 3	• Hold GSK3368715 until resolved to Grade ≤ 1 within ≤ 14 days • Discuss with GSK Medical Monitor • Re-start GSK3368715 at a reduced dose Discontinue GSK3368715 if not resolved to Grade ≤ 1 within ≤ 14 days **Exception:** In case of clinically insignificant laboratory abnormalities resolving ≤ 2 days, re-start at same GSK3368715 dose possible after consultation of GSK Medical Monitor
	Grade 4	• Discontinue GSK3368715 • Restart of GSK3368715 may be considered upon

Toxicity	Dose Adjustment/ Stopping Criteria	Management Guidelines
		agreement between the GSK medical monitor and investigator in case of toxicities such as laboratory abnormalities (1) not associated with severe clinical symptoms requiring hospitalization, (2) lasting ≤ 2 days, and (3) responding to supportive care
Venous Thromboembolism	Grade 2-4	• Medical care including Anticoagulation and follow-up according to standard of care • Discontinue GSK3368715 • Restart of GSK3368715 may be considered upon agreement between the GSK medical monitor and investigator in case the investigator believes there is benefit to the participant, participant is reconsented and the participant is appropriately anticoagulated. • In situations where full anticoagulation is not medically appropriate, discontinue GSK3368715

Note: Exceptions to ≤ the drug-related Grade 1 requirement may be made for certain AEs as defined in Section 4.1.3.

10.13. Appendix 13: Khorana Score

Table 15 Predictive model for chemotherapy-associated VTE in the ambulatory setting

Patient characteristic	Points
CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.	

VTE: venous thromboembolism

Source: Key, 2019

10.14. Appendix 14: Protocol Amendment History

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

This amendment applies to all sites participating in the conduct of the study.

Amendment 02 22-FEBRUARY-2019

This amendment applies to all sites participating in the conduct of the study.

Overall Rationale for the Amendment:

Protocol Amendment 2 includes the following:

- Changes and clarifications made in the Schedule of Activities Tables (Table 1-Table 3). The SoA Tables have been modified to reflect that the first 21 days is the DLT Period. Revisions have also been made in the timings and frequency of some assessments. Visit windows have been added.
- Update to CTCAE version 5.
- Minor change to Inclusion criteria by not allowing participants with potential liver metastases (ALT < 5 x ULN) from Part 1 (Dose Escalation)
- Minor change to Exclusion Criteria by allowing 1st degree AV block and 2nd degree type 1 AV block.
- Addition of higher dose strength capsules (250mg).
- Administrative changes made throughout the document

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis	Intervention Groups and Duration – Change First Cycle to DLT period	Cycle is considered to be study drug dispensation which is 28 days. DLT period is first 21 days and is now defined as this per the Schedule of Activities Table.
1.3 Schedule of Activities: Table 1 Screening Procedures	Added Troponin I or T	Troponin levels > upper limit are exclusionary as per criteria 8j. This testing was not originally included in the Screening Procedures table. Also added testing to Appendix 2 (Table 8).
	Include further details to Tumor	There is a requirement for tumor samples at screening for those in

Section # and Name	Description of Change	Brief Rationale
	biopsy requirements	PK/PD cohort compared to other cohorts
1.3 Schedule of Activities: Table 2 and 3 Schedule of Activities	Significant changes made in the Schedule of Activities tables. • First 21 days changed from First Cycle to DLT period • Day 21 visit changed to Day 22 • Updated collection details for SAEs, AESIs and AEs • Moved Q3W assessments for ECOG and Vital Signs to Q4W • Added Urinalysis and Coagulations to Clinical Chemistry assessments • Modified timepoints for Tumor Imaging • Clarified Telephone Interview is only in Part 2 • Clarified language that the Tumor biopsy is optional unless patient is in PK/PD cohort and increased window for optional biopsy • Clarified language for extended 48 and 72 hour PK timepoints for Day 1 • Add a Day 22 sample for Circulating free (cf) ADMA and SDMA • Replaced Day 2 Whole Blood sample for PD	• First 21 days is DLT period, this is not considered first cycle (Section 1.1 Synopsis) • Visit to occur after DLT period is completed • To align with Section 8.3.1 • To align with PK visit days every 4 weeks • As per Appendix 2 (Table 8), not initially included in Schedule of Activities Table • Reduce imaging requirements after first 8 months on treatment • As described in Section 8.10, not initially added to Schedule of Activities Table • To add clarity for biopsy requirements per cohort • To add clarity • Recent preclinical data suggests that greater reduction of cfADMA may be observed upon longer periods of treatment with GSK3368715 • Recent preclinical data suggest that no significant changes in the levels of intracellular ADMA-hnRNP-A1 would be expected on Day 2. Analysis of

