Protocol Amendment 6

Study ID: 208441

Study Official Title: A randomized, double-blind, placebo-controlled, first time in human study to evaluate the safety, tolerability and pharmacokinetics of single (in both fed and fasted states) and repeat doses of GSK3494245 in healthy participants

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Date of the Document: 22-JUN-2023

TITLE PAGE

Protocol Title: A randomized, double-blind, placebo-controlled, first time in human study to evaluate the safety, tolerability and pharmacokinetics of single (in both fed and fasted states) and repeat doses of GSK3494245 in healthy participants

Protocol Number: 208441 Amendment 06

Compound Number: GSK3494245

Study Phase: Phase 1

Short Title: Safety, tolerability and pharmacokinetics investigation of GSK3494245 in healthy participants.

Sponsor Name and Legal Registered Address:

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Regulatory Agency Identifying Number(s):

EudraCT: 2019-004492-39

Approval Date: 21 Jun 2023

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY		
Document	**Date**	**Document Identifier**
Amendment 06	21 Jun 2023	TMF-16139466
Amendment 05	20-JAN-2022	TMF-13807226
Amendment 04	25-JAN-2021	TMF-11722099
Amendment 03	14-DEC-2020	2019N403028_03
Amendment 02	14-AUG-2020	2019N403028_02
Amendment 01	30-JUN-2020	2019N403028_01
Original Protocol	15-JUN-2020	2019N403028_00

Amendment [06]: 21 Jun 2023

Overall Rationale for the Amendment:
Incorporation of an additional single ascending dose (SAD) cohort to allow for exploration of single doses of GSK3494245 administered in the fed state.
For the multiple ascending dose (MAD) phase of the study, an option to assess three times daily (TID) dosing has been included to assess whether this regimen allows participants to achieve exposures within the predicted therapeutic range.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis 1.2 Schema 4.1 Overall Design 4.1.1 Single Ascending Dose (SAD) 4.4 Scientific Rationale for Study Design 4.6 Dose Escalation 6.3.1 Randomization 9.2 Sample Size Determination 9.3 Sample Size Sensitivity	Addition of SAD cohort Cohort 3a (and optional additional cohort) in order to explore single ascending doses in the fed state.	Based on the study design change allowing assessment of dosing in the fed state
1.1 Synopsis 4.1 Overall Design 4.1.1 Single Ascending Dose (SAD)	Subject numbers increased to 80,following additional of Cohort 3a	Based on the study design change allowing assessment of dosing in the fed state
1.1 Synopsis 4.1 Overall Design 4.1.4 Multiple Ascending Dose (MAD) 4.2 Number of Participants	Addition of three times daily dosing as an alternative MAD dosing regimen	Study design option included as this regimen may allow achievement of exposures in the therapeutic range
1.1 Synopsis 1.3.2 SoA 4.1 Overall Design	MAD dosing amended to be in fed state only	Study design changed based on emerging data
1.1 Synopsis 3 Objectives and Endpoints	MAD PK endpoints amended to include TID regimen endpoints	Based on addition of TID regimen and emerging PK data
1.3 Schedule of Activities (SoA)	Order of assessments clarified to include dosing	Based on addition of TID regimen as timepoints coincide with dosing time
1.3.1 SoA	14 h PK sample timepoint added to fed SAD and to MAD regimens	Sample added to allow for fuller assessment of PK profile
1.3.2 SoA	MAD regimens: TID dosing added; PK sampling scheme included for TID regimen and some amendments to sampling for BID regimen; 8 hour assessment for ECG and vital signs added to coincide with approximate Tmax of second of TID doses	Based on addition of TID regimen and emerging PK data

1.3.1 SoA 1.3.2 SoA 5.2 Exclusion criteria	Text clarified to state that COVID-19 laboratory tests include both polymerase chain reaction and lateral flow tests	Clarification of permitted tests
4.1.1 Single Ascending Dose (SAD)	Scheme updated to include Cohort 3a	Based on the study design change allowing assessment of dosing in the fed state
4.5.3 Predicted Safety Margins	Text updated to include method for calculating safety cover for TID regimen	Based on addition of TID regimen
4.6.1 Dose Escalation Committee	Update department name from SMG to Global Safety	Clarification
4.6.2 Dose Escalation and Safety Review Requirements for SAD part	Minimum data set from Cohort 3 for review prior to commencement of Cohort 3a specified.	Addition of text to include minimum data for review by the Dose Escalation Committee
4.6.3 Dose Escalation and Safety Review Requirements for MAD part	Inclusion of reference to BID or TID dosing; Removal of dosing n fasted state	Based on addition of TID regimen
5.1 Inclusion criteria	Upper age limit increased from 50 to 55 years	Updated, as lower age limit reflected earlier COVID-19 related precautions
5.2 Exclusion Criteria	Clarification of exclusion criteria 28 and 29 with regard to inability to eat gelatin	Clarification
5.3.1 Meals and Dietary Restrictions	Clarification of meal requirements for fed regimen	Clarification
5.4 Screen Failures	Clarification that reserve participants who pass screening but are not required may be rescreened	Clarification
6.2 Preparation/Handling/Storage/Accountability	Text added in case of unintended occupational exposure	Clarification
8 Study Assessments and Procedures	Text added to include rationale for collection sex, race and ethnicity data	Rationale added to provide clarity
8.4.1 Plasma Sample Collection and analyses	Volume of 14 h PK blood sample added	To clarify volume of added sampling timepoint
CCI [redacted]	[redacted]	[redacted]

9.5.2 Pharmacokinetic (PK) Analyses	Addition of analyses specific to TID regimen included. Addition of population PK modelling if feasible	Based on study design changes
10.1.4 Data Protection	Text added to clarify data protection standards for the study	Clarification
Throughout	Minor editorial and document formatting revisions	Minor, therefore have not been summarized

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A randomized, double-blind, placebo-controlled, first time in human study to evaluate the safety, tolerability and pharmacokinetics of single (in both fed and fasted states) and repeat doses of GSK3494245 in healthy participants.

Rationale: Visceral leishmaniasis (VL) is a parasitic disease caused by obligate intracellular protozoan parasites, particularly by the species *Leishmania donovani* and *Leishmania infantum/chagasi*. If left untreated, cases of VL are typically fatal. While therapies are available to treat the disease, none are ideal for use (due to toxicity, route of administration and cost) in resource poor settings where the disease is endemic. As such there is a real unmet medical need for new, short course oral drugs for the treatment of this disease.

The Phase 1 First Time in Human (FTIH) study is comprised of single ascending doses (SAD) and multiple ascending doses (MAD) in healthy participants, incorporating a food effect component to investigate the influence of food on the pharmacokinetics (PK) of GSK3494245. The study will evaluate the safety, tolerability and PK profile of SAD and MAD of GSK3494245. Results of this study are intended to be used to identify appropriate and well tolerated doses of GSK3494245 to be used in further studies. This study will be conducted at a single centre.

Objectives and Endpoints:

Objectives	Endpoints
Primary • To evaluate the safety and tolerability of single and repeat doses of GSK3494245 in healthy participants	• Adverse event reporting, treatment emergent, clinically significant changes from baseline in clinical laboratory, safety data, physical examinations, vital signs, 12 lead electrocardiograms (ECGs) and telemetry.
Secondary • To evaluate the PK profile of single (fasted and fed) and repeat doses of GSK3494245 in healthy participants • To examine dose proportionality following single	• SAD part: Derived PK parameters for GSK3494245 following single dose (fasted and fed) including area under the plasma drug concentration versus time curve (AUC(0-t), AUC(0-∞)), maximum observed plasma drug concentration (Cmax), time to maximum observed plasma drug concentration (Tmax), and apparent terminal half-life (t1/2) as data allow. • MAD part: as appropriate: o Day 1 AUC(0-t), AUC(0-∞), AUC(0-tau), Cmax,Tmax, t1/2

Objectives	Endpoints
doses of GSK3494245 • To assess accumulation and time-invariance ratios of GSK3494245 • To assess steady state following repeat doses of GSK3494245	○ Day 4-7 morning trough plasma concentration (Ctau), ○ Day 7 AUC(0-t), AUC(0-tau), Cmax, Tmax, t1/2, CLss ○ Additionally for TID regimen if conducted) : Day 6 evening dose AUC(0-t), AUC(0-tau), Cmax, Tmax, • Dose-proportionality assessment using derived PK parameters, as data allow: SAD part: AUC(0-∞), Cmax MAD part: • Accumulation ratios assessment*, where data allow: RAUC(0-tau), RCmax, RCtau. Time-invariance ratio calculation as AUC(0-tau on Day 7 to AUC(0-∞) on Day 1. Additionally for TID regimen if conducted:Time-invariance ratio calculation for TID regimen as AUC(0-tau) on Day 6 evening dose to AUC(0-∞) on Day 1 • Steady state assessment for MAD part: Ctau
CCI [redacted]	

* Accumulation ratios calculated as the ratio of last dose to first dose PK parameters: RAUC(0-tau) = AUC(0-tau) on last dose (with the exception of TID for which the evening dose on Day 6 will be used) to AUC(0-tau) on first dose, RCmax = Cmax on last dose to Cmax on first dose, RCtau= Ctau on last dose to Ctau on first dose.

Overall Design: This study will be a randomized, double-blind, placebo-controlled, 2-part study of the oral administration of GSK3494245 in healthy participants. As this will be the first time GSK3494245 is administered to humans, the study design may change based on emerging data as the study progresses.

This study is planned to include approximately 80 participants:

- The SAD part will consist of a single-dose escalation phase in up to 3 cohorts and a food effect cohort.
- Cohorts 1 and 2 will comprise of a 4-way crossover within each cohort. Participants will receive three doses of GSK3494245 and a randomised placebo dose, administered in the fasted state. An optional third cohort may be included to further evaluate safety or PK or to evaluate additional doses.
- Cohort 3 will investigate the effect of food following a single dose. It will comprise of a 4-way crossover in which participants will receive GSK3494245 and placebo in both fasted and fed conditions and in a 1:1 ratio.
- On completion of Cohort 3, Cohort 3a will assess single ascending doses of GSK3494245 taken with food, following the same 4-way crossover design as Cohorts 1 and 2. Participants will receive three doses of GSK3494245 and a randomised placebo dose. An optional cohort may be included to further evaluate safety or PK or to evaluate additional dose levels.
- Up to ~~8~~ 10 different dose levels will be studied in the SAD part.
- The MAD part will be a twice-daily (BID) 7-day repeat dose design in up to 5 cohorts of participants (Cohorts 4, 5, 6, 7 and 8), with doses administered in the fed state. Based on emerging data, the dosing regimen may be altered to a three-times daily (TID) regimen in fed conditions, with the three doses administered 6 hours apart on each day.. Up to a maximum of 5 dose levels will be studied in the MAD part. CCI [redacted]

All participants in the study will attend a screening visit within 28 days prior to their first dose and a follow-up visit within 7-14 days after their final dose. If required, additional follow-up visits may be scheduled.

Disclosure Statement: This is a sequential, cross-over (SAD part, within cohort), parallel group (MAD part), interventional study that is participant, investigator and sponsor study team blinded (apart from unblinded team members, prespecified in the protocol).

Number of Participants:

A sufficient number of participants will be screened to ensure approximately 80 participants are eligible to be randomized, (SAD part: 8 participants into each of Cohorts 1-2 and 3a and up to 16 participants for Cohort 3; MAD part: 8 participants into each of Cohorts 4-8). A participant is considered evaluable if they complete both screening and at least one intervention period in the SAD part, or the 7-day intervention period in the MAD part. Participants that take part in the SAD part of the study cannot take part in the MAD part. If participants prematurely discontinue the study, then additional replacement participants may be recruited and assigned to the same treatment sequence, at the discretion of the Sponsor in consultation with the Principal Investigator in both SAD and MAD parts.

Intervention Groups and Duration:

Single Ascending Dose (SAD) and Food Effect (FE) Study Duration of Cohorts 1-3, 3a

Screening	All screening assessments to be completed within 28 days prior to first-dose.
Intervention Period	Cohorts 1 and 2 will comprise of 4 intervention periods, investigating 4 dosing regimens under fasted conditions. Participants will receive three doses of GSK3494245 and a randomised placebo dose, administered in the fasted state. Cohort 3 will comprise of 4 intervention periods, investigating both a single dose of GSK3494245 and placebo in a randomised cross-over design, i.e. each under fasted then fed conditions and vice versa. Cohort 3a will comprise of 4 intervention periods, investigating 4 dosing regimens under fed conditions. Participants will receive three doses of GSK3494245 and a randomised placebo dose, administered in the fed state. Each regimen will consist of a single dose given on Day 1, with participants in-house for 4 nights and 5 days. Participants will be admitted to the unit the day before dosing (Day -1) and will remain in the unit overnight until Day 4, when they will be discharged after completion of all assessments.
Washout Period	At least 48 hrs or 5-half-lives (whichever is longer) between each dose for an individual participant.
Follow-up	At least 7 days and no greater than 14 days after last study drug administration. If warranted, additional follow-up visits may be scheduled.
Total duration	Cohorts 1, 2, 3 and 3a will be approximately 15-16 weeks each.

Multiple Ascending Dose (MAD)

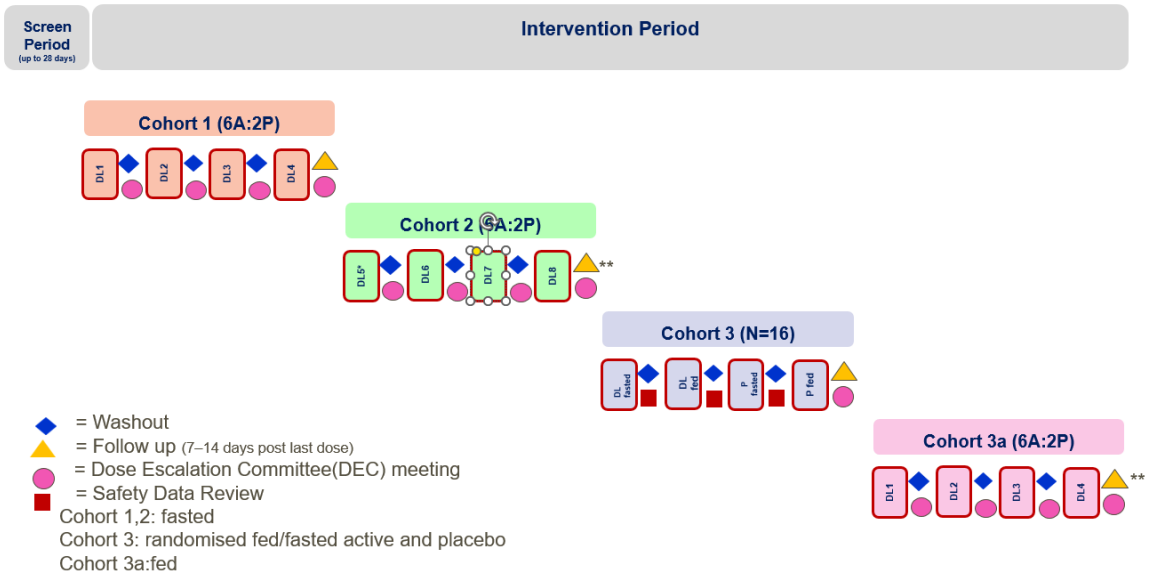
Study Duration of Cohorts 4-8

Screening	All screening assessments to be completed within 28 days prior to first-dose.
Intervention period	Each Cohort will consist of one intervention period, comprising of a 7-day treatment duration (Days 1-7), with participants in-house for 8 nights and 9 days. Participants will be admitted to the unit the day before dosing (Day -1) and will remain in the unit overnight until Day 8, when they will be discharged after completion of all assessments.
Follow-up	At least 7 days and no greater than 14 days after last study drug administration. If warranted, additional follow-up visits may be scheduled.
Total duration	Approximately 7-8 weeks.

Data Monitoring Committee: Yes

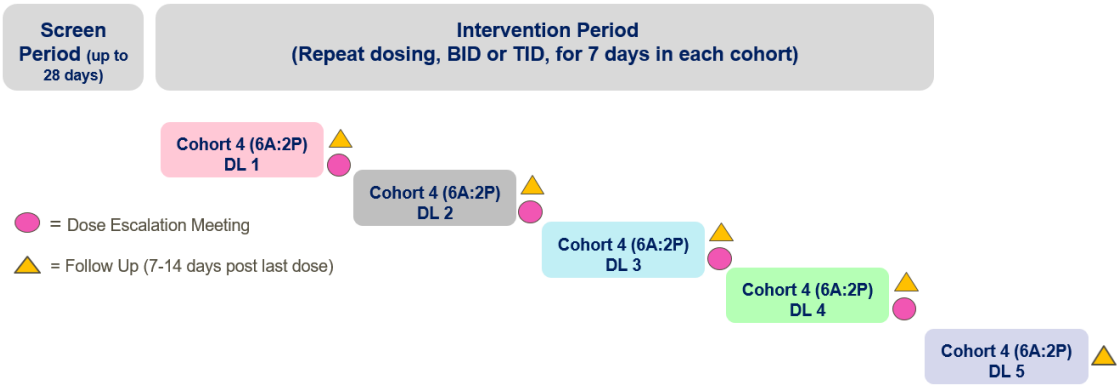
1.2. Schema

Study Design (Single Ascending Dose and Food Effect)



A = active drug; DL = dose level; DLX = dose level to be determined; Fed = fed conditions; P = placebo.
*Depending on the outcome of review of all available safety and PK data from Cohort 1, the DEC may repeat DL4 at the start of Cohort 2. Then escalate to DL5, DL6 and DL7 as needed.
Note: In Cohorts 1, 2and 3a, the first two participants, within each intervention period, will act as sentinels. Cohorts 1, 2, 3 and 3a comprise of a 4-way cross-over design.
** The dosing schedule may be adjusted to add an additional cohort to further evaluate safety or PK findings at a given dose level, or to evaluate additional doses. The additional cohorts will be up to 8 participants following the same design and dose escalation principles as Cohorts 1 and 2.

Study Design (Multiple Ascending Dose)



A = active drug; BID = twice-daily; TID = three times-daily; DL = dose level; P = placebo. Day 7 is morning dose only.
Note: For each new dose level the first two subjects in each cohort will act as sentinels.

1.3. Schedule of Activities (SoA)

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 (SoA) table (Section 1.3.1 and Section 1.3.2), are essential and required for study conduct.

Supplementary study conduct information not mandated to be present in this protocol is provided in the Study Reference Manual (SRM). The SRM will provide the site personnel with administrative and detailed technical information that does not impact participant safety.

This section lists the procedures and parameters of each planned study assessment. The exact timing of each assessment is listed in the SoA table (Section 1.3.1 and Section 1.3.2).

The following points must be noted:

- If assessments are scheduled for the same nominal time, THEN the assessments are recommended to occur in the following order:
    1. 12-Lead ECG
    2. Vital Signs
    3. Blood Draws
    4. Dosing

Note: 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, including safety, pharmacokinetic, or other assessments 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.
- The change in timing or addition of time points for any planned study assessments must be documented in a Note to File, which is 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.
- No more than 500 mL of blood will be collected over the duration of the study, including any extra assessments that may be required.
- The Institutional Review Board/Independent Ethics Committee (IRB/IEC) will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the Informed Consent Form.

  A table defining the allowed variance in timings of assessments without being considered a protocol deviation will be included in the SRM.

