TITLE PAGE

Protocol Title: A randomized, double-blind (sponsor unblinded), 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 GSK3186899 in healthy participants

Protocol Number :208436/Amendment 01

Version: 01

Compound Number: GSK3186899

Study Phase: Phase 1

Short Title: Safety, tolerability and pharmacokinetics investigation of GSK3186899 in healthy participants.

Sponsor Name and Legal Registered Address:

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Regulatory Agency Identifying Number(s): EudraCT 2018-004642-42

Approval Date: 19-MAR-2019

SPONSOR SIGNATORY:

PPD

PPD

Dr Alison Webster
Head, Global Health Clinical

Date

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY List dates of original protocol and all amendments in reverse chronological order.		
Document	**Date**	**DNG Number**
Amendment 1 (version 01)	*19-MAR-2019*	*2018N385133_01*
Original Protocol (version 00)	*09-JAN-2019*	*2018N385133_00*

Amendment 1 19-MAR-2019

Overall Rationale for the Amendment: To amend the protocol with required changes from the Medicines and Healthcare products Regulatory Agency, UK

Section # and Name	**Description of Change**	**Brief Rationale**
3.3.1 Risk Assessment & 6.2 Exclusion Criteria	The exclusion criterion on renal function has been amended to an age appropriate GFR (CKD-EPI) of ≤ 90 (ml/min/1.73m^2). In alignment with this change, the mitigation strategy in the risk assessment table has also been updated.	MHRA requested changes to exclusion criterion.
6.2 Exclusion Criteria	An additional criterion has been added to exclude participants with abnormally low blood pressure, as determined by the Principal Investigator.	MHRA requested changes to add an additional exclusion criterion.
7.3 Measure to Minimize Bias: Randomization and Blinding	Additional wording has been added to include information on general and emergency unblinding.	To correct an omission in the original protocol, as identified by the MHRA.
8.1.2 Dose Escalation / Study Progression Stopping Criteria	One criterion has been updated to remove reference to two or more participants on active treatment experiencing the same / medically similar AE. This wording has now been updated to: "Two or more participants in the same cohort experience a severe non-serious adverse reaction (i.e. severe non-serious adverse events considered as, at least, possibly related to the IMP administration), independent of within or not within the same system-organ-class."	MHRA requested changes to the stopping criterion.

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A randomized, double-blind (sponsor unblinded), 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 GSK3186899 in healthy participants.

Short Title: Safety, tolerability and pharmacokinetics investigation of GSK3186899 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 program will comprise a First Time in Human (FTIH) study of single and repeat ascending doses in healthy participants, incorporating a food effect component to investigate the influence of food on the pharmacokinetics (PK) of GSK3186899. The study will evaluate the safety, tolerability and PK profile of single and repeat ascending doses of GSK3186899. Results of this study are intended to be used to identify appropriate and well tolerated doses of GSK3186899 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 GSK3186899 in healthy participants	• Adverse event reporting, clinical laboratory safety data, vital signs, 12 lead electrocardiogram (ECGs), 24 hours (hr) telemetry.
Secondary	
• To evaluate the systemic PK profile of single (fasted and fed) and repeat doses of GSK3186899 in healthy participants	• Plasma concentrations of GSK3186899 plus derived parameters, as data allow. **For single ascending dose (SAD) part**: Derived PK parameters for GSK3186899 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 (C_{max}), time to maximum observed plasma drug concentration (T_{max}),trough plasma concentration (C_{tau}) and