Section # and Name	Description of Change	Brief Rationale
	biomarkers with a Day 22 sample • Add visit windows	PBMCs from Day 22 will increase the likelihood of observing greater changes for this biomarker. • To add clarity
4.1.1 Part 1: Dose Escalation Phase	Dose Escalation: Move language here for dose increments after a grade 2 drug-related toxicity from statistics Section (9.2.1)	Dosing increments should be found within Study Design Section 4
4.1.3 Dose-Limiting Toxicity, 5.2 Exclusion Criteria 11, 6.2 Dose Modification, 8.3 Adverse Events and Serious Adverse Events, 9.6.2.2 Adverse Events, 9.6.2.3 Clinical Laboratory Evaluations	Update CTCAE to version 5	New version released
5.1 Inclusion Criteria	Criteria 2 Type of Participant and Disease Characteristics - Moved tumor biopsy details here and removed criteria 6 Criteria 3 Adequate organ function – allow ALT <5x ULN only in Part 2	To add clarity
5.2 Exclusion Criteria	Criteria 8d – Remove 1st degree AV block exclusion, clarify 2nd and 3rd degree Criteria 12 – Moved to Section 6.7.1	AV block grade 1 and AV block grade 2 Type 1 (Wenckebach) are frequently observed in normal young healthy volunteers (Am J Cardiol. 1977 Mar;39(3):390-5.) and should not preclude participation in the absence of heart disease and in the absence of symptoms.
5.3.1 Meals and	Clarified that Day 8 is serial PK	Day 8 was omitted initially as a serial

Section # and Name	Description of Change	Brief Rationale
Dietary Restrictions	day.	PK day with requirements for fasting
Table 5 Study Intervention	Added 250mg dose strength	New dose strength added for higher dosing cohorts
6.7.1 Prohibited Medications	Moved radiotherapy here, added allowance for palliative radiotherapy and added Therapy to section title	To add clarity
6.7.1 Prohibited Medications, 8.5 Intervention of Overdose, 9.6.3.1 Pharmacokinetic Parameters, 9.6.3.2 Statistical analysis of Pharmacokinetic data, 10.5 Appendix 5: Genetics	Removed GSK3326595 reference	GSK3326595 is not included in this protocol
7.1 Discontinuation of Study Intervention	Clarified survival follow-up timeframe	To add clarity on participant level
7.1.5 Stopping Rules for Clinical Deterioration	Copied language here for participants receiving clinical benefit but with disease progression from Summary section	To add clarity
7.4 Participant and Study Completion	Clarify definitions for study completion for Part 1 and Part 2	To provide clarity
8.0 Study Assessments and Procedures	The reference to study procedures and their timing changed from Section 1.3 to Table 1-Table 3.	To provide clarity
8.1 Efficacy	Update tumor imaging timepoints to align with updated Schedule of Activities Table	Reduce scan frequency after 8 months.

Section # and Name	Description of Change	Brief Rationale
8.2.4 Holter Monitoring	Clarified screening Holter vs on treatment Holter	To provide clarity
8.7.3 Tumor Biopsy Collection/Surgical Procedures	Clarified tumor biopsy requirements per cohorts to align with updates made to Schedule of Activities Table	To provide clarity
8.10.1 Qualitative Telephone Interviews	Clarified that interviews will only be conducted in Part 2	Align with Schedule of Activities Table
9.4.2.1 Efficacy Analyses	Clarify futility timeframe	To provide clarity
Whole Document	Administrative corrections were made throughout the protocol to correct minor inconsistencies and typographical errors	Provide clarity and correction.

Amendment 01 12-JULY-2018

This amendment applies to all sites participating in the conduct of the study.

Overall Rationale for the Amendment:

All revisions made were as per requirements from FDA.

Section # and Name	Description of Change	Brief Rationale
Section 4.1.3 Dose-Limiting Toxicity – Table 4	Modified DLT definitions to include 1) non-hematologic toxicities of Grade ≥3 regardless of duration except those as indicated in Table 4 and Grade 2 which lead to frequent dose interruptions despite best standard of care and limit dosing of GSK3368715 to <80% of expected dose or a delay of dosing >14 days 2) Grade 3 thrombocytopenia with significant haemorrhage or other hematologic toxicities leading to	Address required changes per FDA.

Section # and Name	Description of Change	Brief Rationale
	frequent dose interruptions despite best standard of care and limit dosing of GSK3368715 to <80% of expected dose	
Section 5.1 Inclusion Criteria, Number 2	Inclusion criteria for transitional cell carcinoma of the Urothelium updated to require participants to have progressed at least one line of systemic therapy.	Address required changes per FDA.
Section 10.12.1 Management of Selected Toxicities – Table 11	Incorporate 1) a hold of study drug, GSK3368715, for most related Grade 3 adverse events with possible re-start at reduced dose level for thrombocytopenia, anemia, diarrhea, nausea/vomiting, and all other non-hematologic toxicities as indicated in Table 11 2) discontinuation of study drug for related Grade 4 adverse events of any duration (excluding most lab abnormalities). Edited incorrect compound number from GSK3326595 to GSK3368715.	Address required changes per FDA.

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