1.3.1. Single Ascending Dose (SAD) Cohorts 1--3, 3a

Procedure	**Screening** (Up to 28 days before Day 1)	**Study Period** (Days)					**Follow-Up** (7-14 days post last dose)[1] **/ Early Withdrawal**[2]	**Notes**
		-1	1	2	3	4		
Outpatient Visit	X						X	
COVID 19 Testing	X	←=====X=====→				X		*Screening: frequency in accordance with site procedures.* *Day -1 to 3: Ad hoc testing based on clinical presentations and site procedures.* *Day 4: Sample collected upon discharge*
Admission to Clinical Unit		X						
Inpatient Stay at Clinical Unit		←======X======→						
Discharge from Clinical Unit						X		*Following completion of all assessments.*
Informed Consent	X							
Inclusion and Exclusion Criteria	X							
Demography	X							
Full Physical Examination, including Weight and BMI Calculation	X*	X		X		X	X	**The full examination will also include height measurement.* *Refer to Section 8.1.1 for details of physical examinations.* *BMI calculation from Screening to Day -1 of first treatment period will be verified against eligibility criteria.*
Drug/Alcohol/Smoking Screen	X	X						*Tests include alcohol breath test, smoking breath test and urine drug screen.*
HIV, Hepatitis B and C Screening	X							
Holter Monitoring (24 hours)	X							*Refer to Section 8.1.4 when rescreening a participant.*
Medical/Medication/Drug/Alcohol History	X							

Procedure	**Screening** (Up to 28 days before Day 1)	**Study Period** (Days)					**Follow-Up** (7-14 days post last dose)[1] **/ Early Withdrawal**[2]	**Notes**
		-1	1	2	3	4		
Haem/Chem/Urinalysis Test (Include Liver Chemistries)	X	X	U	X		X	X	*Blood samples will be collected in a **fasted** state at Day -1, Pre-dose and Follow-Up visit.* ***Urine Sampling:*** • *First void, where possible.* • *If trace protein or blood in urine is detected, a repeat test will be performed within 24 hrs, except if the repeat test is required at Screening the site should repeat as soon as possible within the screening period. If results are considered abnormal (guidance in SRM), further quantification is required at the investigator's discretion.* • *U = Urine sample only. To assess urine creatinine and urine albumin:creatinine ratio.* • CCI [redacted]
Lactate Sampling		X	X	X	X	X		*Blood sample to assess lactate at the following timepoints: Pre-dose, 1hr, 2hr, 4hr, 6hr, 8hr, 12hr, 16hr and 24hr after dosing, Day 3 and Day 4.*
Urine Sampling (metabolism)			← X→					***Pre-dose:** An approx. 20ml urine sample will be taken.* ***Post-dose**: All urine from each participant will be collected from 0-24 hr post dosing. Urine weight will be recorded.* *Details of urine collection and processing are described in the SRM.*

Procedure	**Screening** (Up to 28 days before Day 1)	**Study Period** (Days)					**Follow-Up** (7-14 days post last dose)[1] **/ Early Withdrawal**[2]	**Notes**
		-1	1	2	3	4		
CCI [redacted]								
PK Blood Sampling			X	X	X*			*PK blood samples will be collected at the following time points: Pre-dose, post dose: 10min, 30min, 1hr, 1.5hr, 2hr, 2.5hr, 3hr, 4hr, 5hr, 6hr, 8hr, 10hr, 12hr; 14 hr (Cohort 3 and Cohort 3a only) and 24hr (*and more than 24hr if required).* *The PK sampling time points stated **may be modified** depending on emerging PK information as appropriate.* *Blood volumes to be collected include:* • *2 mL for all time-points from pre-dose to 10 hr.* • *5 mL for time-points 12hr and 24 hr, (*more than 24hr if required)*

Procedure	**Screening** (Up to 28 days before Day 1)	**Study Period** (Days)					**Follow-Up** (7-14 days post last dose)[1] **/ Early Withdrawal**[2]	**Notes**
		-1	1	2	3	4		
12-Lead ECG	T	X	T*	← X →				*Vital signs to include HR, BP, temperature and respiration rate. BP and HR will be assessed in a supine position.* *12-Lead ECG and Vital Signs to be conducted on Day -1 and pre-dose on Day 1 and then at the subsequent time points post-dose: 30 min, 1 hr, 1.5hr, 2hr, 2.5hr, 4hr, 8hs, 12hr, 24 hr, 48 hr* *Timings will be reviewed as cohorts progress and may be adjusted to ensure appropriate measurements relative to peak concentrations for subsequent cohorts.* *T = assessments done in **triplicate**.* **At **Pre-dose** only (except tympanic temperature and respiration rate)* *If any abnormal ECG reading is recorded, refer to Section 7.1.5 for appropriate action.*
Vital Signs	X	X	T*	← X →		X	X	
Telemetry			← X →					*Continuous at least 24hr post-dose. Initiate at least 15 min. prior to dosing.* *If a waveform abnormality is detected, then extend for further 24hr.*

Procedure	**Screening** (Up to 28 days before Day 1)	**Study Period** (Days)					**Follow-Up** (7-14 days post last dose)[1] **/ Early Withdrawal**[2]	**Notes**
		-1	1	2	3	4		
Meals		X	X*	X	X	X		***Fasting regimens:** On Day 1, participants will have fasted 8hr overnight prior to dosing. Breakfast will be served approximately 3 hr s after dosing.* ***Fed regimens:** On Day 1, participants will fast 8hr overnight and an adapted standard breakfast will be served approximately 30 minutes prior to dosing. For the rest of Day 1, meals will be served per site schedule* Meals will be served as per the site schedule on Days -1, 2, 3 and 4. ***Water before dosing**: permitted on an ad lib basis up to 1hr before dosing. No water to be taken in the hour prior to dosing except for the liquid part of the adapted standard breakfast for the Fed regimen.* ***Water to be taken with dose**: At least 8 fl oz (240ml) to be taken.* ***Water after dosing**: no water to be taken within 1 hr after dosing. Permitted on an ad lib basis after 1hr post dosing*
Randomization			X					
Study Treatment			X					
AE Review		←=======X=======→					X	
SAE Review	X	←=======X=======→					X	
Concomitant Medication Review	X	←=======X=======→					X	

1) Follow-Up visit: If a participant meets the criteria of a participant with known COVID-19 positive contacts in the past 14 days, or is determined to have a high clinical index of suspicion for COVID-19, or has a positive laboratory (PCR or lateral flow test) confirmation of COVID-19 infection the Follow-Up visit may be deferred beyond 14 days after the last dose and scheduled/rescheduled at a timepoint as deemed appropriate by the Investigator.

2) Early Withdrawal visit: The Early Withdrawal Visit can be scheduled as needed and does not need to align with the duration allowed for the Follow-Up visit.

Any changes in the timing or addition of time points for any planned study assessments as the result of emerging pharmacokinetic data from this study must be documented and approved by the relevant study team member and then archived in the sponsor and site study files but will not constitute a protocol amendment. The Competent Authority (CA) and ethics committee (EC) will be informed of any safety issues that constitute a substantial amendment and require alteration of the safety monitoring scheme or amendment of the informed consent form (ICF). The changes will be approved by the CA and the EC before implementation.

1.3.2. Multiple Ascending Dose (MAD) Cohorts 4-8

Procedure	**Screening** (Up to 28 days before Day 1)	**Study Period** (Days)									**Follow-up** (7-14 days post last dose) [1] **/ Early Withdrawal**[2]	**Notes**
		-1	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**		
Outpatient Visit	X										X	
COVID 19 Testing	X	←==========X==========→										*Screening: frequency in accordance with site procedures.* *Day -1 to 8: Ad hoc testing based on clinical presentations and site procedures.* *Day 8: Sample collected upon discharge*
Admission to Clinical Unit		X										
Inpatient Stay at Clinical Unit		←==========X==========→										
Discharge from Clinical Unit										X		*Following completion of all assessments.*
Informed Consent	X											
Inclusion and Exclusion Criteria	X											
Demography	X											
Full Physical Examination	X*					X					X	**The full examination will also include height measurement, weight and BMI Calculation. Refer to Section 8.1.1for details of physical examinations.* *§BMI calculation at Screening and Day -1 will be verified against eligibility criteria.* *Additional exams/screens may be performed, or brief exams made full exams, by the Investigator, as deemed necessary (e.g. where safety or laboratory findings indicate). Tests will be conducted within site specified standards.* *Refer to Section 8.1.1 for details of physical*
Brief Physical Examination		X§		X						X		

Procedure	Screening (Up to 28 days before Day 1)	Study Period (Days)									Follow-up (7-14 days post last dose) [1] / Early Withdrawal [2]	Notes
		-1	1	2	3	4	5	6	7	8		
												examinations.
Drug/Alcohol/Smoking Screen	X	X										*Tests include alcohol breath test, smoking breath test and urine drug screen.*
Medical/Medication/ Drug/Alcohol History	X	X										
HIV, Hepatitis B and C Screening	X											
Holter Monitoring (24 hour)	X											
Haem/Chem Test	X*	X*	X	X*	X*	X	X*	X	X*		X*	*Blood samples will be collected in a **fasted** state.* ** Include liver chemistry*
Urinalysis Test	X	X	X	X	X	X	X	X	X		X	***Urine Sampling:*** - *First void, where possible.* - *If trace protein in urine is detected, a repeat test can be performed (within 24 hours, except if the repeat test is required at Screening the site should repeat as soon as possible within the screening period). If results are considered abnormal (guidance in SRM), further quantification is required at the investigator's discretion.* - CCI [redacted]
CCI [redacted]												

Procedure	Screening (Up to 28 days before Day 1)	Study Period (Days)									Follow-up (7-14 days post last dose)[1] / Early Withdrawal[2]	Notes
		-1	1	2	3	4	5	6	7	8		
CCI												
Lactate Sampling			X	X			X					*Blood sample to assess lactate at the following timepoints:* - ***Day 1, 2 and 5**: predose and post morning dose at 2hr, 4hr, 8hr, 12hr*, 16hr.* - ** (prior to evening dose)* *Assessment timepoints may be modified, as deemed necessary by the Investigator and sponsor.*
Telemetry			←X→					←X→				*Continuous at least 48 hr post-morning dose on Day 1 and at least 24 hr post morning dose on Day 6. Initiate at least 15 min. prior to first dose on Day 1 and Day 6 respectively.* *If a waveform abnormality is detected, then extend for further 24hr*
Randomisation			X									
Study Treatment			X	X	X	X	X	X	X*			***BID dosing:** GSK3494245 or placebo will be administered using a 12hr dosing interval (morning and evening dosing).* ***TID dosing:** GSK3494245 or placebo will be administered using a 6 hr dosing interval (morning, afternoon and evening dosing)* *Only single dose on last day of dosing period.
12-Lead ECG	T	X	T	X	X	X	X	X	X		X	*12-Lead ECG to be conducted on Day-1 and pre-dose Day 1 and then at the subsequent time points post first-dose: 30 min, 1 hr, 1.5hr, 2hr, 2.5hr, 4hr, 6hr, 8hr 12hr and 14hr.* *Day 2 to 7: 12-Lead ECG at pre-morning dose* *Timings will be reviewed as cohorts progress and may be adjusted to ensure appropriate measurements relative to peak concentrations for*

Procedure	**Screening** (Up to 28 days before Day 1)	**Study Period** (Days)									**Follow-up** (7-14 days post last dose) [1] **/ Early Withdrawal**[2]	**Notes**
		-1	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**		
												subsequent cohorts *T = assessments done in **triplicate**, **at Pre-dose only**.* *If any abnormal ECG reading is recorded, refer to Section 7.1.5 for appropriate action.*
Vital signs	X	X	T*	X	X	X	X	X	X	X	X	*Vital signs to include HR, BP, temperature and respiration rate.* *BP and HR will be assessed in a supine position.* *Vital Signs to be conducted on **Day-1** and pre-morning dose **Day 1** and then at the subsequent time points **post first-dose**: 2hr, 4hr, 6hr, 8hr, 12hr and 14hr.* ***Days 2-6:** pre-morning dose assessments only.* *Vitals Signs to be conducted on pre-morning dose **Day 7** and then at the subsequent time points post-morning dose; 2hr, 4hr, 6hr, 24hr (Day 8)* *Timings will be reviewed as cohorts progress and may be adjusted to ensure appropriate measurements relative to peak concentrations for subsequent cohorts* *T = assessments done in **triplicate**,* **At **Pre-dose only** (except tympanic temperature and respiration rate)*
PK Blood Sampling			<==========X==========>									*PK samples will be collected at the following time points in case of BID administration:* ***Day 1**: pre-morning dose, 10min, 30min, 1hr, 1.5hr, 2hr, 2.5hr, 3hr, 4hr, 5hr, 6hr, 8hr, 10hr, and 12hr (12hr taken at **pre-dose**).* ***Days 4 – 6:** Morning pre-dose PK samples collected for each dose* ***Day 7**: PK samples will be collected pre- dose and at*

Procedure	**Screening** (Up to 28 days before Day 1)	**Study Period** (Days)									**Follow-up** (7-14 days post last dose) [1] **/ Early Withdrawal**[2]	**Notes**
		-1	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**		
												the following time points post dose: 10min, 30min, 1hr, 1.5hr, 2hr, 2.5hr, 3hr, 4hr, 5hr, 6hr, 8hr, 10hr, 12hr and 14hr *PK samples will be collected at the following time points in case of TID administration:* ***Day 1**: pre-morning dose, 10min, 30min, 1hr, 1.5hr, 2hr, 2.5hr, 3hr, 4hr, 5hr, 6hr (6hr taken at **pre-dose**).* ***Days 4 – 6:** Morning pre-dose PK samples collected for each dose* ***Day 6**: PK samples will be collected pre-evening dose and at the following time points post evening-dose: 10min, 30min, 1hr, 1.5hr, 2hr, 2.5h,3hr, 4hr, 5hr and 6hr* ***Day 7**: PK samples will be collected pre-dose and at the following time points post dose: 10min, 30min, 1hr, 1.5hr, 2hr, 2.5hr, 3hr, 4hr, 5hr, 6hr, 8hr, 10hr, 12hr and 14hr* *Only one dose is administered on Day 7* *The time points stated may be **modified** depending on emerging SAD and MAD PK profiles.* *All samples collected will be 2mL in volume*
Urine Sampling (metabolism)			←X→					←X→				***Pre-dose Day 1:** An approx. 20ml urine sample will be taken.* ***Post-dose Day 1**: All urine from each participant will be collected from 0-24 hr post morning dosing.* ***Day 6** All urine from each participant will be collected from 0-24 hr post morning dosing.* *Urine volume and weight will be recorded. Details of urine collection and processing are described in the*

Procedure	**Screening** (Up to 28 days before Day 1)	**Study Period** (Days)									**Follow-up** (7-14 days post last dose) [1] **/ Early Withdrawal**[2]	**Notes**
		-1	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**		
												SRM.
CCI [redacted]												
Meals		X	X	X	X	X	X	X	X	X		*On Day 1 through to Day 7, participants will receive an adapted standard meal containing 35-40% fat 30 mins prior to each dosing.* *Participants will receive standardized meals scheduled at the same time on each day.* *Meals will be served as per the site schedule on Days -1 and Day 8.* Water is permitted on an ad lib basis apart from 1 hour prior to and after each dose administration. Doses will be taken with approximately 240 mL water.
AE review		←==========X==========→									X	
SAE review	X	←==========X==========→									X	
Concomitant medication review	X	←==========X==========→									X	

1) Follow-Up visit: If a participant meets the criteria of a participant with known COVID-19 positive contacts in the past 14 days, or is determined to have a high clinical index of suspicion for COVID-19, or has a positive laboratory confirmation(PCR or lateral flow test) of COVID-19 infection the Follow-Up visit may be deferred beyond 14 days after the last dose and scheduled/rescheduled at a timepoint as deemed appropriate by the Investigator.

2) Early Withdrawal visit: The Early Withdrawal Visit can be scheduled as needed and does not need to align with the duration allowed for the Follow-Up visit.

Any changes in the timing or addition of time points for any planned study assessments as the result of emerging pharmacokinetic data from this study must be documented and approved by the relevant study team member and then archived in the sponsor and site study files but will not constitute a protocol amendment. The Competent Authority (CA) and ethics committee (EC) will be informed of any safety issues that constitute a substantial amendment and require alteration of the safety monitoring scheme or amendment of the informed consent form (ICF). The changes will be approved by the CA and the EC before implementation.

2. INTRODUCTION

2.1. Study Rationale

Visceral leishmaniasis (VL) is a parasitic disease caused by obligate intracellular protozoan parasites, particularly by the species *Leishmania donovani* and *Leishmania infantum/chagasi*. If left untreated, cases of VL are typically fatal. While therapies are available to treat the disease, none are ideal for use (due to toxicity, route of administration and cost) in resource poor settings where the disease is endemic. As such there is a real unmet medical need for new, short course oral drugs for the treatment of this disease.

The Phase 1 program will comprise a First Time in Human (FTIH) study of single ascending doses (SAD) and multiple ascending dose (MAD) in healthy participants, incorporating a food effect component to investigate the influence of food on the pharmacokinetics (PK) of GSK3494245. The study will evaluate the safety, tolerability and PK profile of SAD and MAD of GSK3494245. Results of this study are intended to be used to identify appropriate and well tolerated doses of GSK3494245 to be used in further studies. This study will be conducted at a single centre.

2.2. Background

Visceral leishmaniasis is identified as a Neglected Tropical Disease by the World Health Organisation. As a systematic approach to drug discovery is relatively new in this neglected disease, GSK3494245 was identified through a phenotypic screening approach. GSK3494245 is a highly selective *Leishmania* proteasome inhibitor for the treatment of visceral leishmaniasis (VL), acting on chymotrypsin like activity. This was established through comprehensive mode of action (MOA) studies utilising different approaches. GSK3494245 is believed to principally be an inhibitor of the ubiquitin-proteasome system (UPS) within the genus *Leishmania,* specifically the beta subunits of the 20s proteasome catalytic complex. The biochemical and molecular basis for the high selectivity of GSK3494245 to the *Leishmania* proteasome vs. human proteasome is described in Wyllie, 2019.

More detailed information relating to non-clinical pharmacology, safety pharmacology, PK and metabolism, toxicology and other pre-clinical data can be found in the GSK3494245 Investigators Brochure (IB) [GlaxoSmithKline Document Number RPS-CLIN-017065].

2.3. Benefit/Risk Assessment

There is no direct benefit to the participants taking part in this study.

To date, GSK3494245 has not been administered to human participants; therefore, no clinical data are available. This is the first study proposed in human participants with GSK3494245.

The risk assessment of GSK3494245 is based on the pre-clinical studies conducted to date. Summaries of findings from these pre-clinical studies can be found in the Investigators Brochure (IB).

The proposed risk assessment and management plan for the study has been developed in accordance with the tenets of European Medicines Agency (EMA) guideline on strategies to identify and mitigate risks for FTIH clinical trials with investigational medicinal products [European Medicines Evaluation Agency (EMEA)/ Committee for Medicinal Products for Human Use EMEA/CHMP/SWP/28367/07]. GSK has assessed this study for any risks that may be posed to participants taking part. Only healthy male participants will participate in this study.

In this study, safety will be monitored closely both by subjective reporting and by objective means, i.e. serial assessments of vital signs, clinical laboratory information and cardiac monitoring. The study will be run in a clinical unit with immediate access to hospital facilities for the treatment of medical emergencies. Participants will remain monitored in the clinic for the duration of each intervention period and will only be discharged from the unit at the end of each intervention period, if the investigator deems it safe to do so. In light of the coronavirus 2019 (COVID-19) pandemic, all participants will be screened for COVID-19 prior to, during and at the end of the study period.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of GSK3494245 may be found in the IB [GlaxoSmithKline Document Number RPS-CLIN-017065].

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data / Rationale for Risk	Mitigation Strategy
Investigational Medicinal Product (IMP) GSK3494245		
Kidney	• Kidney tubular dilatation, tubular basophilia and interstitial inflammatory cell infiltration was noted in male and female mini-pigs dosed at 300 mg/kg/day • Based on in vitro data, GSK3494245 has the potential to inhibit renal transporters involved in the excretion of creatinine.	Inclusion criteria: • Urinary analysis at screening to be free of blood and protein. If trace protein or blood is found, a repeat test will be performed within 24 hrs, or as soon as possible within screening period. Exclusion criteria: • History of current or past significant renal diseases to be excluded, e.g. Acute Kidney Injury, parenchymal kidney disease. Not to exclude history of renal calculi • Screening eGFR (CKD-EPI) <90 ml/min/1.73m^2 • Screening urine albumin:creatinine ratio >30 mg/g (>3 mg/mmol) Monitoring: • Serum renal function and urinary analysis monitoring (first void if possible) • Urine albumin: creatinine ratio (first void if possible) • Urine glucose by dipstick, if dipstick is positive then send for laboratory urine

Potential Risk of Clinical Significance	Summary of Data / Rationale for Risk	Mitigation Strategy
		glucose with contemporaneous serum glucose. • By observing the PK safety margin for renal findings by targeting up to the total daily AUC and Cmax to be below the female mini pig NOAEL (AUC24h of 48700 ng×h/mL and a mean plasma Cmax of 6100 ng/mL). • Monitor for clinical symptoms of polyuria and polydipsia; if symptoms suggestive then exclude endocrine causes and quantify urine output. Participant withdrawal • New onset of any clinically significant and persistent (within 48 hrs) haematuria as confirmed by microscopy. • New onset of clinically significant and persistent (within 48 hrs) proteinuria (Spot Urine Albumin Creatinine (ACR) ratio ≥30mg/mmol) in the absence of another clinical explanation e.g. calculus / infection. • Change in serum creatinine >26 µmol/L (0.3 mg/dl) from baseline or > 50 % from baseline. If change in serum creatinine measures at >26 µmol/L (0.3 mg/dl), repeat within 24 hrs. If confirmed, the participant will be withdrawn. If a participant meets the

Potential Risk of Clinical Significance	Summary of Data / Rationale for Risk	Mitigation Strategy
		withdrawal criteria for serum creatinine, then further investigations will be performed. Study Stopping criteria The study will be halted if 1 or more participants across all study parts develop any of the above withdrawal criteria and it is considered to be related to GSK3494245 (in the opinion of the investigator in consultation with the Medical Monitor). CCI  Renal transporter effects (for MAD part): • For any participant with a persistent (2 consecutive readings) rise in SrCr≥30% or a fall in eGFR≥30% from baseline, a sample will be taking for Cystatin-C evaluation of eGFR to aid understanding of

Potential Risk of Clinical Significance	Summary of Data / Rationale for Risk	Mitigation Strategy
		whether changes in creatinine levels are related to effects on renal transporters. • If no other renal markers are abnormal (serum urea, phosphate, potassium, calcium magnesium white blood counts, urine glycosuria, uACR), dosing of the individual participant may continue while eGFR with Cystatin-C is being evaluated. • If any other renal markers are abnormal (serum urea, phosphate, potassium, calcium, magnesium, white blood counts, urine glycosuria, uACR) in addition to a persistent rise in SrCr≥30% or a fall in eGFR≥30% from baseline, the participant will be withdrawn from the study (Cystatin-C still checked) • If two or more participants have a fall in eGFR≥30% or rise in SrCr≥30% accompanied by abnormality in any other renal markers, the study will be temporarily halted for evaluation.