Objectives	Endpoints
	apparent terminal half-life ($T_{1/2}$) as data allow. Predicted accumulation Ratio (AR_{pred})# will be calculated. **For multiple ascending dose (MAD) part**: AUC(0-t), AUC(0-∞), AUC(0-tau), C_{max}, T_{max} and $T_{1/2}$.
• To examine dose proportionality following single and multiple doses of GSK3186899	• Dose-proportionality assessment using derived PK parameters, as data allow: **For SAD part:** AUC(0-∞), C_{max} **For MAD part:** AUC(0-tau), C_{max}, C_{tau}
• To assess accumulation and time-invariance ratios of GSK3186899 after multiple doses	• Accumulation ratios assessment*, where data allow: RAUC(0-tau), RC_{max}, RCtau. Time-invariance ratio calculation as AUC(0-12) on day 10 to AUC(0-∞) on day 1.
Exploratory	
• To collect residual plasma following GSK3186899 analysis, and urine samples, for analysis of metabolites of GSK3186899	• Metabolites of GSK3186899 in plasma and urine. These analyses will be run and reported separately from this protocol.
• To collect bile samples for analysis of metabolites of GSK3186899 (Part A Cohort 3 only)	• Metabolites of GSK3186899 in bile. These analyses will be run and reported separately from this protocol.

** Accumulation ratios calculated as the ratio of last dose to first dose PK parameters: $RAUC_{(0\text{-}tau)}$ = $AUC_{(0\text{-}tau)}$ on last dose to $AUC_{(0\text{-}tau)}$ on first dose, RCmax = Cmax on last dose to Cmax on first dose, RCtau= Ctau on last dose to Ctau on first dose. # ARpred = 1/(1-e^(k*tau)) where k is elimination rate constant following the single dose and tau is the dosing interval for the intended repeat dosing.*

Overall Design: This study will be a randomized, double-blind (sponsor unblinded), placebo-controlled, 2-part study of the oral administration of GSK3186899 in healthy participants. As this will be the first time GSK3186899 is administered to humans, the study design may change based on emerging data as the study progresses.

This study is planned to include approximately 54 participants and will consist of 2 parts:

- Part A will include a single-ascending, sequential crossover design in up to 3 cohorts of participants (Cohorts 1, 2 and 3). Part A Cohorts 1-2 will comprise of a 4-way crossover which includes 4 dosing regimens under fasted conditions. Part A Cohort 3 will comprise of a 2-way crossover which includes 1 dosing regimen under fasted conditions and 1 regimen under fed conditions. The fed conditions regimen will investigate the effect on safety, tolerability and PK of a single dose of GSK3186899 following food administration.
- Part B will be a twice-daily (BID) 10-day repeat dose design in up to 3 parallel cohorts of participants (Cohorts 4, 5 and 6), although the dosing regimen may be altered depending on emerging data (Appendix 5). Part B may include drug administration after either fed or fasted conditions; this will be dependent on the interim results from Part A. If under fasted conditions, participants will be required to fast at least 2 hours before and after drug administration.

All participants in the study will attend a screening visit within 28 days prior to their first dose and a follow-up visit within 14-21 days after their final dose. If required, additional follow-up visits may be scheduled.

Disclosure Statement: This is a sequential cross-over (Part A) and parallel (Part B) treatment study with 6 arms that is participant and investigator blinded.

Number of Participants: A sufficient number of participants will be screened to ensure that a planned minimum of 54 are eligible to be randomized (Part A: 8 participants into each of Cohorts 1-2 and up to 14 participants for Cohort 3; Part B: 8 participants into each of Cohorts 4-6). A participant is considered evaluable if they complete both screening and at least one treatment period in Part A, or the 10-day treatment period in Part B. Participants that take part in Part A of the study cannot take part in Part B.

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 Parts A and B.

Treatment Groups and Duration:

Part A

For the dose escalation phase in Part A, up to 3 cohorts may be used (Cohorts 1-3). Cohorts 1 and 2 will consist of 8 healthy participants each. Cohort 3 will consist of up to 14 healthy participants.

Cohorts 1 and 2 will each comprise of 4 treatment periods. Each participant will receive a maximum of 3 ascending oral doses of GSK3186899 and 1 placebo dose under fasted conditions. At each dose level, GSK3186899 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 7 dose levels will be studied in Part A.

Cohort 3 will comprise of 2 treatment periods and investigate the effect of food on the safety, tolerability and PK of a single dose of GSK3186899, with a dose level (DLX)

previously selected from Cohorts 1-2. Dose selection will be based on in silico modelling, where the maximum exposure would not be exceeded following fed administration. The decision on the dose level of GSK3186899 to be administered will be made by the dose escalation committee (DEC). Each participant will receive a maximum of 2 oral doses of GSK3186899 under fasted and fed conditions. Bile samples will be collected under both fed and fasted conditions for the analysis of GSK3186899 and any metabolites.

Study Duration of Cohorts 1-3

Screening	All screening assessments to be completed within 28 days prior to first-dose.
Treatment Period	Cohorts 1 and 2 will comprise of 4 treatment periods, investigating 4 dosing regimens under fasted conditions. Cohort 3 will comprise of 2 treatment periods, investigating 2 dosing regimens under fasted and fed conditions. 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 10 days between each dose for an individual participant.
Follow-up	At least 14 days and no greater than 21 days after last study drug administration. If warranted, additional follow-up visits may be scheduled.
Total duration	Cohorts 1 and 2 will be approximately 11-12 weeks each Cohort 3 will be approximately 8-9 weeks

Part B

For the repeat dose escalation phase in Part B, there will be up to 3 cohorts (Cohorts 4, 5 and 6), each cohort will consist of 8 healthy participants. Participants will only participate in one cohort. In each cohort, participants will be randomized to receive repeat doses of either GSK3186899 or placebo, administered in a 3:1 ratio according to the randomization schedule in a blinded manner. For BID dosing, GSK3186899 or placebo will be administered using a 12hr dosing interval. If another dosing regimen is selected for Part B based on emerging data, the interval between doses is outlined in Appendix 5.

Participants will receive each dose after either fed or fasted conditions, dependent upon the interim results from Part A. If under fasted conditions, participants will be required to fast at least 2 hours before and after drug administration. Up to a maximum of 3 dose levels will be studied in Part B.

Study Duration of Cohort 4-6

Screening	All screening assessments to be completed within 28 days prior to first-dose.
Treatment Period	Each Cohort will consist of a 10-day treatment duration (Days 1-10), with participants in-house for 14 nights and 15 days. Participants will be admitted to the unit the day before dosing (Day -2) and will remain in the unit overnight until Day 13, when they will be discharged after completion of all assessments.
Follow-up	At least 14 days and no greater than 21 days after last study drug administration. If warranted, additional follow-up visits may be scheduled.
Total duration	Approximately 8-9 weeks

Data Monitoring Committee: No

2. SCHEDULE OF ACTIVITIES (SOA)

Protocol waivers or exemptions are not allowed with the exception of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the Schedule of Activities (SoA) tables (Section 2.1 and Section 2.2), 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 tables (Section 2.1 and Section 2.2).

The following points must be noted:

- If assessments are scheduled for the same nominal time, THEN the assessments should occur in the following order:

    1. 12-Lead ECG
    2. Vital Signs
    3. Blood Draws

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 course of the study based on newly available data (e.g. to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.

- 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.