Potential Risk of Clinical Significance	Summary of Data / Rationale for Risk	Mitigation Strategy
Stomach	• Erosion of glandular region of stomach of female rats dosed at 100mg/kg/day and also in male and female rats dosed at 300 mg/kg/day	Contact time with stomach in humans are likely to be short (less than 2 hrs) and concentrations considered in the human study are much lower than in the Rat study. Inclusion/exclusion criteria: • Participants with current or history of clinically significant gastritis or gastroduodenal ulcers or regular NSAID use, will be excluded from the study based on medical history at screening. Monitoring: • Participants will be monitored for GI symptoms reported as adverse events. Participant withdrawal: • Any reported symptoms which in the investigator's opinion raises a clinical suspicion of gastric erosion/ulcers, will be referred to a gastro enterology specialist for further management, and endoscopy (if required).
Cardiovascular	• Isolated Non-Sustained Ventricular Tachycardia (NSVT) - 5 episodes of >3 abnormal beats	Inclusion/exclusion criteria: • Holter monitoring at study screening.

Potential Risk of Clinical Significance	Summary of Data / Rationale for Risk	Mitigation Strategy
	observed in one mini-pig administered low dose of 60 mg/kg only	• Exclusion of participants with waveform abnormalities including premature ventricular contraction (PVC) triplets and more than 500 single PVCs in 24 hrs, or any other abnormalities at the discretion of investigator. Monitoring: • In SAD: Telemetry monitoring for 24 hrs post-treatment. In MAD: Telemetry on Day 1, 0-48 hours post-treatment and Day 6 for 0-24 hours, post morning treatment). If waveform abnormality detected then extend for further 24hr. • Participant withdrawal: • NSVT > 3 beats or PVC triplets on telemetry.
Liver	• Hepatocellular hypertrophy noted in female rats dosed 100mg/kg/day and male and female rats dosed at 300mg/kg/day • Increase in glutamate dehydrogenase and alanine aminotransferase activities in female rats dosed at 100 mg/kg and 300 mg/kg	Exclusion criteria: • History of current or past significant hepatic diseases excluded: HBsAg positive, HCV Ab positive (with RNA positive) • Known hepatic or biliary abnormalities to be excluded.

Potential Risk of Clinical Significance	Summary of Data / Rationale for Risk	Mitigation Strategy
	• Increase in serum bile acids, total bilirubin, alkaline phosphatase in female rats dosed at 300 mg/kg • Hepatic inflammatory cell infiltration, portal and bile duct epithelial hypertrophy noted in male and female mini-pigs dosed at 300 mg/kg/day • Increase in sorbitol dehydrogenase and aspartate aminotransferase activities in female minipigs dosed at 300 mg/kg • Increase in serum bile acids, total bilirubin in female and male mini-pigs dosed at 300 mg/kg	• Abnormal liver function tests excluded: ALT > ULN at screening or Day -1, Total Bilirubin > 1.5xULN • Consumption of >14 units/week (men) alcohol • Co-medications are excluded except for e.g. acetaminophen (capped to ≤2 grams/day) Monitoring: • Liver enzyme and bilirubin assessments • By observing the PK safety margin for renal findings by targeting up to exposure from female mini pig NOAEL (AUC24h of 48700 ng×h/mL and a mean plasma Cmax of 6100 ng/mL). • CCI [redacted] Participant Withdrawal and Study Stopping criteria as per GSK guidance on Liver Chemistry stopping criteria in Section 7.1.4. • ALT ≥ 3xULN – discontinue treatment and refer to Liver Safety Required Actions and

Potential Risk of Clinical Significance	Summary of Data / Rationale for Risk	Mitigation Strategy
		Follow up Assessments section in Appendix 5 (Section 10.5)
Olfactory	• Olfactory epithelial degeneration observed in nasal turbinates of female rats dosed at 300mg/kg/day	Exclusion criteria: • Current or history of change in taste or smell without any plausible clinical explanation based on the investigator's clinical judgement. Monitoring: • As part of the medical interview and during routine physical examination, participants will be assessed for changes in smell or taste Participant withdrawal: • New onset changes in smell which cannot be explained by other causes - following further investigations carried out as per investigator's discretion in consultation with the Medical Monitor.
Mitochondrial toxicity	• DILIsym* modelling suggested main mechanism of DILI at doses higher than proposed therapeutic dose is mitochondrial dysfunction - compound modelled as an ATP synthesis inhibitor with ROS production.	At the proposed maximum clinical free Cmax, the inhibition of isolated ATP synthase was estimated to not exceed 10% at the lower 95% confidence interval, with the reduction in isolated mitochondrial respiration estimated to be lower still. It is considered that small

Potential Risk of Clinical Significance	Summary of Data / Rationale for Risk	Mitigation Strategy
		reductions in ATP synthase and mitochondrial respiration, of the magnitude estimated for GSK3494245 at the maximum free Cmax concentrations currently proposed for healthy human volunteer studies, would not impact overall bioenergetic reserve sufficiently to be of biological significance. Monitoring: • Liver, cardiovascular, gastrointestinal, renal monitoring as outlined in mitigation strategies relating to those systems in this Section 2.3.1. • Cranial and peripheral nerve examinations • Abnormal changes in body temperature • Serial venous lactate measurements (with further investigations at the investigator's discretion to exclude other causes of hyperlactataemia and evaluate for lactic acidosis) • Serum glucose • Fasting lipids (cholesterol and trigycerides)

Potential Risk of Clinical Significance	Summary of Data / Rationale for Risk	Mitigation Strategy
		If a participant develops acidosis (where low pH is confirmed by the Investigator) during the study, the following actions should be considered: • Measurement of serum and urine ketones, chloride and calcium to be performed contemporaneously with low pH. If an acidosis adverse event is observed on a venous blood gas, an arterial blood gas test **may be performed** if deemed appropriate by the Investigator to inform the clinical care of the participant. Participant withdrawal: • Unexplained lactic acidosis • Clinical symptoms and signs and clinical chemistry and haematology parameters would be reviewed by the Investigator, Safety and Medical Governance (SMG) lead and Medical Monitor during dose escalation meetings and a decision to withdraw individual participants or stop the study

Potential Risk of Clinical Significance	Summary of Data / Rationale for Risk	Mitigation Strategy
		based on potential mitochondrial toxicity would be made following this review.
Study Procedures		
CCI [redacted]		
Unblinding to potential urine colour change	During toxicokinetic studies of GSK3494245 in the Gottingen Minipig a visually detectable colour change in urine was observed post dosing, which was raised as a potential unblinding risk.	• Urine samples will be collected in coloured or opaque collection vessels. • Independent laboratory staff will process urine samples to ensure blinding of site staff. • Coloured filters installed in lighting fixtures in the Clinical Unit in areas where participants reside.

Potential Risk of Clinical Significance	Summary of Data / Rationale for Risk	Mitigation Strategy
		• Blue colouring of water in toilet facilities of the Clinical Unit. • Exclusion of female participants.
Other		
COVID-19	Participation within a hospital environment may increase risk of contracting COVID-19. Exposure to other participants and staff may increase risk of exposure.	• Monitoring of clinical presentation of COVID-19 signs/symptoms. • Conduct study at a site which has appropriate mitigation strategies in place.

2.3.2. Benefit Assessment

The proposed study with GSK3494245 will be conducted in healthy volunteers; no medical benefit will be derived by volunteers' participation. Participants will indirectly gain through their contribution to the process of developing new therapies in an area of unmet need.

2.3.3. Overall Benefit: Risk Conclusion

The known risks associated with GSK3494245 can be appropriately mitigated by the careful selection of study participants and the proposed safety monitoring procedures. As such, the risk to potential participants is considered low. Routine safety and tolerability will be evaluated from reported AEs, scheduled physical examinations, vital sign measurements, cardiac rhythm monitoring, 12-lead ECGs, and clinical laboratory test results as well as continued observation by clinical staff.

The study will be conducted in a hospital-based unit or unit with immediate access to hospital facilities for the treatment of medical emergencies. The in-house periods as detailed in the SoA (Section 1.3) will allow for continuous medical monitoring for all participants following the first dose in each intervention group. Participants will only be discharged from the unit 72 hrs post-dose if the Investigator deems it safe to do so.

Taking into account the measures taken to minimize risk to participants participating in this study, the potential risks identified in association with GSK3494245 are justified by the anticipated benefits that may be afforded by the future development of a new therapy in an area of unmet need.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary • To evaluate the safety and tolerability of single and repeat doses of GSK3494245 in healthy participants	• Adverse event reporting, treatment emergent, clinically significant changes from baseline in clinical laboratory safety data, physical examinations, vital signs, 12 lead electrocardiograms (ECGs) and telemetry.
Secondary • To evaluate the PK profile of single (fasted and fed) and repeat doses of GSK3494245 in healthy participants	• SAD part: Derived PK parameters for GSK3494245 following single dose (fasted and fed) including area under the plasma drug concentration versus time curve (AUC(0-t), AUC(0-∞)), maximum observed plasma drug concentration (Cmax), time to maximum observed plasma drug concentration (Tmax), and apparent terminal half-life (t1/2) as data allow.

Objectives	Endpoints
• To examine dose proportionality following single doses of GSK3494245 • To assess accumulation and time-invariance ratios of GSK3494245 • To assess steady state following repeat doses of GSK3494245	• MAD part: as appropriate: ○ Day 1 AUC(0-t), AUC(0-∞), AUC(0-tau), Cmax, Tmax, t1/2 ○ Day 4-7 morning trough plasma concentration (Ctau), ○ Day 7 AUC(0-t), AUC(0-tau), Cmax, Tmax, t1/2, CLss ○ Additionally for TID regimen if conducted): also Day 6 evening dose AUC(0-t), AUC(0-tau), Cmax, Tmax, • Dose-proportionality assessment using derived PK parameters, as data allow: SAD part: AUC(0-∞), Cmax MAD part: • Accumulation ratios assessment*, where data allow: RAUC(0-tau), RCmax, RCtau. • Time-invariance ratio calculation for BID regimen as AUC(0-tau) on Day 7 to AUC(0-∞) on Day 1. Additionally for TID regimen if conducted) Time-invariance ratio calculation for TID regimen as AUC(0-tau) on Day 6 evening dose to AUC(0-∞) on Day 1 • Steady state assessment for MAD part: Ctau

CCI

[redacted]

Objectives	Endpoints

* Accumulation ratios calculated as the ratio of last dose to first dose PK parameters: RAUC(0-tau) = AUC(0-tau) on last dose to AUC(0-tau) on first dose, RCmax = Cmax on last dose to Cmax on first dose, RCtau= Ctau on last dose to Ctau on first dose.

4. STUDY DESIGN

4.1. Overall Design

This study will be a randomised, double-blind, placebo-controlled, 2-part study of the oral administration of GSK3494245 in healthy participants. As this will be the first time GSK3494245 is administered to humans, the study design may change based on emerging data as the study progresses.

This study is planned to include approximately 80 participants and will consist of 2 parts:

- The SAD part will consist of a single-dose escalation phase in up to 3 cohorts and a food effect cohort.
- Initially, Cohorts 1 and 2 will comprise of a 4-way crossover within each cohort which includes 4 dosing regimens under fasted conditions. An optional third cohort may be included to further evaluate safety or PK or to evaluate additional dose levels.
- Cohort 3 will investigate the effect of food on the safety, tolerability and PK of a single dose. It will comprise of a 4-way crossover in which participants will receive GSK3494245 and placebo in both fasted and fed conditions and in a 1:1 ratio.
- On completion of Cohort 3, Cohort 3a will assess single ascending doses of GSK3494245 taken with food, following the same 4-way crossover design as Cohorts 1 and 2. An optional cohort may be included to further evaluate safety or PK or to evaluate additional dose levels.
- Up to a maximum of 10 different dose levels will be studied in the SAD part.

- The MAD part will be a twice-daily (BID) 7-day repeat dose design in up to 5 cohorts of participants (Cohorts 4, 5, 6, 7 and 8) although the dosing regimen may be altered to TID dosing depending on emerging data, with doses administered 6 hours apart on each day. Up to a maximum of 5 dose levels will be studied in the MAD part, with doses administered in the fed state. CCI [redacted]

All participants in the study will attend a screening visit within 28 days prior to their first dose and a follow-up visit within 7-14 days after their final dose. If required, additional follow-up visits may be scheduled. Participants may only take part in one study cohort.

4.1.1. Single Ascending Dose (SAD)

For the dose escalation phase in the SAD part, up to 3 cohorts may be used (Cohorts 1-2, 3a). Cohorts will consist of 8 healthy participants each.

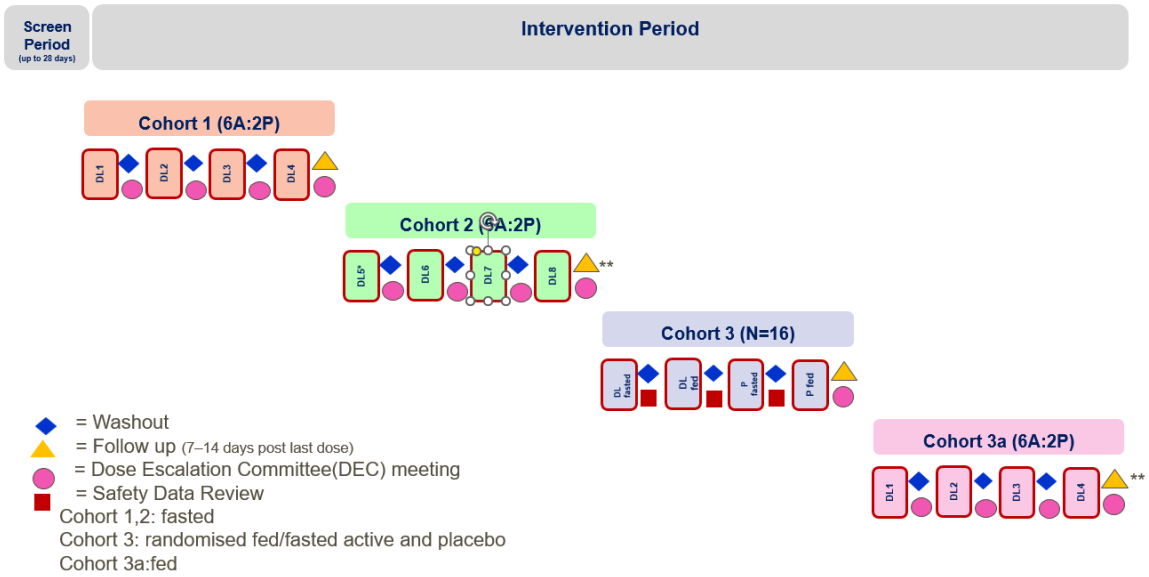
For Cohorts 1 and 2, each participant will receive a maximum of 3 ascending oral doses of GSK3494245 and 1 placebo dose under fasted conditions. At each dose level, GSK3494245 and placebo will be administered in a 3:1 ratio, within each period, according to the randomization schedule in a blinded manner. Up to a maximum of 8 dose levels will be studied as illustrated in Table 1.

In the event the DEC decide there is a need to address any concerns from a safety or PK point of view, the 4th dose level (DL4, see Figure 1) may be repeated at the start of Cohort 2. Thereby allowing up to 7 dose levels to be studied, in this scenario.

Cohort 3a will commence on completion of the food effect comparison in Cohort 3. In Cohort 3a each participant will receive a maximum of 3 ascending oral doses of GSK3494245 and 1 placebo dose under fed conditions. The cohort will follow the same design as Cohorts 1 and 2. Doses will be determined by the DEC.

In addition, following completion of Cohorts 2 and 3a the DEC may decide, based on emergent safety and PK data to include an additional cohort of up to 8 participants following the same design as Cohorts 1 and 2, as indicated in Section 4.6.

Figure 1 Study Design (SAD part)



A = active drug; DL = dose level; DLX = dose level to be determined; Fed = fed conditions; P = placebo.
*Depending on the outcome of review of all available safety and PK data from Cohort 1, the DEC may repeat DL4 at the start of Cohort 2. Then escalate to DL5, DL6 and DL7 as needed.
Note: In Cohorts 1 and 2, the first two participants, within each intervention period, will act as sentinels. Cohorts 1, 2 and 3 comprise of a 4-way cross-over design.
** The dosing schedule may be adjusted to add an additional cohort to further evaluate safety or PK findings at a given dose level, or to evaluate additional doses. The additional cohort will be up to 8 participants following the same design and dose escalation principles as Cohort 1 and 2.

4.1.2. Sentinel Dosing in SAD

For each cohort and within each intervention period (except Cohort 3), the first 2 participants will act as sentinels. No participant will be a sentinel participant more than once. On Day 1, 1 of the 2 sentinel participants will receive the active dose and the other will receive placebo. Based on the Principal Investigator's review of the 2 sentinel participants after at least the first 24 hr post-dose safety data (e.g. vital signs, ECGs and AEs), the remaining 6 participants can then be randomised to dosing.

4.1.3. Initiation of Food Effect (SAD part, Cohort 3)

Cohort 3 will consist of up to 16 healthy participants. The selected dose level (DLX) to investigate the effect of food on the safety, tolerability and PK of a single dose of GSK3494245 will be one already evaluated from a previous intervention period. The maximum exposure following fed administration should not exceed the highest safe exposure explored in fasted conditions. The decision on the dose level of GSK3494245 to be administered will be made by the dose escalation committee (DEC). In this Cohort, participants will also receive two doses of placebo, in the fed and fasted states

respectively, in order to gain more information of background changes in safety parameters.

Table 1 Study Duration of Cohorts 1-3, 3a

Screening	All screening assessments to be completed within 28 days prior to first dose.
Intervention Period	Cohorts 1 and 2 will comprise of 4 intervention periods, investigating 4 dosing regimens under fasted conditions. Participants will receive three doses of GSK3494245 and a randomised placebo dose, administered in the fasted state. Cohort 3 will comprise of 4 intervention periods, investigating a single dose of GSK3494245 in both fasted and fed conditions and also two doses of placebo also given under fasted and fed conditions. Cohort 3a will comprise of 4 intervention periods, investigating 4 dosing regimens under fed conditions. Participants will receive three doses of GSK3494245 and a randomised placebo dose, administered in the fed state. Each regimen will consist of a single dose given on Day 1, with participants in-house for 4 nights and 5 days. Participants will be admitted to the unit the day before dosing (Day -1) and will remain in the unit overnight until Day 4, when they will be discharged after completion of all assessments.
Washout Period	At least 48 hrs or 5-half-lives (whichever is longer) between each dose for an individual participant.
Follow-up	At least 7 days and no greater than 14 days after last study drug administration. If warranted, additional follow-up visits may be scheduled.
Total duration	Cohorts 1, 2, 3 and 3a will be approximately 15-16 weeks each.

4.1.4. Multiple Ascending Dose (MAD)

Prior to initiation of the MAD part, a review of all available safety, tolerability and PK data from the SAD part will be conducted. A formal interim analysis is not planned.