2.1. PART A (Cohorts 1-3)

Procedure	**Screening** (Up to 28 days before Day 1)	**Study Period** (Days)					**Follow-Up** (14-21 days post last dose) **/Early Withdrawal**	**Notes**
		-1	1	2	3	4		
Outpatient Visit	X						X	
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							*Additional exams/screens may be performed, or brief exams can be made into full exams, by the Investigator, as deemed necessary (e.g. where safety or laboratory findings indicate). Tests will be conducted within site specified standards.*
Brief Physical Examination		X		X		X	X	
Drug/Alcohol/Smoking Screen	X	X						*Tests include alcohol breath test, smoking breath test and urine drug screen.*
Medical/Medication/Drug/Alcohol History	X							
Human immunodeficiency virus (HIV), Hepatitis B and C Screening	X							
Follicle stimulating hormone (FSH) + Oestradiol	X							*Females only, if required*
Holter Monitoring (48 hours)	X							
Haematology/ Clinical Chemistry /Urinalysis Test (Include Liver Chemistries)	X	X		X		X	X	*If trace protein in urine is detected, a repeat test can be performed (within 24 hours). If tests are considered abnormal, further quantification is required.* *Non-fasted samples can be collected on Day -1 and the Follow-Up Visit. All other samples to be collected in a fasted state.*
Urine Sampling (metabolism)			X	X				*A urine sample will be taken pre-dose (approx. 20mL) All urine from each participant will be collected from 0-24 hrs post dosing. 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** (14-21 days post last dose) **/Early Withdrawal**	**Notes**
		-1	1	2	3	4		
Safety biomarkers (KIM1, NGAL, Urinary albumin)			X	X				*First urine sample of the morning to be collected (Day 1 sample collection should be pre-dose).* *Additional samples may be collected, as deemed necessary by the Investigator (e.g. where safety or laboratory findings indicate).*
PK Blood Sampling			X	X				*PK blood samples to be taken pre-dose on Day 1 and then at the following time points post first-dose: 10min, 30min, 1hr, 1.5hr, 2hr, 2.5hr, 3hr, 4hr, 5hr, 6hr, 8hr, 10hr, 12hr; 24hr.* *The time points stated may be modified depending on emerging SAD PK information as appropriate.* *Blood volumes to be collected include 2 mL for all time-points from pre-dose to 10hrs, and 5 mL for time-points 12hr and 24 hr.*
12-Lead ECG	X	X	T	X	←X→			*Vital signs to include heart rate (HR), blood pressure (BP), temperature and respiration rate. BP will be conducted in both a supine and standing position if participant develops any signs/symptoms which in the investigator's opinion are suggestive of adrenal insufficiency.* *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, 1hr, 1.5hr, 2hr, 2.5hr, 4hr, 8hs, 12hr, 24hr, 48hr* *Timings will be reviewed as cohorts progress and may be adjusted to ensure appropriate measurements relative to peak concentrations for subsequent cohorts.* *T = Triplicate (for all assessments, except temperature and respiratory rate).* *If any abnormal ECG reading is recorded, refer to Section 8.1.6 for appropriate action.*
Vital Signs	X	X	T	X	←X→		X	

Procedure	**Screening** (Up to 28 days before Day 1)	**Study Period** (Days)					**Follow-Up** (14-21 days post last dose) **/Early Withdrawal**	**Notes**
		-1	1	2	3	4		
Telemetry			←X→					*Continuous at least 24hr post-dose. Initiate at least 15 min. prior to dosing.*
Meals		X	X	X	X	X		***Fasting regimen:*** *On Day 1, participants will have fasted 8hr overnight prior to dosing. An adapted standard breakfast will be served approximately 3hrs after dosing.* ***Fed regimen:*** *On Day 1, participants will fast 8hr overnight and an adapted standard breakfast will be served approximately 30 mins prior to dosing.* Meals will be served as per the site schedule on Days -1, 2, 3 and 4. *Water 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. At least 8 fl oz (240ml) to be taken 1hr after dosing. No water to be taken in the hour after dosing except for the rinse of the dose.*
Bile Sampling (Entero-test)			X					***Cohort 3 only.*** *Entero-test bile string swallowed 2hr post-dose, after 5hr the bile string will be removed.*
Randomization			X					
Study Treatment			X					
Adverse event (AE) Review		←=======X=======→					X	
Serious adverse event (SAE) Review	X	←=======X=======→					X	
Concomitant Medication Review	X	←=======X=======→					X	