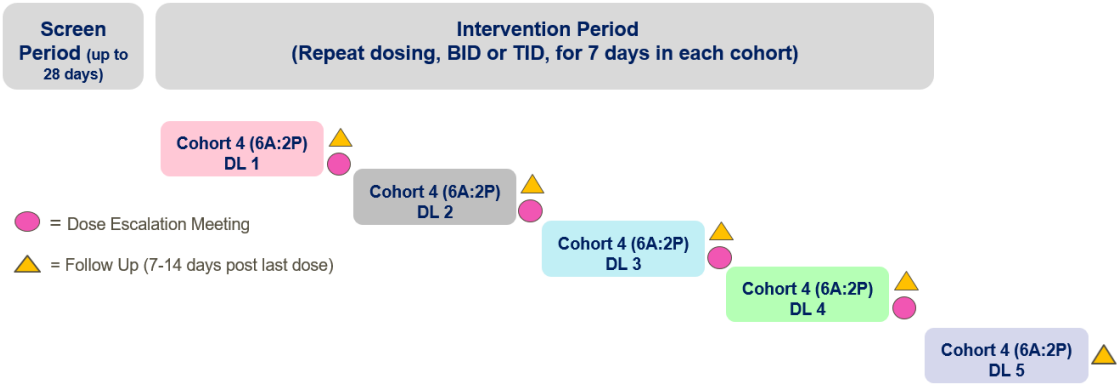
MAD consists of 5 cohorts (Cohorts 4, 5, 6, 7 and 8), each including 8 participants. Participants in each cohort will be randomised to receive repeat doses in the fed state of either GSK3494245 or placebo (blinded), administered in a 3:1 ratio according to the randomization schedule.

GSK3494245 or placebo will be administered BID for 7 days using a 12 h dosing interval, with only one dose administered on Day 7. Based on emerging data, the dosing regimen

may be altered to a three-times daily (TID) regimen, with doses administered 6 hours apart on each day

Up to a maximum of 5 dose levels will be studied in the MAD part as illustrated below:

Figure 2 Study Design (MAD part)



A = active drug; BID = twice-daily; TID = three-times daily; DL = dose level; P = placebo. Day 7 is morning dose only.
Note: For each new dose level the first two subjects in each cohort will act as sentinels.

4.1.5. Sentinel Dosing in MAD part

For each cohort, the first 2 participants will act as sentinels. One sentinel participant will be randomised to active treatment and the other to placebo. Based on the Principal Investigator's review of the 2 sentinel participants after at least the first 48 hr post-dose safety and tolerability data (e.g. vital signs, ECGs and AEs), the remaining 6 participants can then be randomised to dosing.

Table 2 Study Duration of Cohorts 4-8

Screening	All screening assessments to be completed within 28 days prior to first-dose.
Intervention Period	Each Cohort will consist of a 7-day intervention period (Days 1-7), with participants in-house for 8 nights and 9 days. Participants will be admitted to the unit the day before dosing (Day -1) and will remain in the unit overnight until Day 8, when they will be discharged after completion of all assessments.
Follow-up	At least 7 days and no greater than 14 days after last study drug administration. If warranted, additional follow-up visits may be scheduled.
Total duration	Approximately 7-8 weeks

4.2. Number of Participants

Sufficient participants will be screened to ensure that approximately 80 participants are eligible to be randomised (SAD part: 8 participants into each of Cohorts 1, 2 and 3a and up to 16 participants for Cohort 3; MAD part: 8 participants into each of Cohorts 4-8). A participant is considered evaluable if they complete both screening and at least one intervention period in the SAD part, or the 7-day intervention period in the MAD part. Participants that take part in the SAD part of the study cannot participate in the MAD part.

If participants prematurely discontinue the study, then additional replacement participants may be recruited and assigned to the same intervention sequence, at the discretion of the Sponsor in consultation with the Principal Investigator, in both SAD and MAD parts.

4.3. End of Study Definition

A participant is considered to have completed the study if he has completed all periods of the study including the last scheduled procedure shown in the SoA (Section 1.3).

The end of the study is defined as the date of the last visit of the last participant in the study or last scheduled procedure shown in the SoA for the last participant in the study.

4.4. Scientific Rationale for Study Design

This study will be the first administration of GSK3494245 in human participants. The primary purpose of the current study is to characterise the safety and tolerability of GSK3494245 in healthy participants within a controlled PK range. The study will additionally seek to understand the secondary and exploratory endpoints. Specific scientific considerations which contribute to the study design include:

- In the SAD part, this study employs a randomised sequential crossover design to allow for dose comparison between and within participants at different dose levels. In addition, this design minimises participant numbers across the SAD part of the study and is appropriate given the short-estimated half-life of GSK3494245 (approximately 4 h), which enables a short washout period.

- Furthermore, a food-effect evaluation is planned to support progression into patient studies. An assessment of food effect on the exposure to GSK3494245 will be incorporated into the SAD part of the study. Preliminary assessment of food-effect hinted a marginal decrease in the drug exposure which could possibly be attributed to high stomach solubility in the fasted acidic stomach that is not present in the fed state due to a higher pH. In the presence of food, the exposure may be slightly lower or the same in terms of overall trend. Please see Section 9 for further details on how sample size was determined for the food effect cohort. The exact sample size for the evaluation of the food effect will be determined based on the variability of the AUC and C_{max} observed in Cohorts 1 and 2. Up to a maximum of 16 participants will be recruited to allow for 12 evaluable participants, however as few as 10 evaluable participants may be required, in which case the number of participants recruited could be slightly lower. The

dose to be determined with food will be selected such that, if there is a change in exposure, it would be anticipated to be around the therapeutically relevant dose and within safety margins. Participants will receive an adapted standard meal containing a 35-40% fat content. This Cohort will also include 2 dosing arms in which participants will receive placebo in the fed and fasted states respectively. The participants will be randomized to 4 treatment sequences as seen in Section 6.3.1. The aim of these dosing arms is to gain additional safety data on placebo which may aid interpretation of any changes in safety biomarkers. On completion of the food effect cohort (Cohort 3), a further dose escalation cohort, Cohort 3a, will commence to investigate ascending doses of GSK3494245 administered in the fed state.

- CCI

- GSK3494245 is proposed for VL oral short therapy. The MAD part is therefore designed as a 7-day repeat-dosing regimen.

4.5. Justification for Dose

4.5.1. Human Predicted Pharmacokinetics

The preclinical pharmacokinetic (PK) data (mouse, rat and dog) was used to predict human blood PK parameters. Briefly, mouse, rat and dog in vitro and in vivo ADME datasets were employed to get the human PK estimates using various scaling approaches. The GlaxoSmithKline software package PK Predictor Pro (GUI v1.1.45 Calculation Engine v1.4.4) was used for IVIVE (in vitro-in vivo extrapolation), LBF (liver blood flow) and allometric scaling. GastroPlus 9.0 (Simulation Plus, inc.) was applied for the PBPK modelling [GlaxoSmithKline Document Number 2018N371507_02]. NONMEM 7.4.3 (Icon Development Solutions) was used for PK simulations in human, based on GastroPlus parameters.

The different scaling methods predicted a clearance (CL) range of 3-11 mL/min/kg. Two clearance values were obtained based on the fact that the hepatocytes intrinsic clearance

in dog and human was shown to be saturated at increasing concentrations of the compound: a low clearance CL=3.81 mL/min/kg, and a high clearance CL=6.67 mL/min/kg. Both values were considered to predict human PK. The predicted steady state volume of distribution (VDSS) ranged from 0.7 to 2.2 L/kg with an average estimate of 1.28 L/kg, which was used to predict human PK. Taking into account only the liver extraction, human oral bioavailability is expected to be moderate (47 to 78%). Across the preclinical species (mouse, rat, beagle dog), a range of bioavailability values from 18 to 86% was observed. A value of 80% bioavailability was used for human PK prediction in the low clearance scenario, while a 64% bioavailability in the high clearance scenario [GlaxoSmithKline Document Number 2018N371507_02].

A first order absorption rate constant (KA) of $0.7h^{-1}$ was assumed based on data from formulations with immediate release profiles. The human PK profiles were simulated in both low and high clearance scenarios using a population PK analysis approach assuming relevant inter-individual variabilities (IIVs – log normal distribution) around the PK parameters as shown in Table 3. For each scenario, at each dose level, 500 participants (with varying body weight; median weight assumed to be 70kg) were simulated with CL and V scaled to body weight using the allometric exponents of 0.75 and 1, respectively. Maximum blood concentrations after single dose (C_{max} and C_{max_SS}, respectively) were determined from the maximum simulated concentration. Area under the blood concentration curve (AUC) from time zero to infinity for single dose ($AUC_{0-\infty}$), AUC over 24 h, time above EC50 over 24 h, and time above EC90 over 24 h at steady state for multiple dose (AUC_{24h}, $TEC50_{24h}$, and $TEC90_{24h}$, respectively) were calculated using the numerical integrator embedded in ADVAN6 routine in NONMEM 7.4.3. Human PK was predicted for a range of doses from 1 mg to 900 mg with anticipated variability, assuming dose-independent F. Indeed, even though the compound is a P-GP substrate, P-GP effect (important in mouse and rat, but not in dog) is not expected to influence human bioavailability at the predicted clinical dose based on GastroPlus simulations [GlaxoSmithKline Document Number 2018N371507_02].

Table 3 Predicted human blood PK parameters for GSK3494245 that were employed for simulation of human PK profile

Parameter	Predicted Value		%CV[#]
	Scenario 1 (low clearance)	Scenario 2 (high clearance)	
Clearance (mL/min/kg)	3.81	6.67	30
Vdss (L/kg)	1.28	1.28	30
KA (hr-1)	0.7	0.7	10
F (%)	80	64	NA

[#] assumed variability for human PK simulation; **NA** = not applicable

4.5.2. Background on Pharmacology for Human Dose Selection

No full information is available on the relevance of endpoints for efficacy for VL, therefore a combination of different approaches has been considered for human dose prediction. Whole blood concentration was used as surrogate marker of PK at bio-phase and different potential efficacy endpoints were explored, including blood AUC_{24h} (computed as $2xAUC_{12h}$), $TEC50_{24h}$, $TEC90_{24h}$, and area of the effect (% of parasite reduction) over 24 hrs $AUEC_{24h}$ (computed as $2\times AUEC_{12h}$); see [GlaxoSmithKline Document Number 2020N429413_00] for more details.

In Balb-C mice, the best predictor of drug effect was found to be total blood $AUEC_{24h}$. From the relationship between effect and $AUEC_{24h}$ obtained in the preclinical animal model, it was estimated that on average an $AUEC_{24h}$ value of 1104.1 % of parasite reduction × h corresponds to 95% of parasite reduction (considered as efficacy threshold).

Human PK projections were done assuming BID dosing (12h), simulating both a low clearance (scenario 1) and a high clearance (scenario 2) case; more details on human PK simulation settings are reported in [GlaxoSmithKline Document Number 2020N429413_00]. Human blood $AUEC_{24h}$ was computed and compared to the above-mentioned threshold for efficacy. By interpolation of mean $AUEC_{24h}$ values at the simulated doses in Scenario 1 and 2, a mean $AUEC_{24h}$ equal to 1104.1% of parasite reduction × h corresponds on average to a mean plasma AUC_{24h} around 8000 ng/mL × h. By graphical inspection, in scenario 1, on average the effective dose corresponds approximately to 65 mg BID, while in scenario 2 approximately to 165 mg BID. A dose of approximately 125 mg BID in scenario 1, and a dose in the range of approximately 345-450 mg BID for scenario 2 (where a flatter AUEC vs dose profile is obtained), respectively, would be needed instead to achieve efficacy in 95% of participants.

A starting dose of 20 mg is proposed for this study as at least 3-fold below the expected therapeutic dose range; moreover, GSK3494245 is not expected to have pharmacological activity in human volunteers. The exposure following a single dose of 20 mg is expected to be at least 24.5-fold lower (in terms of 95th percentile of $AUC_{0-\infty}$) than the stopping criteria (see Section 4.5.3 for details).

4.5.3. Predicted Safety Margins for SAD and MAD parts

A maximum of eight dose levels will be used for the SAD part starting from a 20 mg dose. The selection of the subsequent appropriate doses will be performed upon consideration of available safety, tolerability and PK data from previous dose levels. A maximum of five dose levels will be used for the MAD part. The lowest dose for the MAD part is expected to be 30 mg BID. The selection of the subsequent appropriate doses will be performed upon consideration of available safety, tolerability and PK data from previous dose levels. The limiting exposure criteria for both the SAD and MAD parts will be the NOAEL observed for female mini-pig at 120 mg/kg/day (60 mg/kg/dose), corresponding to a mean plasma AUC_{24h} of 48700 ng×h/mL and a mean plasma C_{max} of 6100 ng/mL [GlaxoSmithKline Document Number 2018N371726_00].

Toxicology cover in humans after single dose was predicted based on the above-mentioned stopping criteria and predicted human plasma exposures obtained converting the simulated human blood exposures based on the blood: plasma ratio in humans, equal to 0.88. [GlaxoSmithKline Document Number 2018N371507_02]. Table 4 and Table 5 below list the predicted safety cover for GSK3494245 administered as a single dose at various dose levels in scenario 1 and scenario 2, respectively, in terms of plasma $AUC_{0-\infty}$ and plasma C_{max}. The doses described in Table 4 and Table 5 are illustrative and not necessarily the doses that will be investigated in the study. Human plasma exposure vs single dose level is depicted in Figure 3.

Table 6 below lists the predicted safety cover for GSK3494245 administered as a repeated BID dose at various dose levels based on preliminary PK data observed in the SAD part of the study, in terms of plasma AUC_{0-24h} and plasma C_{max} at steady state. The doses described in Table 6 are illustrative and not necessarily the doses that will be investigated in the study.

Table 6 list the proposed dose levels for the MAD part of the study, together with exposure predictions (based on current study data from the SAD part up to 160mg) and expected safety cover for the 95th percentile of the population. Dose levels are only illustrative and actual doses might slightly differ once complete PK up to the highest dose in the SAD part of the study is available. However, the starting dose level for MAD will not exceed 30 mg BID or TID. It should be noted that calculated steady state plasma AUC_{24h} exposure on Day 7 will be used as part of PK stopping criteria following repeat dosing. PK sampling on Day 7 at steady state is proposed for 0-12h for BID dosing or 0-6h for TID dosing (in the event that TID schedule is selected). Hence, AUC_{24h} (Day 7) will be derived as $2\times AUC_{12h}$ or $3\times AUC_{6h}$ for BID or TID dosing, respectively.

Table 4 Projected plasma GSK3494245 $AUC_{0-\infty}$ and C_{max} (mean and 95th percentile) following single oral doses of GSK3494245 in scenario 1, with Fold Cover to preclinical NOAEL

Dose (mg)	Predicted Human Plasma Exposures*				Safety Margins with respect to NOAEL#			
	$AUC_{0-\infty}$ (ng×h/mL)		C_{max} (ng/mL)		$AUC_{0-\infty}$ (ng×h/mL)		C_{max} (ng/mL)	
	mean	p95	mean	p95	mean	p95	mean	p95
20$	1209.8	1983.8	130.7	199.8	40.3	24.5	46.7	30.5
60$	3642.1	6033.8	395.9	570.0	13.4	8.1	15.4	10.7
120$	7284.3	12067.6	791.7	1140.1	6.7	4.0	7.7	5.4
200	11968.9	19589.5	1309.4	1964.2	4.1	2.5	4.7	3.1
300	17995.6	28360.9	1938.2	2841.8	2.7	1.7	3.1	2.1
400	23699.1	37665.2	2585	3755	2.1	1.3	2.4	1.6
500	30185.2	49827.2	3193.2	4727.6	1.6	1	1.9	1.3
600	36198.1	58042	3909.9	5640.9	1.3	0.8	1.6	1.1

* The predicted human exposures are in blood and the animal exposures are in plasma. Human Blood to plasma ratio (B/P ratio = 0.88) is used for conversion of predicted blood exposures to obtain human plasma exposures.
# NOAEL exposures in female minipig: AUC = 48700 ng×h/mL; C_{max} = 6100 ng/mL. Safety margin = NOAEL exposure parameter value/predicted human plasma exposure parameter.
$Dose not included in simulations, exposure derived proportionally from simulated doses.

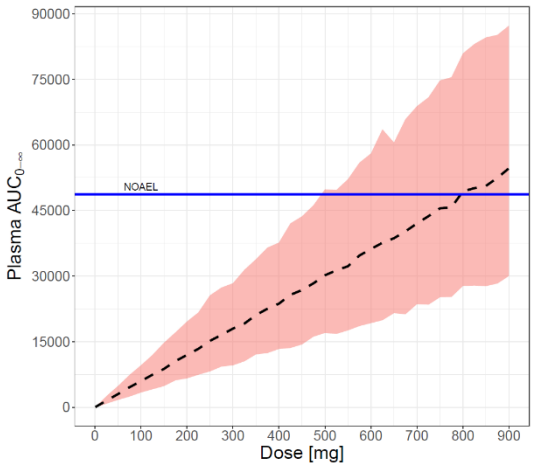
Table 5 Projected plasma GSK3494245 $AUC_{0-\infty}$ and C_{max} (mean and 95th percentile following single oral doses of GSK3494245 in scenario 2, with Fold Cover to preclinical NOAEL

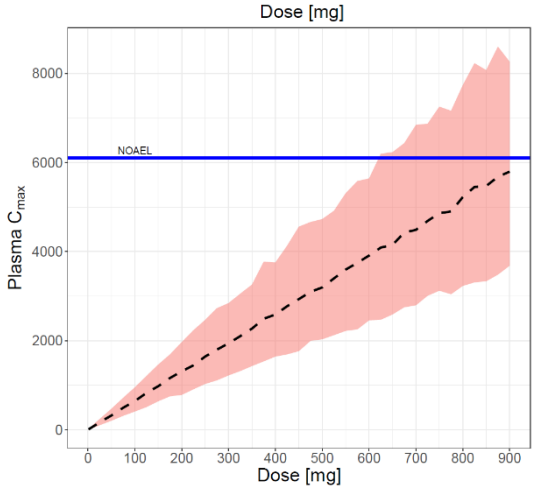
Dose (mg)	Predicted Human Plasma Exposures*				Safety Margins with respect to NOAEL#			
	$AUC_{0-\infty}$ (ng×h/mL)		C_{max} (ng/mL)		$AUC_{0-\infty}$ (ng×h/mL)		C_{max} (ng/mL)	
	mean	p95	mean	p95	mean	p95	mean	p95
20$	552.8	906.5	86.8	133.2	88.1	53.7	70.3	45.8
60$	1664.4	2757.2	262.3	381.5	29.3	17.7	23.3	16.0
150	4009.6	6737.1	646	957.5	12.1	7.2	9.4	6.4
300	8223.5	12960.2	1288.3	1874.8	5.9	3.8	4.7	3.3
450	12248.4	19950.1	1943.3	2991.7	4	2.4	3.1	2
650	17669.2	27663.7	2752.4	4091.4	2.8	1.8	2.2	1.5
900	24980.4	39885.6	3858.9	5501.1	1.9	1.2	1.6	1.1
1200$	33082.9	53046.1	5186.9	7484.8	1.5	0.9	1.2	0.8

* The predicted human exposures are in blood and the animal exposures are in plasma. Human Blood to plasma ratio (B/P ratio = 0.88) is used for conversion of predicted blood exposures to obtain human plasma exposures.
# NOAEL exposures in female minipig: AUC = 48700 ng×h/mL; C_{max} = 6100 ng/mL. Safety margin = NOAEL exposure parameter value/predicted human plasma exposure parameter.
$Dose not included in simulations, exposure derived proportionally from simulated doses.

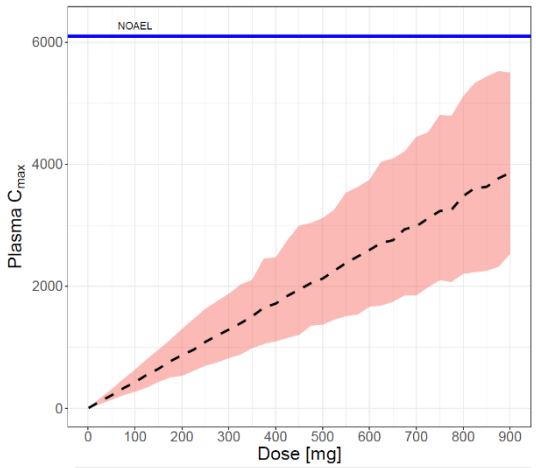
Figure 3 **GSK3494245 predicted human systemic plasma exposures ($AUC_{0-\infty}$ & C_{max}) in scenario 1 and scenario 2 after single dose at various doses with anticipated variability**

Scenario 1: CL=3.81 mL/min/kg and F=80%





Scenario 2: CL=6.67 mL/min/kg and F=64%



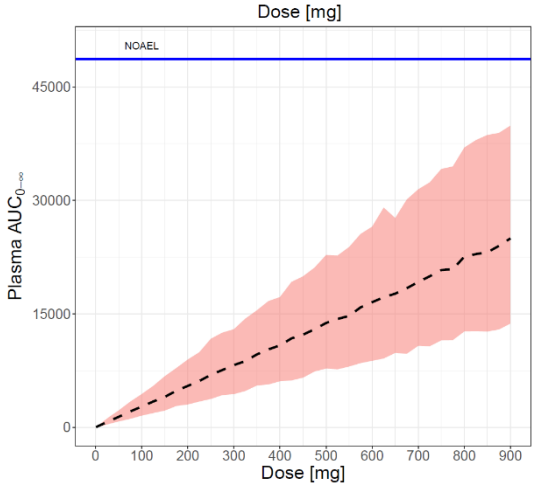


Table 6 **Proposed dose levels for the MAD part of the study with exposure predictions and expected tox cover for the 95P of the population**

BID Dose (mg)	Total Daily Dose (mg)	Cmax (ng.mL)		AUC0-24 (ng h/mL)		Tox cover for P95 to NOAEL	
		Mean	95th percentile	Mean	95th percentile	Cmax	AUC0-24h
30	60	464.1	891.4	1819	3282	6.8	14.8
60	120	862.4	1637	3828	6854	3.7	7.1

BID Dose (mg)	Total Daily Dose (mg)	Cmax (ng.mL)		AUC0-24 (ng h/mL)		Tox cover for P95 to NOAEL	
		Mean	95th percentile	Mean	95th percentile	Cmax	AUC0-24h
120	240	1603	3102	8057	14610	2.0	3.3
180	360	2303	4567	12450	22954	1.3	2.1
240	480	2978	6042	16955	31744	1.0	1.5

4.6. Dose Escalation

As part of this decision-making process, the DEC may decide to escalate or de-escalate the dose in the SAD part and/or the MAD part of the study. The dosing schedule may also be adjusted to add up to two cohorts to further evaluate safety or PK findings at a given dose level, or to evaluate additional dose levels. Two optional cohorts are permitted to allow for assessment in the fasted (after Cohort 2) and fed(after Cohort 3a) states respectively. In the SAD part of the study, additional cohorts will be up to a maximum of two cohorts of 8 participants, investigating up to four dose levels. Addition of extra cohorts may occur if there is greater variability in the PK parameters than expected, or if more dose levels are needed to reach the potentially efficacious exposure. If an additional cohort is required, in either the fasted or fed state, then the nominal illustrative doses in Table 4 and Table 5 may be adjusted. Dosing may also be halted before all planned dose levels have been completed if the stopping criteria has been met, or for any safety concerns, or if review of the data determines that evaluation of further dose levels are not necessary to meet the study objectives.

There will be an open and closed part to the dose escalation meeting. At the beginning of the meeting blinded data will be discussed in an open forum with the Principal Investigator in attendance. If required, the data will then be reviewed in an unblinded fashion by the unblinded members of the DEC. These unblinded members include the CPMS pharmacokineticist and Global Safety representative.

4.6.1. Dose Escalation Committee

The decision to proceed to the next dose level of GSK3494245 in each cohort will be made by a DEC consisting of the Principal Investigator (or appropriate designee), Medical Monitor, GSK Clinical Science Lead and/or Study Team Leader, GSK CPMS pharmacokineticist, a GSK Global Safety representative and GSK Statistician. GSK DEC members will remain blinded throughout the course of the study, **except** for the CPMS pharmacokineticist and Global Safety representative. See also Table 8. Additional

internal GSK safety representatives may be consulted and included in the dose escalation decision making, in a blinded or unblinded manner as deemed necessary by the DEC.

Details of the DEC membership, data to be reviewed and stopping criteria will be outlined in the DEC plan.

4.6.2. Dose Escalation and Safety Review Requirements for SAD part

Dose escalation meeting: The decision to proceed to the next dose level of GSK3494245 and select the dose of GSK3494245 for Cohort 3 will be made at a DEC meeting based on:

- All available safety and tolerability data from a minimum of 48 hrs post-dose from a minimum of 4 or more participants who have received GSK3494245 at the current dose level. Individual safety data (AEs, laboratory safety tests, telemetry, ECGs and vital signs) will be reviewed.
- All available safety and tolerability data accumulated from preceding dose levels and available PK data from current (minimum of 4 or more participants) and preceding dose levels.
- Dose will be escalated by no more than 3-fold of the highest dose level administered in the study and not more than the dose predicted to provide maximum exposure within PK stopping criteria (NOAEL).
- The dose escalation will be halted in case of any tolerability considerations. This will allow careful evaluation of all available data for dose escalation. Based on emerging clinical data, appropriate changes to the dose escalation step-size will be made. The decision to dose escalate will be made by the DEC and will be guided by the safety and SAD PK stopping criteria as outlined in Section 7.1.2 'Dose escalation/stopping criteria'.
- Following completion of Cohort 3, the DEC will review safety, tolerability and PK data from a minimum of 12 evaluable participants in Cohort 3 prior to determining the starting dose for Cohort 3a.

Safety review meeting: The decision to proceed from Cohort 3 Period 1 to subsequent dosing periods will be made by the Principal Investigator and Medical Monitor based on:

- All available safety and tolerability data from a minimum of 48 hrs post-dose from a minimum of 4 or more participants who have received GSK3494245 at the current dose level. Individual safety data (AEs, laboratory safety tests, telemetry, ECGs and vital signs) will be reviewed.

4.6.3. Dose Escalation and Safety Review Requirements for MAD part

A DEC meeting based on all available safety, tolerability and PK data accumulated from the SAD part of the study and the dose modification / stopping criteria will be used to decide:

- The progression to the MAD part

- The starting dose level for Cohort 4 (BID or TID)

The decision for the next repeat dose level (Cohort 5 onwards) will be made at a DEC meeting following completion of a minimum 7 days dosing in no fewer than 4 participants who have received GSK3494245 from the previous repeat dose cohort and will be based on:

- Assessment of safety, plasma GSK3494245 PK concentrations obtained from a minimum of 4 participants from the previous repeat dose cohort. Individual safety data (AEs, laboratory safety tests, telemetry, ECGs and vital signs) will be reviewed.
- Evaluation of all available safety, tolerability and PK data accumulated from the previous repeat dose cohort.
- Doses will be escalated by no more than 3-fold and up to a dose predicted to provide maximum exposure within PK stopping criteria
- The dose escalation will be halted in case of any tolerability considerations. This will allow careful evaluation of all available data for dose escalation. Based on emerging clinical data, appropriate changes to the dose escalation step-size will be made. The decision to dose escalate will be made by the DEC and will be guided by the safety and MAD PK stopping criteria as outlined in Section 7.1.2 'Dose escalation/stopping criteria'.
- CCI [redacted]

5. STUDY POPULATION

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

5.1. Inclusion Criteria

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

AGE
1. Participant must be 18 to ≤ 55 years of age, at the time of signing the informed consent.

TYPE OF PARTICIPANT AND DISEASE CHARACTERISTICS
2. Healthy as determined by the Investigator or medically qualified designee based on a medical evaluation including medical history, physical examination, laboratory tests and cardiac monitoring.

TYPE OF PARTICIPANT AND DISEASE CHARACTERISTICS
A participant with a clinical abnormality or laboratory parameter(s) which is/are not specifically listed in the inclusion or exclusion criteria, outside the normal reference range for the population being studied may be included only if the Investigator in consultation with the Medical Monitor (if required) agree and document that the finding is unlikely to introduce additional risk factors and will not interfere with the study procedures. Note: Screened participants with laboratory values outside of the normal range may be repeated once for inclusion into the study at the discretion of the Investigator.

WEIGHT
3. Body weight ≥50 kg and body mass index (BMI) within the range 18.5 - 28 kg/m^2 (inclusive).

SEX
4. Male participants only. a. A male participant with a female partner of reproductive potential must agree to use contraception as detailed in Appendix 4 of this clinical study protocol during the intervention period and for at least 90 days after the last dose of study treatment and refrain from donating sperm during this period.

INFORMED CONSENT
5. Capable of giving signed informed consent as described in Appendix 1, which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

5.2. Exclusion Criteria

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

MEDICAL CONDITIONS
1. History or presence of cardiovascular, respiratory, hepatic, renal, gastrointestinal, endocrine, hematological, or neurological disorders capable of significantly altering the absorption, metabolism, or elimination of drugs; constituting a risk when taking the study treatment; or interfering with the interpretation of data. 2. Abnormal blood pressure, as determined by the investigator. 3. Previous history of leishmaniasis. 4. Alanine transaminase (ALT) > upper limit of normal (ULN) at screening or Day - 1. 5. Total bilirubin >1.5xULN (isolated bilirubin >1.5xULN is acceptable if total bilirubin is fractionated and direct bilirubin <35%). 6. Current or chronic history of liver disease or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones). 7. Current or history of clinically significant gastritis or gastroduodenal ulcers or regular use of non-steroidal anti-inflammatory drugs (NSAID). 8. Consumption of > 14 units/week alcohol (male volunteers). 9. Current or history of change in taste or smell without any plausible clinical explanation based on investigator’s clinical judgement. 10. QTc >450 msec based on average of triplicate ECGs. NOTES: The QTc is the QT interval corrected for heart rate according to Bazett’s formula (QTcB), Fridericia’s formula (QTcF), and/or another method, machine-read or manually over-read. The specific formula that will be used to determine eligibility and discontinuation for an individual participant should be determined prior to initiation of the study and used throughout the study for an individual participant. In other words, several different formulae cannot be used to calculate the QTc for an individual participant and then the lowest QTc value used to include or discontinue the participant from the trial. For purposes of data analysis, QTcB, QTcF, another QT correction formula, or a composite of available values of QTc will be used as specified in the Reporting and Analysis Plan (RAP). 11. Waveform abnormalities including premature ventricular contraction (PVC) triplets and more than 500 single PVCs in 24 hrs, or any other abnormalities at the discretion of investigator.

MEDICAL CONDITIONS
12. Medical history of cardiac arrhythmias or cardiac disease or a family or personal history of long QT syndrome.

PRIOR/CONCOMITANT THERAPY
13. Past or intended use of over-the-counter or prescription medication, including herbal medications, NSAIDs, PPIs or anti-H2 antagonists within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is the longest) prior to dosing. Other concomitant medication may be considered on a case by case basis by the investigator in consultation with the medical monitor. Paracetamol is permitted (capped to ≤2 grams/day).

PRIOR/CONCURRENT CLINICAL STUDY EXPERIENCE
14. Participation in the study that would result in loss of blood or blood products in excess of 500mL within a 56-day period. 15. Exposure to more than 4 new chemical entities within 12 months prior to the first dosing day. 16. Current enrollment or past participation within the last 30 days before signing of consent in any other clinical study involving an investigational study intervention or any other type of medical research. 17. Current enrollment or past participation in this clinical study.

DIAGNOSTIC ASSESSMENTS AND OTHER CRITERIA
18. Participants with renal function defined as Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) with an age appropriate GFR < 90 (ml/min/1.73m^2). 19. Screening urine albumin:creatinine ratio > 30 mg/g (> 3 mg/mmol) 20. Presence of hepatitis B surface antigen (HBsAg) test result at screening. 21. Positive hepatitis C antibody test result at screening. NOTE: Participants with positive hepatitis C antibody due to prior resolved disease can be enrolled, **only** if a confirmatory negative hepatitis C RNA test is obtained 22. Positive hepatitis C RNA test result at screening. NOTE: Test is optional and participants with negative hepatitis C antibody test are not required to also undergo hepatitis C RNA testing. 23. Positive human immunodeficiency virus (HIV) antibody test. 24. Presence of clinically significant haematuria and/or proteinuria. 25. Carbon monoxide levels indicative of smoking or history or regular use of tobacco- or nicotine-containing products within 3 months prior to screening.

DIAGNOSTIC ASSESSMENTS AND OTHER CRITERIA
26. Positive pre-study drug/alcohol screen. 27. Regular use of known drugs of abuse. 28. **Fed regimens only:** Participant must have no dietary restrictions (e.g., lactose intolerance) or inability to eat an adapted standard meal (includes 35-40% fat content). 29. CCI [redacted] 30. Participants must not have travelled to an area (as determined by the investigator) with a high prevalence of leishmanial/parasitic infections in the **6** months before screening or intend to do so in the 3 months after the final dose of study treatment. Note: guidance on areas considered as having high prevalence of leishmania/parasitic infections is provided in the SRM. 31. Sensitivity to any of the study treatments, or components thereof, or drug or other allergy that, in the opinion of the Investigator or GSK Medical Monitor, contraindicates participation in the study. 32. A positive laboratory confirmation of COVID-19 infection (validated polymerase chain reaction (PCR) or lateral flow test), or high clinical index of suspicion for COVID-19.

5.3. Lifestyle Considerations

5.3.1. Meals and Dietary Restrictions

- Refrain from consumption of red wine, Seville oranges, grapefruit or grapefruit juice, pomelos, exotic citrus fruits, grapefruit hybrids, or fruit juices from 7 days prior to each first dose of study treatment in the SAD part or prior to the first dose of study treatment in the MAD part up until discharge from the unit.
- For fed regimens,, after an overnight fast of at least 8 hrs, participants should start eating their meal 30 minutes prior to each dose of study drug and should consume the entire meal within 25 minutes. The study drug should be administered within 5 minutes of the completion of the meal. Participants will receive an adapted standard meal. 8 fl oz (240ml) of water is to be taken at the time of dosing. Water is permitted on an ad lib basis up to 1hr before and 1hr after dosing. No water to be taken in the hour prior to dosing except for the liquid part of the adapted standard meal for the fed regimen.
- For fasted regimens, no water is allowed 1 hr before the dose and 1 hr after dosing, water is allowed ad libitum at all other times.

5.3.2. Caffeine, Alcohol, and Tobacco

- During each dosing session, participants will abstain from ingesting caffeine- or xanthine-containing products (e.g., coffee, tea, cola drinks, and chocolate) for 24 hrs before the start of dosing until after collection of the final PK sample.
- During each dosing session, participants will abstain from alcohol for 24 hrs before the start of dosing until after collection of the final PK sample.
- Use of tobacco products will not be allowed from 3 months prior to screening until after the final follow-up visit.

5.3.3. Activity and Travel

- Participants will abstain from strenuous exercise for 72 hrs before each blood collection for clinical laboratory tests. Participants may participate in light recreational activities during studies (e.g., watching television, reading).
- Participants must not have travelled to an area (as determined by the investigator) with a high prevalence of leishmanial/parasitic infections in the 6 months before screening or intend to do so in the 3 months after the final dose of study treatment

5.4. Screen Failures

A screen failure occurs when a participant consents to participate in the clinical study but is not subsequently randomized. 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 at the discretion of the Principal Investigator, and Medical Monitor if required. Rescreened participants will be assigned a new participant number. Reserve subjects that meet eligibility criteria are not considered screen failures and may undergo repeated re-screening to confirm eligibility requirements if randomization into study is planned outside of initial screening window.

5.5. Self-Isolation

Where it is site policy to do so, participants will be asked to attend the Clinical Unit a few days prior to admittance to receive a COVID-19 test. Once they have had this test, they may be asked to self-isolate at home until their admittance to the Clinical Unit for their next dosing period.

6. STUDY TREATMENT

Study treatment is defined as any investigational treatment(s) or placebo intended to be administered to a study participant according to the study protocol.

6.1. Study Treatment(s) Administered

	Study Treatment	
Compound Number	GSK3494245	Placebo
Type	Drug Product	Placebo
Formulation description	API in capsule [HPMC Swedish Orange, Size 0]	Placebo to match [HPMC Swedish Orange, Size 0]
Dose form	Capsule	Capsule
Unit Dose Strength(s)	10 – 250 mg (extemporaneous compounded)	To match 10 – 250 mg (extemporaneous compounded)
Dosage Level(s)	Dosage levels in each cohort to be set by dose escalation committee. Individual doses to be made up by combining tablets of appropriate strengths	To match the active dose amounts and frequency.
Route of Administration	Oral	Oral
Use	Experimental	Sham comparator
IMP and NIMP	IMP	IMP

	Study Treatment	
Sourcing	Study treatment is supplied by GlaxoSmithKline	Study treatment is supplied by GlaxoSmithKline
Packaging and Labelling	Study treatment will be provided in round, opaque white, high density polyethylene (HDPE) bottles with child resistant closures. Each round, opaque white, high density polyethylene (HDPE) bottles with child resistant closures will be labelled as required per country requirement.	Study treatment will be provided in round, opaque white, high density polyethylene (HDPE) bottles with child resistant closures. Each round, opaque white, high density polyethylene (HDPE) bottles with child resistant closures will be labelled as required per country requirement.
Current/Former Name(s) or Alias(es)	n/a	n/a

6.2. Preparation/Handling/Storage/Accountability

Refer to the Technical Terms of Supply (TTS) for details on preparation, handling and storage of study treatment.

- The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.
- Only participants enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments 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.
- The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
- Further guidance and information for the final disposition of unused study treatment are provided in the Study Reference Manual (SRM).
- Under normal conditions of handling and administration, study treatment is not expected to pose significant safety risks to site staff.
- A Material Safety Data Sheet (MSDS)/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or is available upon request from GSK. In the case of unintentional occupational exposure notify the monitor, Medical Monitor and/or GSK study contact**.**
-

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Randomization

On Day 1, participants will be assigned a unique number (randomization number) in ascending numerical order. The randomization number encodes the participant's assignment to either GSK3494245 or placebo, according to the randomization schedule generated prior to the study by the Statistics Department at GSK, using validated internal software.

All participants will be randomized using the Clinical Unit's internal procedure. Details of their randomisation procedure are described in the SRM and study communications plan.

Study treatment will be dispensed at the study visits summarized in SoA. Each participant will be dispensed blinded study treatment, labelled with his unique randomization number, throughout the study. Returned study treatment should not be re-dispensed to the participants.

In the SAD part (Cohorts 1, 2 and 3a) participants will be randomized in a 3:1 ratio to either GSK3494245 or placebo per period. In the MAD part (Cohorts 4-8) participants will be randomised to receive repeat doses of either GSK3494245 or placebo in a 3:1 ratio. In Cohort 3 (SAD part), all participants will receive GSK3494245 as well as placebo. They will be randomized to one of the 4 sequences with up to 4 participants per sequence (see Table 7) in a 1:1:1:1 ratio.

Table 7 Cohort 3

Sequence	Period 1	Period 2	Period 3	Period 4
1	DL X Fasted	P Fed	DL X Fed	P Fasted
2	DL X Fed	DL X Fasted	P Fasted	P Fed
3	P Fasted	DL X Fed	P Fed	DL X Fasted
4	P Fed	P Fasted	DL X Fasted	DL X Fed

Once a randomization number has been assigned to a participant, it cannot be reassigned to any other participant.

6.3.2. Blinding

This will be a double-blind study with respect to allocation of GSK3494245 or placebo to participants.

The following will apply:

- The investigator or treating physician may unblind a participant's treatment assignment only in the case of an emergency OR in the event of a serious medical condition when knowledge of the study treatment is essential for the appropriate clinical management or welfare of the participant as judged by the investigator.
- Investigators have direct access to the participant's individual study treatment
- It is preferred (but not required) that the investigator first contacts the Medical Monitor or appropriate GSK study personnel to discuss options before unblinding the participant's treatment assignment.
- If GSK study personnel are not contacted before the unblinding, the investigator must notify GSK as soon as possible after unblinding, but without revealing the treatment assignment of the unblinded participant, unless that information is important for the safety of participants currently in the study.
- The investigator (or designee) will complete the memo: "Participant Unblinding Memo – Blinded Information" to document the call with the Medical Monitor or appropriate GSK study personnel. The memo will not contain unblinding information. The memo will be filed in the TMF.

- If required, the investigator (or designee) should also complete the memo "Participant Unblinding Memo – Unblinded Information", which will include relevant unblinded information to document the emergency unblinding event. This will be filed in a repository separate from the main study TMF (for unblinded documentation) whilst the study is ongoing. Templates of the participant unblinding memos will be supplied separately to the site.
- The date and reason for the unblinding must be fully documented in the CRF.
- A participant will be withdrawn if the participant's treatment code is unblinded by the investigator or treating physician. The primary reason for discontinuation (the event or condition which led to the unblinding) will be recorded in the CRF.
- GSK's Global Safety staff may unblind the treatment assignment for any participant with an SAE. If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the participant's treatment assignment, may be sent to investigators in accordance with local regulations and/or GSK policy.
- The statistician is partially unblinded due to the randomization strategy that will need to be implemented. This is documented in the Randomization and Container Code Strategy (RCCS) document which will therefore contain sensitive information. This RCCS will be maintained securely until the study is unblinded. If needed, the Biostatistics team may be unblinded to support the team with any potential safety/data evaluations.
- There is a risk that GSK3494245 may discolour the urine of participants and unblind participants or clinical site staff as to who was administered GSK3494245 or placebo. To mitigate this risk, procedures will be put in place and followed at the site to minimise the risk of participants or site staff from observing the colour of participants' urine during the study. These mitigating procedures will not interfere with ongoing monitoring or study procedures and details will be described in the SRM. The ongoing need for these mitigating procedures will be determined by the DEC.
- All GSK study personnel will remain blinded throughout the course of the study, except for those indicated in Table 8.

Table 8 Unblinded Central Study Team or Study Site Staff Members

Role of Unblinded Central Study Team or Study Site Staff Member(s)	Type of Unblinded Information
GSK CPMS Clinical Pharmacokineticist	Access to investigational product assignments to participants
GSK Global Safety Representative	Access to investigational product assignments to participants
Site pharmacy staff	Access to investigational product assignments to participants

Role of Unblinded Central Study Team or Study Site Staff Member(s)	Type of Unblinded Information
Site laboratory staff	Visibility of participants' samples that may indicate investigational product assignment.
GSK Medical Monitor	May potentially be provided investigational product assignments during evaluation of CCI other safety data at any study timepoint as deemed necessary.
GSK Statistician(s)/Biostats members	Partially unblinded given they have access to the Randomization and Container Code Strategy (RCCS) document, containing sensitive information about the randomization strategy. May potentially be provided investigational product assignment to support the team with any potential safety/data evaluations as needed
GSK Clinical Sciences Lead	In a non-emergency situation, this role may potentially be provided investigational product assignments to contribute to evaluation of CCI other safety data at any study timepoint as deemed necessary, for example to contribute to preparations for internal safety reviews and/or governance to facilitate key decision making with regards to study progression. Investigational product assignments may only be provided after obtaining relevant internal approval(s), as per company SOP.

6.4. Study Treatment Compliance

- When the individual dose for a participant is prepared from a bulk supply, the preparation of the dose will be confirmed by a second member of the site pharmacy staff.
- When participants are dosed at the site, they will receive study treatment directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents. The dose of study treatment and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study treatment. Study site staff will examine each participant's mouth to ensure that the study treatment was ingested.
- A record of the quantity of study treatment dispensed to and administered by each participant must be maintained and reconciled with study treatment and compliance records. Treatment start and stop dates, including dates for treatment delays and/or dose changes will also be recorded.

6.5. Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, recreational drugs, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study must be recorded 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 must abstain from taking prescription or non-prescription drugs (including vitamins, recreational drugs and dietary or herbal supplements, NSAIDs, PPIs and anti-H2 antagonists) within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) before the start of study treatment until completion of the follow-up visit, unless, in the opinion of the investigator and sponsor, the medication will not interfere with the study.

Paracetamol at doses of ≤ 2 grams/day is permitted for use any time during the study. Other concomitant medication, or paracetamol at doses of >2g, may be considered on a case-by-case basis by the investigator, in consultation with the Medical Monitor if required.

7. DISCONTINUATION OF STUDY TREATMENT AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

Discontinuation of specific sites or of the study as a whole are detailed in Appendix 1, Section 10.1.

7.1. Discontinuation of Study Treatment

Discontinuation of study treatment is considered “permanent”. Once a participant is discontinued, they will not be allowed to restart.
See the SoA for data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that need to be completed.

All criteria for discontinuing, stopping and escalating doses in this study will comply to the most recent EMA guidelines (EMEA/CHMP/SWP/28367/07).

7.1.1. Dose Adjustment/Stopping Pharmacokinetic Criteria

The following dose adjustment / PK stopping criteria will apply:

- Dose escalation will be stopped if any single participant reaches exposures greater than PK stopping criteria threshold exposures (AUC(0-∞)] of 48700 ng×h/mL and Cmax of 6100 ng/mL in the SAD part of the study; AUC24h of 48700 ng×h/mL and Cmax of 6100 ng/mL for the MAD part of the study at steady state). (see

Section 4.5.3). We intend to use the PK dose escalation rule for progression to the next dose or dose adjustment which will involve establishing a relationship between exposures (AUC & Cmax) vs dose using a power model and linear mixed effect modeling once PK data are available from a minimum of two prior dose levels. This model will be continually updated with incorporation of new dose levels as they become available. This developed model will be used to project exposure for the next dose level.

- If 95th percentile of predicted exposure from the maximum total daily dose is predicted to reach the PK stopping criteria exposure, dose escalation will be stopped, or dose adjustment will be planned, as appropriate. The Dose Escalation Committee will decide based on emerging safety, tolerability and PK information whether to evaluate any lower doses or repeat doses already evaluated in remaining periods to collect additional safety and PK data.

7.1.2. Dose Escalation / Study Stopping Criteria

The Principal Investigator and the GSK Medical Monitor will review the following and study dosing **will be** stopped if any of these criteria are met:

- Two or more participants from the previous dose level on active treatment experience an AE which is of severe intensity and reasonably attributable (in the opinion of the investigator) to dosing with GSK3494245.
- One or more participants across all study parts develop an adverse renal event as defined in the renal withdrawal criteria below (Section 7.1.3) considered to be related to GSK3494245 (in the opinion of the investigator in consultation with the Medical Monitor).
- One or more participants from any dose level experiences a serious adverse event which has a reasonable possibility of relation to investigational product.
- The dose escalation/study progression will be temporarily halted, and no further dosing will occur until a full safety review of the study has taken place. Relevant reporting and discussion with the GSK medical monitor, relevant GSK personnel, regulatory authorities and the Independent Ethics Committee will then take place prior to any resumption of dosing.

All other stopping criteria will apply even if no PK stopping criteria have been met.

7.1.3. Renal Stopping Criteria

For SAD and MAD - A participant that meets any of the following bulleted criteria will be withdrawn from the study:

- New onset of any clinically significant and persistent (within 48 hrs) haematuria as confirmed by microscopy.
- New onset of clinically significant and persistent (within 48 hrs) proteinuria (Spot Urine Albumin Creatinine (ACR) ratio ≥ 30mg/mmol) in the absence of another clinical explanation e.g. calculus / infection.

- If there is any change in serum creatinine > 26 µmol/L (0.3 mg/dl) from baseline or > 50 % from baseline. If change in serum creatinine measures at > 26 µmol/L (0.3 mg/dl), repeat within 24 hrs. If confirmed, the participant will be withdrawn, and further investigations will be performed.

For MAD only - If two or more participants have a fall in eGFR≥30% or rise in SrCr≥30% accompanied by abnormality in any other renal markers, the study will be temporarily halted for evaluation.

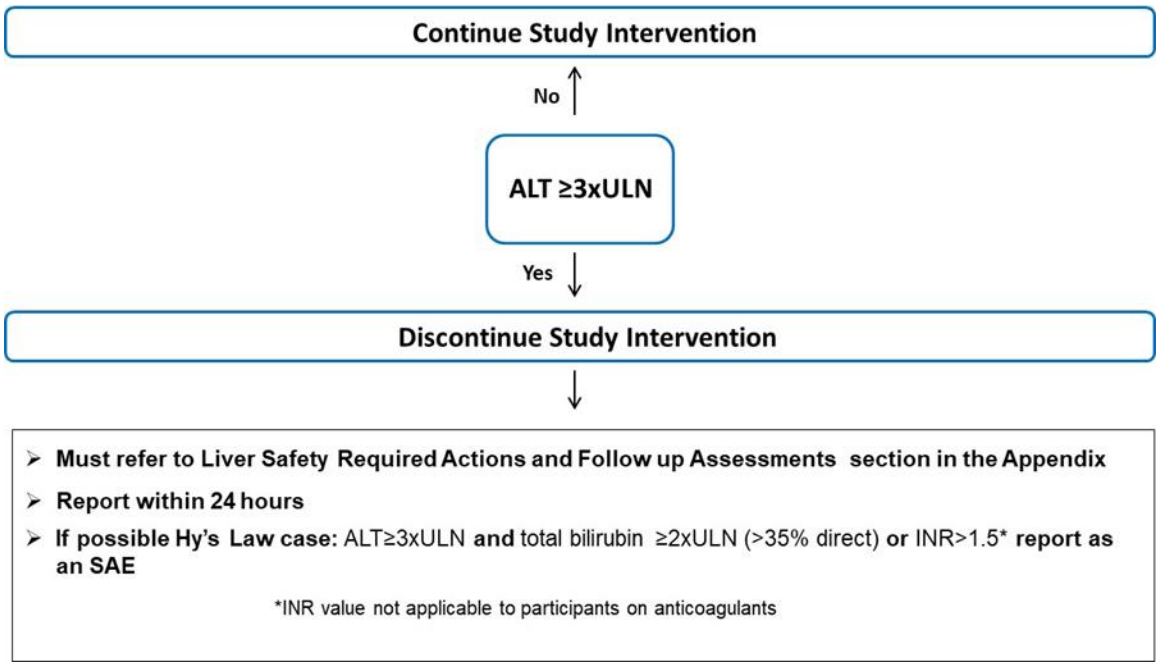
7.1.4. Liver Chemistry Stopping Criteria

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

Discontinuation of study treatment for abnormal liver tests is required when:

- a participant meets one of the conditions outlined in the algorithm or
- when in the presence of abnormal liver chemistries not meeting protocol-specified stopping rules, if the investigator believes study treatment discontinuation is in the best interest of the participant.

Phase I Liver Chemistry Stopping Criteria – Liver Stopping Event Algorithm



Abbreviations: ALT = alanine transaminase; INR = international normalized ratio; SAE = serious adverse event; ULN = upper limit of normal.

Refer to Appendix 5 for required Liver Safety Actions and Follow up Assessments.

7.1.4.1. Study Treatment Restart or Rechallenge after Liver Stopping Criteria Met

Study treatment restart or rechallenge after liver chemistry stopping criteria are met by any participant in this study is not allowed.

7.1.5. ECG and Telemetry Stopping Criteria

A participant that meets either bulleted criterion based on the average of triplicate ECG readings will be withdrawn from study treatment.

QTc > 500 msec,

Change from baseline: QTc > 60 msec

- The *same* QT 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. For example, if a participant is eligible for the protocol based on QTcB, then QTcB must be used for discontinuation of this individual participant as well.
- Once the QT correction formula has been chosen for a participant's eligibility, the *same formula* must continue to be used for that participant *for all QTc data being collected for data analysis*. Safety ECGs and other non-protocol specified ECGs are an exception.
- The average of triplicate ECG readings obtained over a brief (e.g., 5-10 minute) recording period.
- Withdrawal of participants is to be based on an average QTc value of triplicate ECGs. If an ECG demonstrates a prolonged QT interval, then obtain 2 more ECGs over a brief period of time and then use the mean QTc values of the 3 ECGs to determine whether the participant should be discontinued from the study.

  OR

- Non-Sustained Ventricular Tachycardia (NSVT) > 3 beats or PVC triplets on telemetry.

7.1.6. Olfactory Stopping Criteria

- New onset changes in smell which cannot be explained by other causes following further investigations carried out as per Investigator's discretion, in consultation with the Medical Monitor.

7.1.7. Mitochondrial Toxicity Stopping Criteria

- Unexplained lactic acidosis as determined by the Investigator, in consultation with the Medical Monitor.
- Clinical symptoms, signs and clinical chemistry and haematology parameters will be reviewed by the Investigator, Safety and Medical Governance (SMG) lead and Medical Monitor during dose escalation meetings. A decision to withdraw individual

participants or stop the study based on potential mitochondrial toxicity would be made following this review.

- If a participant develops acidosis (where low pH is confirmed by the investigator) during the study, the following actions should be considered. Measurement of serum and urine ketones, chloride and calcium to be performed **contemporaneously** with low pH.

- If an acidosis adverse event is observed on a venous blood gas, an arterial blood gas test **may be performed** if deemed appropriate by the Investigator to inform the clinical care of the participant.

7.1.8. Individual Safety Stopping / Withdrawal Criteria

- If a participant experiences a serious or severe clinically significant AE that in the clinical judgement of the Investigator is possibly, probably or definitely related to investigational product. It is **recommended** that the medical monitor is consulted before a decision is made.
- The participant initiates treatment with any prohibited medications.
- If any of renal, liver chemistry, ECG and telemetry, olfactory or mitochondrial toxicity stopping criteria are met (see Section 7.1.3, Section 7.1.4, Section 7.1.5, Section 7.1.6 and Section 7.1.7).
- The participant develops stomach erosion as confirmed clinically and following a gastro enterology specialist's opinion for further management, and endoscopy (if required).
- If a participant develops COVID-19 like symptoms during the study the following actions should be taken:
  - Participants who develop a high clinical index of suspicion for COVID-19 disease should be isolated and tested for COVID-19 in accordance with site procedures.

  - Assessments should be continued as per the protocol during this period; withdrawal of participants from the study will be at the discretion of the Principal Investigator but should first be discussed and agreed with the Medical Monitor.

7.1.9. Group Safety Stopping Criteria

In addition to the criteria specified above, AEs, SAEs, laboratory abnormalities, ECG abnormalities and changes in vital signs occurring across all randomized participants will be regularly reviewed by the DEC in order to ensure appropriate participant safety. Any changes to the study due to safety reasons will be promptly communicated to the appropriate Regulatory Authorities and Independent Research Ethics Committee.

7.1.10. Study Treatment Restart or Rechallenge

If any stopping criteria are met by any participant in this study, study treatment restart or rechallenge is not allowed.

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, or compliance reasons. This is expected to be uncommon.

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

The participant will be permanently discontinued both from the study treatment 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.

7.3. Lost to Follow Up

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

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

The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.

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

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

8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarised in the SoA, Section 1.3.
- 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 treatment. Except in cases where contacting the sponsor first may adversely impact the safety of a participant.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and was performed within the time frame defined in the SoA.
- Laboratory results that could unblind the study will not be reported to site staff or other study team members, with the exception of site staff/ study team members described in Table 8.
- The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed 500 mL.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.
- Collection of sex, race and ethnicity data is necessary to assess and monitor the diversity of the trial participants, and to determine if the trial participants are truly representative of the impacted population.

8.1. Safety Assessments

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

8.1.1. Physical Examinations

- A complete physical examination will include, at a minimum, assessments of the Skin, Cardiovascular, Respiratory, Gastrointestinal and Neurological systems (including cranial and peripheral nerve exams). Weight and BMI will also be measured and recorded.
- At the Screening visit, Height will also be measured and recorded.

- Investigators should pay special attention to clinical signs related to previous serious illnesses.
- Additional exams/screens may be performed by the Investigator, as deemed necessary (e.g. where safety or laboratory findings indicate). Tests will be conducted within site specified standards.

8.1.2. Vital Signs

- Tympanic temperature, pulse rate, respiratory rate, and blood pressure will be assessed.
- Blood pressure and pulse measurements will be assessed in a supine position with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (e.g., television, cell phones).
- On Day 1, vital signs (to be taken before blood collection for laboratory tests) will consist of 3 pulse and 3 blood pressure measurements pre-dose on Day 1 (3 consecutive blood pressure readings will be recorded at intervals of at least 1 minute). The average of the 3 heart rate and 3 blood pressure readings will be recorded.

8.1.3. Electrocardiograms

Triplicate 12-lead ECG will be obtained as indicated in the SoA (see Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. Refer to Section 7.1.5 for ECG and Telemetry stopping criteria and additional QTc readings that may be necessary.

At each time point at which triplicate ECGs are required, 3 individual ECG tracings should be obtained at least 2 minutes apart but no more than 10 minutes apart.

Continuous cardiac telemetry will start in a supine position after at least 5 minutes rest at the time point indicated in the SoA (Section 1.3). Participants are not required to remain in a supine position during the remaining duration of collection of cardiac telemetry, as indicated in the SoA. Full disclosures will be reviewed in detail and the review maintained as part of the participant's source documents. Based on 24 h telemetry results, telemetry may be extended to 48 h as deemed necessary by the investigator.

8.1.4. Holter Monitoring

Holter monitoring will be performed at screening. This 24-hour Holter ECG will be performed to eliminate participants with non-clinically overt cardiac arrhythmias. Holter monitoring does not need to be repeated for the same participant being rescreened within three months of original screening, or who is rescreened for a different cohort within the same part of the study (SAD and MAD part).

If necessary, additional or extended monitoring (e.g., telemetry or Holter) may be performed at the Investigator or Sponsor's discretion to further characterize any emerging safety signals.

8.1.5. Clinical Safety Laboratory Assessments

See Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA (Section 1.3) for the timing and frequency.

The investigator must review the laboratory reports, document this review, and record any clinically significant change(s) occurring during the study as an AE. The laboratory reports must be filed with the source documents.

Abnormal laboratory findings are not considered clinically significant, unless judged by the investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or baseline or are no longer considered clinically significant abnormal by the investigator or medical monitor.

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

All protocol-required laboratory tests, as defined in Appendix 2, must be conducted in accordance with the SRM and the SoA.

If laboratory values from non-protocol specified laboratory tests performed at the site's local laboratory require a change in participant management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification), then the results must be recorded.

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

The definitions of adverse events (AE) or serious adverse events (SAEs) can be found in Appendix 3.

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

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

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

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

All SAEs will be collected from the signing of the informed consent form until the follow-up visit at the time points specified in the SoA (Section 1.3).

All AEs will be collected from the start of treatment 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 treatment but after obtaining informed consent will be recorded as Medical History/Current Medical Conditions not as AEs.

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

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

8.2.2. Method of Detecting AEs and SAEs

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

8.2.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, and non-serious AEs of special interest (namely stomach erosion, renal or hepatic impairment and cardiovascular , abnormalities as defined under the stopping and withdrawal criteria, Section 7.1), 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.

8.2.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment 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 treatment under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs), and investigators.

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

8.2.5. Pregnancy

- Details of all pregnancies of female partners of male participants will be collected after the start of study treatment and until 90 days after the last dose of study intervention.
- If a pregnancy is reported, the investigator will record pregnancy information on the appropriate form and submit it to GSK within 24 hrs of learning of the pregnancy of female partner of male participant (after obtaining the necessary signed informed consent from the female partner). While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, foetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.
- The pregnant female partner will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the pregnant female partner and the neonate and the information will be forwarded to the sponsor.
- Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.2.4. While the investigator is not obligated to actively seek this information in pregnant female partners, he or she may learn of an SAE through spontaneous reporting.

8.3. Treatment of Overdose

GSK does not recommend specific treatment for an overdose. The investigator will use clinical judgement to treat an overdose as and when they are made aware of this.

In the event of an overdose, the investigator should:

1. Contact the Medical Monitor immediately.

2. Closely monitor the participant for AE/SAE and laboratory abnormalities until study treatment can no longer be detected systemically (at least 2 days or 5 half-lives, whichever is longer).

3. Obtain a plasma sample for PK analysis as soon as possible after being notified of the overdose and inform the Medical Monitor and discuss further follow up (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.

8.4. Pharmacokinetics

8.4.1. Plasma Sample Collection and analyses

- Plasma samples of approximately 1 mL (from 2 mL of blood) will be collected for measurement of plasma concentrations of GSK3494245 as specified in the SoA. Plasma samples of approximately 2.5 mL (from 5 mL of blood) will be collected from time-points 12, 14 and 24 hrs post-dose in the SAD (and more than 24 hrs, if required, based on emerging data).
- Instructions for the collection and handling of biological samples will be provided in the SRM. The actual date and time (24-hour clock time) of each sample will be recorded.
- Samples will be analysed using an appropriately validated assay method by or under the supervision of the sponsor. Samples collected for analyses of GSK3494245 plasma concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.
- Once the plasma has been analyzed for GSK3494245 any remaining plasma may be analyzed for other compound-related metabolites and the results reported under a separate protocol.

Drug concentration information that may unblind the study will not be reported to the investigative site or blinded personnel until the study has been unblinded. CCI [redacted]

8.4.2. Urine Sample Collection

- Urine samples for analysis of GSK3494245 and its metabolites, CCI [redacted] will be collected at the time-points listed in the SoA. The timing of urine samples may be altered and/or samples may be obtained at additional time points to ensure thorough PK and/or safety monitoring.

- Details of urine sample processing, storage and shipping procedures are provided in the SRM.

CCI [redacted]

[redacted]

[redacted]

8.5. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.6. Genetics

Genetics are not evaluated in this study.

CCI [redacted]

8.8. Health Economics / Medical Resource Utilization and Health Economics

Health Economics/Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

The focus of this FTIH study, both single and repeat dose phases, is to evaluate the safety, tolerability and PK of GSK3494245. As such there is no formal hypothesis being tested, however, where appropriate, an estimation approach has been taken, and point estimates and confidence intervals (CIs) will be constructed.

9.2. Sample Size Determination

The planned sample size is up to 80 participants for this study (8 participants each for Cohorts 1, 2 and 3a and up to 16 participants for Cohort 3) and up to 40 participants for the MAD part (8 participants into each of Cohorts 4-8). Additional participants may be recruited as replacements for withdrawn participants. Cohort 1 and 2 are split by a 2:6 for ratio of placebo participants to active participants per period. For Cohort 3 the regimens are split by a 1:1:1:1 ratio.

For Cohorts 1,2, 3a and 4-8 assuming a between-participant CV (CVb) of 30% for clearance, it is estimated that, with 6 participants per dose, the 95% confidence interval around the mean of the clearance for a dose would lie within 36% of the point estimate (Table 10).

Sample size in Cohort 3 was calculated based on the precision estimate for fed versus fasted status. The objective of Cohort 3 (SAD part) is to determine if food effects the PK of GSK3494245 and to inform the dosing regimen for the MAD part. A precision estimate was therefore used to determine the sample size, based on assumed within subject coefficient of variation (CVw) for AUC of 20% and Cmax of 30% respectively. A maximum of 16 participants will be recruited with the aim of getting evaluable data from 12 participants. If the estimates for the CVw decrease following review of the data from Cohorts 1 and 2, then fewer participants may be recruited, with the aim of obtaining as few as 10 evaluable participants.

Assuming a point estimate for fed versus fasted status of 1 (i.e. no food effect), under the variability assumptions described above, and a sample of 12 evaluable participants, the precision estimates and 90% confidence intervals (CI) for AUC and Cmax are:

Parameter	CVw	Sample size	Precision estimate	90% CI
AUC	20%	12	16%	(0.84, 1.19)
Cmax	30%	12	24%	(0.76, 1.32)

9.3. Sample Size Sensitivity

For Cohorts 1,2, 3a and 4-8 the sensitivity of the precision estimate is calculated with respect to three different sample sizes and between subject CV as presented below in Table 10..

Table 10 Sample Size Sensitivity for Cohorts 1,2, and 4-8 Precision Estimates

Between subject CV, CVb (%)	Between subject standard deviation, SDb	Sample size	Actual distance from mean to limits (log transformed scale)	Distance from Point estimate (%)
20	0.198	4	0.315	37
	0.198	6	0.208	23
	0.198	8	0.166	18
30	0.294	4	0.468	60
	0.294	6	0.309	36
	0.294	8	0.246	28
40	0.385	4	0.613	85
	0.385	6	0.404	50
	0.385	8	0.322	38

For the assumed variability of AUC and C_{max} respectively, for Cohort 3, the impact of different numbers of evaluable participants on the precision estimates and 90% confidence intervals were assessed with the results presented in Table 11.

Table 11 Sample size sensitivity for fixed within subject coefficient of variation

Parameter	CVw	Sample size (n)	Point estimate (PE) fed vs fasted	Precision Estimate	90% CI of PE
AUC	20%	6	1	26%	(0.74, 1.35)
		8	1	21%	(0.79, 1.27)
		10	1	18%	(0.82, 1.22)
		12	1	16%	(0.84, 1.19)
		14	1	14%	(0.86, 1.16)
		16	1	13%	(0.87,1.15)
	30%	6	1	41%	(0.59, 1.69)*
		8	1	32%	(0.68, 1.47)
		10	1	27%	(0.73, 1.37)
		12	1	24%	(0.76, 1.32)
		14	1	22%	(0.78, 1.28)
		16	1	20%	(0.8, 1.25)
Cmax	30%	6	1	41%	(0.59, 1.69)
		8	1	32%	(0.68, 1.47)
		10	1	27%	(0.73, 1.37)
		12	1	24%	(0.76, 1.32)
		14	1	22%	(0.78, 1.28)
		16	1	20%	(0.8, 1.25)
	40%	6	1	57%	(0.43, 2.33)
		8	1	44%	(0.56, 1.79)
		10	1	37%	(0.63, 1.59)
		12	1	33%	(0.67, 1.49)
		14	1	29%	(0.71, 1.41)
		16	1	27%	(0.73, 1.37)

* Based on a CVw of 30%, it is estimated that for a sample size of 6 participants, the lower bound of the 90% CI will be within approximately 41% of the point estimate and the upper bound of the CI within 69%, i.e. assuming a point estimate of 1 (i.e, no difference) the CI would be as wide as (0.59, 1.69).

9.4. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Screened	All participants who were screened for eligibility
Enrolled	• All participants who passed screening and entered the study. Included are: Randomized Participants *Note: screening failures (who never passed screening even if rescreened) and participants screened but never enrolled into the study (Reserve, Not Used) are excluded from the Enrolled population as they did not enter the study.*
Safety	• All randomized participants who received at least one dose of study treatment. • This population will be based on the treatment the participant actually received. *Note: Participants who were not randomized but received at least one dose of study treatment should be listed.*
PK	All participants in the Safety population who had at least 1 non-missing PK assessment (Non-quantifiable [NQ] values will be considered as non-missing values).

9.5. Statistical Analyses

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

Further details including strategies for intercurrent events (related to COVID-19 or not), visit windows etc. if applicable will be described in the analysis plan.

9.5.1. Safety Analyses

The primary analyses are to evaluate safety and tolerability of single and repeat doses of GSK3494245.

The safety population will be used for the primary analyses.

Endpoint	Statistical Analysis Methods
Primary	Safety and tolerability data comprising of • adverse events • clinical laboratory data • physical examinations • vital signs • 12 lead ECGs • 24-48 hr telemetry will be presented in tabular and/or graphical format and summarized descriptively according to GSK's Integrated Data Standards Library (IDSL) standards. Additional plots will be created using the data from Cohort 3 to assess changes in certain lab parameters with respect to the food effect and presence/absence of the drug. Further details will be provided in the Reporting and Analysis Plan (RAP).

9.5.2. Pharmacokinetic (PK) Analyses

All PK analyses will be performed on the PK Population.

Endpoint	Statistical Analysis Methods
Secondary	Pharmacokinetic analysis will be the responsibility of the Clinical Pharmacology Modeling and Simulation Department, (CPMS), GlaxoSmithKline. Plasma GSK3494245 concentration-time data will be analyzed by non-compartmental methods with WinNonlin 8.0 or higher. From the plasma concentration-time data, the following PK parameters will be determined, as data permit: from SAD: • maximum observed plasma concentration (C_{max}) • time to C_{max} (T_{max}) • area under the plasma concentration time curve [AUC(0-t) and AUC(0-∞)]

Endpoint	Statistical Analysis Methods
	• apparent terminal phase half-life (t1/2) from MAD: • Day 1 AUC(0-t), AUC(0-∞), AUC(0-tau), Cmax,Tmax, t1/2., • trough concentration (C_{tau}). Trough concentration (Ct_{au}) samples collected on the specified days may be used to assess attainment of steady state. To estimate the extent of accumulation after repeat dosing, the observed accumulation ratio for AUC (($RAUC_{(0\text{-}tau)}$)), C_{max} (RC_{max}) and Ctau (RCtau) may be determined. To estimate time-invariance after repeat dosing, the ratio of AUC(0-tau) on Day 7 to AUC(0-∞) on Day 1 may be obtained. Time-invariance ratio calculation for TID regimen, if conducted,as AUC(0-tau) on Day 6 evening dose to AUC(0-∞) on Day 1 Statistical analyses of the pharmacokinetic parameter data will be the responsibility of Biostatistics, GlaxoSmithKline. No formal hypotheses will be tested. Pharmacokinetic data will be presented in graphical and/or tabular form and will be summarized descriptively. Full details on the statistical aspects will be detailed in the Reporting and Analysis Plan (RAP). A population PK approach may be used if data permit. In this case the analysis may be reported separately from the clinical study report. **Estimand** Intercurrent events, the estimand strategy to handle these events and the changes to the respective analysis to implement the strategies will be highlighted in the RAP. **Food Effect (SAD part)** The effect of food on the pharmacokinetics of GSK3494245 will be examined. AUC(0-t), AUC(0-∞) and C_{max} of GSK3494245 will be analyzed after a $\log_e$-transformation of the data. An analysis of variance model will be fitted along with 90% confidence intervals using a mixed effects model, with fed/fasted condition as a fixed effect and participant as a random effect. Point estimates and corresponding 90% confidence intervals will be constructed for the comparisons of interest of GSK3494245 fed – GSK3494245 fasted, using the residual variance. These will then be back-transformed to provide point estimates and corresponding 90% confidence intervals for the geometric mean ratios fed: fasted.

Endpoint	Statistical Analysis Methods
	Dose Proportionality (SAD part) Dose proportionality will be assessed following single doses of GSK3494245 for fasted and fed cohorts separately(SAD part) via analyses of AUC(0-∞) and C_{max}. A statistical analysis will be performed using the power model. The analysis will be performed on log_e-transformed data. For each of these parameters a mixed effects model will be fitted with log_e (dose) as a fixed effect and individual participant fitted as random effects. Estimates of the mean slopes of log_e (dose) will be reported along with corresponding 90% confidence intervals (slope≈1 implies dose proportionality). **Accumulation (MAD part)** The extent of accumulation of GSK3494245 will be based on AUC ($RAUC_{(0\text{-}tau)}$), C_{max} (RC_{max}) and Ctau (RCtau). The focus of the statistical analysis will be to estimate the accumulation ratio, Ro, on the pharmacokinetics of GSK3494245. Following log_e-transformation, AUC(0-tau) on Day 1 and AUC(0-tau) on the day of last dose will be analysed by a mixed effect model, fitting fixed effect terms for dose, day, and day by dose interaction, and fitting subject as a random effect. For each dose, point estimates and 90% confidence intervals for the differences "Day 7 - Day 1" (for BID) or "Day 6 evening dose – Day 1 morning dose" (for TID) will be constructed using the appropriate error term. The point estimates and associated 90% confidence intervals will then be exponentially back-transformed to provide point and 90% confidence interval estimates for the ratios "Day 7: Day 1" (for BID) or "Day 6- Day 1" (for TID) for each active dose. If both the dose and day by dose interaction terms are not significant, a single point estimate and confidence interval pooled across all doses will also be constructed. RC_{max} and RCtau will be estimated in a similar approach. **Steady State analysis (MAD part)** Steady state will be assessed following repeat dose of GSK3494245 (MAD part) via analyses of trough plasma concentration (Ctau) A statistical analysis will be performed using mixed effect model on log_e transformed endpoint. A mixed effects model will be fitted with loge (dose) as a fixed effect and subject fitted as random effect. The coefficients of the slopes for the day effect on log scale for each dose, along with corresponding 90% confidence intervals, will be used to determine whether steady state was achieved.

9.6. Interim Analyses

No formal interim analyses are planned for this study. However, safety, tolerability, and PK data will be reviewed before each dose escalation in the SAD part and the MAD part, prior to the investigation of the food effect and between the SAD and MAD part.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with:

Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) international ethical guidelines

Applicable ICH Good Clinical Practice (GCP) guidelines

Applicable laws and regulations

The protocol, protocol amendments, ICF, IB, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IEC/IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC

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, including the risk and benefits, to the participant and answer all questions regarding the study.

Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, privacy and data protection requirements, where applicable, and the IRB/IEC or study center.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

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

A copy of the ICF(s) must be provided to the participant.

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

The ICF may contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. 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.

GSK will ensure protection of the personal data of the investigator and site staff which is collected within the framework of and for the purpose of the study.

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), that their data will be used as described in the informed consent..

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

Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access

10.1.5. Committees Structure

Refer to the study Dose Escalation Plan for the structure of the Dose Escalation Committee (DEC).

10.1.6. Dissemination of Clinical Study Data

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.

GSK will also provide all investigators who participated in the study with a summary of the study results and will tell the investigators what treatment their participants received. Investigators are encouraged to share the summary results with the study participants, as appropriate.

Under the framework of the SHARE initiative, GSK intends to make anonymized participant-level data from this trial available to external researchers for scientific analyses or to conduct further research that can help advance medical science or improve patient care. This helps ensure the data provided by trial participants are used to maximum effect in the creation of knowledge and understanding. Requests for access may be made through www.clinicalstudydatarequest.com.

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 protocol and results summary and for development of a manuscript for publication for this study will be in accordance with GSK Policy.

GSK intends to make anonymized patient-level data from this trial available to external researchers for scientific analyses or to conduct further research that can help advance medical science or improve patient care. This helps ensure the data provided by trial participants are used to maximum effect in the creation of knowledge and understanding

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

10.1.7. Data Quality Assurance

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

Guidance on completion of CRFs will be provided in CRF Guidelines.

Quality tolerance limits (QTLs) will be pre-defined in relevant study plans to identify systematic issues that can impact participant safety and/or reliability of study results.

These pre-defined parameters will be monitored during and at the end of the study and all deviations from the QTLs and remedial actions taken will be summarized in the clinical study report.

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

Monitoring details describing strategy including definition of study critical data items and processes (e.g., risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan.

The sponsor or designee is responsible for the data management of this study including quality checking of the data.

The sponsor assumes accountability for actions delegated to other individuals (e.g., contract research organizations).

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

10.1.8. Source Documents

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

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

Definition of what constitutes source data and its origin can be found in Source Document Agreement.

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

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

10.1.9. Study and Site Start and Closure

First Act of Recruitment

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

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

Study/Site Termination

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

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

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

For study termination:

- Discontinuation of further study intervention development

For site termination:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines.
- Inadequate or no recruitment of participants (evaluated after a reasonable amount of time) by the investigator.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.10. Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.

- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2. Appendix 2: Clinical Laboratory Tests

The tests detailed Table 12will be performed by the central laboratory, The Doctor's Laboratory, unless otherwise specified in the table.

Local laboratory results may be used if the central laboratory results are not available in time for either study intervention administration and/or response evaluation. If the local laboratory results are used to make a study intervention decision or response evaluation, the results must be recorded.

Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 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. CCI [redacted]

Table 12 Protocol-Required Safety Laboratory Tests

Laboratory Assessments[1]	Parameters			
Haematology	Platelet Count RBC Count Hemoglobin Hematocrit	RBC Indices: Mean Corpuscular Volume (MCV) Mean Corpuscular Haemoglobin (MCH) %Reticulocytes	WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Clinical Chemistry[2]	BUN	Potassium	Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total and direct bilirubin
	Creatinine	Sodium[6]	Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT), Gamma GT	Total Protein
	Glucose (Fasted)	Calcium[6] (Corrected)	Alkaline phosphatase	Albumin
	Magnesium	Phosphate	Creatine phosphokinase (CPK)[3]	C-reactive protein (CRP)

Laboratory Assessments[1]	**Parameters**			
	Triglycerides (Fasted)	Lactate (test conducted by clinic staff)	Cholesterol (fasted)	Urea
	Chloride [6]	Ketones[6]	Bicarbonate(test conducted by clinic staff)[6]	pH (test conducted by clinic staff)
Routine Urinalysis	Urinalysis parameters to include: • Specific gravity • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick • Microscopic examination (if there is any abnormality) • Urine albumin:creatinine ratio, if trace urine protein is identified by dipstick • Urine creatinine • Urine phosphate (only in the event a participant has persistent hypophosphataemia)[4].			
Other Tests	• Alcohol breath test and urine drug screen (to include at a minimum: amphetamines, methamphetamine, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines, methadone, phencyclidine and tricyclic antidepressants) • Serology (HIV 1 & 2 antibody, hepatitis B surface antigen [HBsAg], and hepatitis C virus antibody). • Estimated glomerular filtration rate (eGFR) will be calculated using the creatinine-based CKD-EPI formula. Additionally, eGFR may be estimated using the Cystatin C CKD-EPI formula if for any participant there is a persistent (2 consecutive readings) rise in SrCr≥30% or a fall in eGFR≥30% from baseline, or at the PIs discretion • COVID-19 testing The results of each test must be entered into the CRF[5].			

Laboratory Assessments[1]	Parameters

NOTES :

1. The investigative site may assess other laboratory parameters as needed, according to standard site practice and results will be recorded in source documents.
2. Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 8.1.5 and Appendix 5. 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).
3. CPK cut off value will be determined at the discretion of the investigator taking into account context of change.
4. Urine phosphate to be assessed only in the event a participant has persistent hypophosphataemia. (less than 0.8mmol/L) confirmed by repeat testing.
5. The investigative site may screen for additional drugs of abuse as part of standard site practice and will be recorded in source documents. The study CRF will only collect drug screen results of those that are positive.
6. Serum chloride, calcium, ketones, sodium and bicarbonate to be measured by the local lab in the event of confirmed low pH

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

10.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of a study treatment, whether or not considered related to the study treatment. • 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 treatment.

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected intervention-intervention interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment 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.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments that 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.

Events NOT Meeting the AE Definition
• Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

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

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

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed:
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) Is a suspected transmission of any infectious agent via an authorised medicinal product
g) Other situations: • Possible Hy's Law case: ALT≥3xULN AND total bilirubin ≥2xULN (>35% direct bilirubin) or international normalized ratio (INR) >1.5 must be reported as SAE • Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. o Examples of such events include invasive or malignant cancers, intensive treatment for allergic bronchospasm, blood dyscrasias, convulsions, or development of intervention dependency or intervention abuse.

10.3.3. Recording and Follow-Up of AE and SAE

AE and SAE Recording
• When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event. • The investigator will then record all relevant AE/SAE information. • It is **not** acceptable for the investigator to send photocopies of the participant's medical records to GSK in lieu of completion of the GSK required form. • There may be instances when copies of medical records for certain cases are requested by GSK. In this case, all participant identifiers, 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: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Moderate: Minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living (ADL). Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
- Severe: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling, limiting self care ADL. Self care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Assessment of Causality

- The investigator is obligated to assess the relationship between study treatment and each occurrence of each AE/SAE. The investigator will use clinical judgment to determine the relationship.
- 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.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment 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 will 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 hrs of receipt of the information.

10.3.4. Reporting of SAE to GSK

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

SAE Reporting to GSK via Paper CRF
• Facsimile transmission of the SAE paper data collection tool is the preferred method to transmit this information to the **medical monitor or the SAE coordinator**. • In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.

SAE Reporting to GSK via Paper CRF
• 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. Contraception Guidance:

Male participants

Male participants with female partners of child-bearing potential are eligible to participate if they agree to the following during the study intervention period and for at least 90 days after the last dose of study intervention:

- Refrain from donating fresh unwashed semen

  Plus either:

- Be abstinent from heterosexual 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 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 a male condom when engaging in any activity that allows for passage of ejaculate to another person

• **CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:**
• **Highly Effective Methods[b] That Have Low User Dependency** *Failure rate of <1% per year when used consistently and correctly.*
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)[c]
• Bilateral tubal occlusion
• Azoospermic partner (vasectomized or due to a medical cause) • Azoospermia 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. Note: documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
• **Highly Effective Methods[b] That Are User Dependent** *Failure rate of <1% per year*

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

10.4.2. Collection of Pregnancy Information:

Male participants with partners who become pregnant

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

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 hrs of learning of the partner's pregnancy.

- The female 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 foetal status (presence or absence of anomalies) or indication for procedure.

10.5. Appendix 5: Liver Safety: Required Actions and Follow-up Assessments

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

Phase I Liver Chemistry Stopping Criteria and required Follow Up Assessments

<table>
<tr><th colspan="2">Liver Chemistry Stopping Criteria</th></tr>
<tr><td>ALT-absolute</td><td>ALT≥3xULN
If ALT≥3xULN AND total bilirubin ≥2xULN (>35% direct bilirubin) or international normalized ratio (INR) >1.5, report to GSK as an SAE[1,2].
See additional Actions and Follow Up Assessments listed below</td></tr>
<tr><th colspan="2">Required Actions, Monitoring and Follow up Assessments</th></tr>
<tr><th>Actions</th><th>Follow Up Assessments</th></tr>
<tr><td>• Immediately discontinue study treatment
• Report the event to GSK within 24 hrs
• Complete the liver event form and complete an SAE data collection tool if the event also meets the criteria for an SAE[2]
• Perform liver event follow up assessments as described in the Follow Up Assessment column.
• Do not restart or rechallenge participant with study intervention
• Monitor the participant until liver chemistries resolve, stabilise, or return to within baseline (see MONITORING)
MONITORING:
If ALT≥3xULN AND total bilirubin ≥ 2xULN or INR >1.5
• Repeat liver chemistries (include ALT, aspartate transaminase [AST], alkaline phosphatase, total bilirubin and INR) and perform liver event follow up assessments within 24 hrs
• Monitor participant twice weekly until liver chemistries resolve, stabilise or return to</td><td>• Viral hepatitis serology[3]
• Obtain INR and recheck with each liver chemistry assessment until the aminotransferases values show downward trend.
• Obtain blood sample for pharmacokinetic (PK) analysis, obtained within 1 hr of of the most recent dose, if possible[4]
• Obtain serum creatine phosphokinase (CPK), lactate dehydrogenase (LDH), gamma-glutamyl transferase (GGT), glutamate dehydrogenase (GLDH) and serum albumin.
• 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 liver event form
• Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, recreational drugs, and other</td></tr>
</table>

Liver Chemistry Stopping Criteria	
within baseline • A specialist or hepatology consultation is recommended	over the counter medications. • Record alcohol use on the liver event alcohol intake case report form
If ALT≥3xULN AND total bilirubin < 2xULN and INR ≤1.5: • Perform liver chemistries (include ALT, AST, alkaline phosphatase, total bilirubin and INR) and perform liver event follow up assessments within **24-72 hrs** • Monitor participant weekly until liver chemistries resolve, stabilize or return to within baseline	**If ALT≥3xULN AND total bilirubin ≥ 2xULN or INR >1.5** obtain the following in addition to the assessments listed above**:** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG) or gamma globulins. • Assess potential acetaminophen contribution to liver injury. Serum acetaminophen adduct high should be done (where available), or ACETA assay, a serum or heparinized plasma acetaminophen enzymatic method analysed on COBAS INTEGRA systems. Unless acetaminophen use is very unlikely in the preceding week (e.g. where the participant has been resident in the clinical unit throughout). • Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging form. • Liver biopsy may be considered and discussed with local specialists if available, for instance: o In patients when serology raises the possibility of autoimmune hepatitis (AIH) o In patients when suspected DILI progresses or fails to resolve on withdrawal of study intervention o In patients with acute or chronic atypical presentation. • If liver biopsy is conducted, then complete liver biopsy form.

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation testing is unavailable**, record the absence/presence of detectable urinary bilirubin on dipstick**, which is indicative of direct bilirubin elevations suggesting liver injury.
2. All events of ALT ≥ 3xULN and total bilirubin ≥ 2xULN (>35% direct bilirubin) or ALT ≥ 3xULN and INR>1.5, which may indicate severe liver injury (possible 'Hy's Law'), must be reported **to GSK** as an SAE (excluding studies of hepatic impairment or cirrhosis); the INR threshold value stated will not apply to participants receiving anticoagulants.
3. Includes: hepatitis A immunoglobulin (IgM) antibody; HBsAg and HBcAb; hepatitis C RNA; cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, heterophile antibody or monospot testing) and hepatitis E IgM antibody.
4. PK sample may not be required for participants known to be receiving placebo. Record the date/time of the PK blood sample draw and the date/time of the last dose of study treatment prior to PK 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.

10.6. Appendix 6: COVID-19 Appendix

10.6.1. Overall Rationale for this Appendix

COVID-19 pandemic may impact the conduct of clinical studies. Challenges may arise from quarantines, site closures, travel limitations, interruptions to the supply chain for the investigational product or other considerations if site personnel or study participants become infected with COVID-19. These challenges may lead to difficulties in meeting protocol-specified procedures, including administering or using the investigational product or adhering to protocol-mandated visits and laboratory/diagnostic testing.

This protocol appendix outlines measures that may be applicable for any site impacted by the COVID-19 pandemic. The purpose of the appendix is to provide information on the measures to be taken to protect participants' safety, welfare and rights, and promote data integrity.

These measures will remain in place until study completion.

10.6.2. Study Procedures During COVID-19 Pandemic

During the special circumstances caused by the current COVID-19 pandemic, you should consider specific public health guidance, the impact of any travel restrictions implemented by local/regional health authorities and local institutions, and individual benefit /risk when making enrollment and treatment decisions for trial participants.

As outlined in Section 8, Protocol waivers or exemptions are not allowed and every effort should be made to adhere to protocol-specified assessments for participants on study intervention, including follow up however when not possible, for the duration of these special circumstances, the following measures may be implemented for enrolled participants:

- Clinical investigators should document in site files and in participant notes as appropriate how restrictions related to COVID-19 led to the changes in study conduct and duration of those changes and indicate which trial participants were impacted and how those trial participants were impacted (as per the current local COVID-19 related regulatory guidance).
- Missing protocol required data/visits due to COVID-19 should be noted in participant notes and recorded as a COVID-19 protocol deviation.

10.6.3. Protocol Defined Procedures/Visits:

- The protocol defined interval for the collection of samples during the Follow-up visit (see Section 1.3 Schedule of Activities), may be extended up to a maximum length of 14 days.

10.6.4. Data Management/Monitoring:

- If a situation arises where on-site monitoring is no longer permitted, GSK will consider remote Source Data Verification/Source Document Review (SDV/SDR) where permitted by the clinical site/institution. Remote SDV/SDR will be proposed to study sites to meet a participant and/or critical quality need, e.g., to assess participant safety or to ensure data integrity. In case of remote SDV/SDR, GSK will work with the site to ensure participant privacy.
- eCRF/CRF Final or Interim Sign off Process: The Principal Investigator (PI) is responsible for ensuring that the data within the eCRF casebook and any other data sources utilized during the study for each study participant is complete and consistent with source documents throughout the study (ICH GCP 4.9.1 4.9.2). The PI may sign/re-sign the eCRF from any computer/location by accessing InForm (or other eDC platform) using his/her unique eCRF log-in credentials. The PI may delegate this activity to another medically qualified and trained sub-investigator and this must be documented on the Delegation of Responsibilities (DoR) Log. It is recommended that the PI identifies a sub-investigator as a back-up for eCRF signatures. The sub-investigator must be appropriately trained on the protocol and eCRF requirements (with training documented), and the DoR log updated accordingly.
- Essential Document Sign Off Process: If an investigator is unable to print and sign essential documents such as Protocol /Amendment signature page then Email approval can be accepted by replying to the relevant email that is sent by GSK

10.7. Appendix 7: Abbreviations and Trademarks

µg	Micrograms
µmol	Micromolar
A	Active Drug
ADME	Absorption, Distribution, Metabolism, and Excretion
AE	Adverse Event
ALT	Alanine Transaminase
API	Active Pharmaceutical Ingredient
AR_{pred}	Predicted accumulation ratio
AUC	Area under concentration time-curve
$AUC_{(0-\infty)}$	Area under the plasma concentration-time curve from time 0 to extrapolated to infinity
$AUC_{(0-12)}$	Area under the plasma concentration-time curve from time 0 to 12 hrs
$AUC_{(0-24)}$	Area under the plasma concentration-time curve from time 0 to 24 hrs
AUEC	Area under effective curve
BID	Twice daily
BMI	Body Mass Index
BP	Blood Pressure
CA	Competent Authority
CHMP	Committee for Medicinal Products for Human Use
CIOMS	Council for International Organizations of Medical Sciences
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CL	Clearance
CLr	Renal Clearance
C_{max}	Maximum observed plasma drug concentration
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	Coronavirus Disease 2019
CPK	Creatine phosphokinase
CPMS	Clinical Pharmacology Modeling and Simulation Department
CRF	Case Report Form
CRP	C-reactive protein
CSR	Clinical Study Report
C_{tau}	Trough plasma concentration
CVw	Subject Coefficient of Variation
DBR	Database Release
DEC	Dose Escalation Committee
DILI	Drug induced liver injury
DL	Dose Level
DLX	Dose Level to be determined
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eGFR	Estimated Glomeruli Filtration Rate
EMA	European Medicines Agency
EMEA	European Medicines Evaluation Agency
FDA	Food and Drug Administration
FE	Food Effect
FSH	Follicle Stimulating Hormone
FTIH	First Time In Human

GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
GSK	GlaxoSmithKline
h	hour(s)
HBsAg	Hepatitis B surface antigen
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HPLC	High Performance Liquid Chromatography
HR	Heart Rate
hr	hour(s)
HRT	Hormonal Replacement Therapy
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IDSL	Integrated Data Standards Library
IEC	Independent Ethics Committee
IIV	Inter-individual variabilities
IMP	Investigational Medicinal Product
INR	International Normalized Ratio
IRB	Institutional Review Board
IVIVE	In Vitro-In Vivo Extrapolation
IVRS/IWRS	Interactive Voice/Web Response System
KA	Absorption rate constant
CCI [redacted]	[redacted]
LBF	Liver Blood Flow
LDH	Lactate dehydrogenase
MAD	Multiple Ascending Dose
MCH	Mean Corpuscular Haemoglobin
MCV	Mean Corpuscular Volume
MOA	Mode of Action
MRI	Magnetic Resonance Imaging
MSDS	Material Safety Data Sheet
mg	Milligrams
min	Minute(s)
mL	Millilitres
mmol	Millimolar
CCI [redacted]	[redacted]
NIMP	Non-Investigational Medicinal Product
NOAEL	No observable adverse effect limit
NSAID	Non-Steroidal Anti-Inflammatory Drugs
NSVT	Non-Sustained Ventricular Tachycardia
P	Placebo
PBPK	Physiologically Based Pharmacokinetic Modelling
P-GP	P-glycoprotein
PK	Pharmacokinetics
PVC	Premature Ventricular Contraction
QTc	Electrocardiogram QT interval corrected for heart rate
QTcB	Electrocardiogram QT interval corrected for heart rate using Bazett's formula

QTcF	Electrocardiogram QT interval corrected for heart rate using Fridericia's formula
RAP	Reporting and Analysis Plan
RAUC	Relative Area Under the Curve
RBC	Red Blood Cells
RCCS	Randomization and Container Code Strategy
RR	Respiratory Rate
SAD	Single Ascending Dose
SAE	Serious Adverse Event
SGOT	Serum Glutamic-Oxaloacetic Transaminase
SGPT	Serum Glutamic-Pyruvic Transaminase
SMG	Safety and Medical Governance
SoA	Schedule of Activities
SOP	Standard Operating Procedures
SRM	Study Reference Manual
SUSAR	Suspected unexpected serious adverse reaction
T	Temperature
$t_{1/2}$	Apparent terminal half-life
T_{max}	Time to maximum observed plasma drug concentration
TTS	Technical Terms of Supply
ULN	Upper limit of normal
UPS	Ubiquitin-proteasome system
V	Volume
VDSS	Steady state volume of distribution
VL	Visceral Leishmaniasis
WBC	White Blood Cells

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
None

Trademarks not owned by the GlaxoSmithKline group of companies
COBAS INTEGRA
Entero-Tracker
SAS
WinNonlin

10.8. Appendix 8: Protocol Amendment History

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

Overall Rationale for Amendment 05:

Incorporation of a multiple-ascending dose (MAD) part..
Amendment of the food effect cohort (Cohort 3) to include fed and fasted placebo arms to allow for assessment of biomarkers in the absence of drug.

CCI [redacted]

Addition of renal monitoring in the event of marked changes in estimated glomerular filtration rate (eGFR) or serum creatinine and use of Cystatin C to estimate GFR when necessary to understand whether changes in these two parameters reflect an effect on transporters involved in creatinine excretion.

Section # and Name	Description of Change	Brief Rationale
Protocol Title on Title Page Sponsor Signatory Page Section 1.1 Synopsis	Minor edit, word *repeat* is added	Based on the study design change
Section 1.1 Synopsis Section 1.2 Schema Section 1.3.1 SoA Section 2 Introduction Section 3 Objectives and Endpoints 4 Study Design 5 Study Population 5.3.1 Meals and Dietary Restrictions 6.1 Study Treatments Administered 6.3.1 Randomization 7.1.3 Renal Stopping Criteria 8.1.4 Holter Monitoring CCI [redacted] 9.5 Statistical Analyses	Multiple ascending dose cohorts added to the study	Assess safety, tolerability and PK of multiple doses of GSK2494245
Section 1.1 Synopsis Section 1.2 Schema Section 1.3 SoA 4 Study Design 5.3.1 Meals and Dietary Restrictions 6.3.1 Randomization 6.3.2 Blinding 9.2 Sample Size Determination	Cohort 3 (food effect cohort) amended to add two placebo arms: fed and fasted. Subject numbers increased to 72 to allow for randomization schedule Cohort 3 changed from open label to double blind	To understand the impact of drug-effect on various biomarkers
CCI [redacted]		
Section 2.3.1 Risk assessment	Reference to potential inhibition of renal transporters added together with calculation of eGFR using Cystatin-C	Estimating GFR using Cystatin-C may aid understanding of transporter effects on creatinine levels

Section # and Name	Description of Change	Brief Rationale
Section 2.3.1 Risk assessment 7.1.7 Mitochondrial stopping criteria Appendix 2 Table 12	Inclusion of a requirement to conduct additional laboratory tests (serum ketones, chloride and calcium and, if clinically indicated, arterial blood gases) in the event of confirmed acidosis	Additional safety measures
6.3.2 Blinding	Addition of text describing completion of documentation in the event of unblinding Table 8 updated to reflect roles which may be unblinded	Clarification of procedure
9.2 Sample Size Determination 9.3 Sample Size Sensitivity	Samples size sensitivity updated to reflect changes in the subject numbers (sample size increased to 16) for Cohort 3 to allow for randomization.	Number of participants in Cohort 3 updated from 14 to 16
Throughout	Minor editorial and document formatting revisions	Minor, therefore have not been summarized

Overall Rationale for Amendment 04: This amendment is to address recommendations following GSK's safety governance review of emerging data.

Section # and Name	Description of Change	Brief Rationale
Section 1.2 Schema	Schema updated to include "**" which refers in the footnote to the optional aspect of the study design. Footnote updated to include: "** The dosing schedule may be adjusted to add an additional cohort to further evaluate safety or PK findings at a given dose level, or to evaluate additional doses. The additional cohort will be up to 8 participants following the same design and dose escalation principles as Cohort 1 and 2."	Schema and footnote updated for clarity to reflect optional aspect of the study design as indicated in Section 4.6
Section 2.3.1 Risk Assessment	Changed from: "Abnormal liver function tests excluded: ALT > 1.5x ULN" To: "Abnormal liver function tests excluded: ALT > ULN at screening or Day -1"	Updated to reflect recommendations following GSK's safety governance review
Section 4.1.2 Figure 1	Schema updated to include "**" which refers in the footnote to the optional aspect of the study design. Footnote updated to include: "** The dosing schedule may be adjusted to add an additional cohort to further evaluate safety or PK findings at a given dose level, or to evaluate additional doses. The additional cohort will be up to 8 participants following the same design and dose escalation principles as Cohort 1 and 2."	Schema and footnote updated for clarity to reflect optional aspect of the study design as indicated in Section 4.6
Section 5.2 Exclusion Criteria	Changed from: "Alanine transaminase (ALT) >1.5x upper limit of normal (ULN)" To: "Alanine transaminase (ALT) > upper limit of normal (ULN) at screening or Day -1"	Updated to reflect recommendations following GSK's safety governance review

Overall Rationale for Amendment 03:

The overall rationale for this amendment is that in the absence of a validated bioanalytical assay, preliminary estimates of GSK3494245 and its metabolites in urine can be determined from measurements being taken from the exploratory endpoint.

Section # and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis	Removed "Amount of GSK3494245 excreted in urine over 24h (Ae0-24h) after single, fraction of dose excreted in urine over 24h (fe%), renal CL (CLr)" from Secondary Endpoint CCI [redacted]	CCI [redacted]
Section 3 Objectives and Endpoints	Removed "Amount of GSK3494245 excreted in urine over 24h (Ae0-24h) after single, fraction of dose excreted in urine over 24h (fe%), renal CL (CLr)" from Secondary Endpoint CCI [redacted]	CCI [redacted]
Section 9.5.2 Pharmacokinetic (PK) Analyses	Removed – "From the urine concentration-time data, the following PK parameters will be determined, as data permit: • Amount excreted in urine over 24h post dose (Ae0-24h) • Fraction of the dose excreted in urine over 24h post dose (fe%)	Removed to reflect change in Secondary Endpoint

Section # and Name	Description of Change	Brief Rationale
	• Renal Clearance (CLr)"	

Overall Rationale for Amendment 02:

This amendment is considered substantial based on the criteria set forth in Article 10a of Directive 2001/20/EC of the European Parliament and the Council of the European Union. This amendment was to address comments in response to external regulatory review of Amendment 01.

Section # and Name	Description of Change	Brief Rationale
Section 4.1.1 Single Ascending Dose (SAD) – 3rd paragraph Section 4.6 Dose Escalation	Added: In addition, the DEC may decide, based on emergent safety and PK data to include an additional cohort of up to 8 participants following the same design as Cohorts 1 and 2, as indicated in Section 4.6. Change from: "As part of this decision-making process, the DEC may decide to escalate or de-escalate the dose in study. The dosing schedule may also be adjusted to expand a cohort to further evaluate safety or PK findings at a given dose level, or to add cohorts to evaluate additional dose levels. Dosing may also be halted before all planned dose levels have been completed if the stopping criteria has been met or if review of the data determines that evaluation of further dose levels is not necessary to meet the study objectives." To: "As part of this decision-making process, the DEC may decide to escalate or de-escalate the dose in study. The dosing schedule may also be adjusted to add a cohort to further evaluate safety or PK findings at a given dose level, or to evaluate additional dose levels. Expansion to an additional cohort will be up to a maximum of one cohort of 8 participants, investigating up to four dose levels. Addition of an extra cohort may occur if there is greater variability in the PK parameters than expected, or if more dose levels are needed to reach the potentially efficacious exposure. If an additional cohort is required, then the nominal illustrative doses in Table 3 and Table 4 may be adjusted. Dose levels will not result in exposure exceeding 3-fold of the highest dose level administered in the study. Dosing may also be halted before all planned dose levels have been completed if the stopping criteria has been met, or for any safety concerns, or if review of the data determines that evaluation of further dose levels are not necessary to meet the study objectives." Change from:	To define the maximum number of cohorts/ participants that can be added to the study and define any dosing schedule adjustments that may be implemented.

Section # and Name	Description of Change	Brief Rationale
Section 4.6.2 Dose Escalation and Safety Review Requirements	• Dose will be escalated by no more than 3-fold and up to a dose predicted to provide maximum exposure within PK stopping criteria (NOAEL). To: • Dose will be escalated by no more than 3-fold of the highest dose level administered in the study and not more than the dose predicted to provide maximum exposure within PK stopping criteria (NOAEL).	
Section 2.3.1 Risk Assessment Table, Kidney.	Change from: "The study will be halted if 2 or more participants across all study parts develop any of the above withdrawal criteria." To: "The study will be halted if 1 or more participants across all study parts develop any of the above withdrawal criteria and it is considered to be related to GSK3494245 (in the opinion of the investigator in consultation with the Medical Monitor)".	Changes to accommodate study stopping criterion for adverse renal events in Section 7.1.2, being adjusted to a single event that is considered related to GSK3494245
Section 7.1.2. Dose Escalation / Study Stopping Criteria	Change from: "The Principal Investigator and the GSK Medical Monitor will review the following and study dosing **will be** stopped if any of these criteria is met: • Two or more participants from the previous dose level on active treatment experience the same / medically similar AE which is of severe intensity and are reasonably attributable (in the opinion of the investigator) to dosing with GSK3494245. • Two or more participants across all study parts develop an adverse renal event as defined in the renal withdrawal criteria below (Section 7.1.3)." To: "The Principal Investigator and the GSK Medical Monitor will review the following and study dosing **will be** stopped if any of these criteria are met: • Two or more participants from the previous dose level on active treatment experience an AE which is of severe intensity and reasonably attributable (in the opinion of the investigator) to dosing with GSK3494245. • One or more participants across all study parts develop an adverse renal event as defined in the renal withdrawal criteria below (Section 7.1.3) considered to be related to GSK3494245 (in the	

Section # and Name	Description of Change	Brief Rationale
	opinion of the investigator in consultation with the Medical Monitor)."	
Section 7.1.3. Renal Stopping Criteria	Removed: "The study will be temporarily halted if 2 or more participants across all study parts develop any of the above withdrawal criteria."	Considered duplicative, because this is covered in changes to Section 7.1.2
Section 6.1 Study Treatment Administered	Placebo indicated as "NIMP" and changed to "IMP".	Placebo mistakenly indicated as a non-investigational medicinal product (NIMP). Updated to IMP accordingly.
Section 4.1.1	Change from: "(DL4, see Table 1)" To: "(DL4, see Figure 1)"	Corrected cross-reference error.

Overall Rationale for Amendment 01:
This amendment was to correct typographical errors in sections describing renal exclusion criteria.

Section # and Name	Description of Change	Brief Rationale
Section 2.3.1 Risk Assessment	Change of symbol and correction of units from "Screening eGFR (CKD-EPI) >90 ml / min" to "Screening eGFR (CKD-EPI) <90 ml/min/1.73 m²"	Correction of renal exclusion criteria due to typographical errors.
Section 5.2 Exclusion Criteria	Change of symbols in criterion 24 from "Screening urine albumin:creatinine ratio < 30 mg/g (< 3 mg/mmol)" to "Screening urine albumin:creatinine ratio > 30 mg/g (> 3 mg/mmol)"	
Section 2.3.1 Risk Assessment	Added exclusion of female participants to "unblinding to potential urine colour change" risk mitigation strategy	One of the unbinding risk mitigation strategies was erroneously missed from the original protocol.
Section 6.1	Study Treatment table: Inserted "Sourcing" as identifier of information type for that row. Realigned the row.	Row identifier was erroneously deleted in original protocol and caused misalignment of row.

Section # and Name	Description of Change	Brief Rationale
Section 10.4.1 Contraception Guidance	Table of contraception guidance allowed during the study: reference to footnote “c” was corrected from lowercase to superscript.	Formatting error.
Section 10.2 Appendix 2 Clinical Laboratory Tests	Removed urine protein:creatinine ratio from list of routine urinalysis parameters.	Left in error in the original protocol and not required, because albumin:creatinine ratio will be assessed.

11. REFERENCES

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