2.2. PART B (Cohorts 4-6)

Procedure	**Screening** (Up to 28 days before Day 1)	**Study Period** (Days)															**Follow-up** (14-21 days post last dose) / **Early Withdrawal**	**Notes**
		-2	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**		
Outpatient Visit	X																X	
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																	*Additional exams/screens may be performed, or brief exams can be made into full exams, by the Investigator, as deemed necessary (e.g. where safety or laboratory findings indicate). Tests will be conducted within site specified standards.*
Brief Physical Examination			X		X					X						X	X	
Drug/Alcohol/Smoking Screen	X		X															*Tests include alcohol breath test, smoking breath test and urine drug screen.*
Medical/Medication/ Drug/Alcohol History	X																	
HIV, Hepatitis B and C Screening	X																	
FSH + Oestradiol	X																	*Females only, if required*
Holter Monitoring (48 hour)	X																	

Procedure	**Screening** (Up to 28 days before Day 1)	**Study Period** (Days)														**Follow-up** (14-21 days post last dose) / **Early Withdrawal**	**Notes**
		-2	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	
Haematology/ Clinical Chemistry /Urinalysis Test	X		X		X		X		X		X		X		X	X	X	*If trace protein is detected, a repeat test can be performed.* *Sample to be drawn pre-dose on Days 2, 4, 6, 8 and 10.* *Non-fasted samples can be collected on Day -1 and Follow-Up Visit. All other samples to be collected in fasted state.*
Cortisol Test			X											X				*Tests to be performed in the early morning on Day -1 and Day 11.* *If levels are <420 nmol/L, then a adrenocorticotropic hormone (ACTH) stimulation test will be performed to assess hypothalamic pituitary adrenal (HPA) axis.*
Safety biomarkers (KIM1, NGAL, Urinary albumin)				X				X										*First urine sample of the morning to be collected (pre-dose).* *Additional samples may be collected, as deemed necessary by the Investigator (e.g. where safety or laboratory findings indicate).*
Telemetry				X	X													*Continuous at least 24 hr post-evening dose. Initiate at least 15 min. prior to dosing.*
Randomization				X														
Study Treatment				X	X	X	X	X	X	X	X	X	X					***BID dosing:*** *GSK3186899 or placebo will be administered using a 12hr dosing interval. If a different dosing regimen is used, refer to Appendix 5.*

Procedure	**Screening** (Up to 28 days before Day 1)	**Study Period** (Days)														**Follow-up** (14-21 days post last dose) / **Early Withdrawal**	**Notes**
		-2	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	
12-Lead ECG	X		X	T	X		X		X		X		X		X	X	X	*Vital signs to include HR, BP, temperature and respiration rate. BP will be conducted in both a supine and standing position if participant develops any signs/symptoms which in the investigators opinion are suggestive of adrenal insufficiency.* *12-Lead ECG and Vital Signs 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, 13hr and 14hr* ***For Days 2-10:** pre-dose assessments only.* *Timings will be reviewed as cohorts progress and may be adjusted to ensure appropriate measurements relative to peak concentrations for subsequent cohorts* *If a different dosing regimen is used, refer to Appendix 5 for alternative ECG and Vital Signs time-points.* *T = Triplicate (for all assessments except temperature and respiratory rate).* *If any abnormal ECG reading is recorded, refer to Section 8.1.6 for appropriate action.*
Vital signs	X		X	T	X	X	X	X	X	X	X	X	X	X	X	X	X	

Procedure	**Screening** (Up to 28 days before Day 1)	**Study Period** (Days)														**Follow-up** (14-21 days post last dose) / **Early Withdrawal**	**Notes**
		-2	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	
PK Blood sampling				<==========X==========>													*PK samples will be collected pre-dose and at the following time points post first-dose:* ***Day 1****: 10min, 30min, 1hr, 1.5hr, 2hr, 2.5hr, 3hr, 4hr, 5hr, 6hr, 8hr, 10hr, and 12hr* ***Days 2 – 9:*** *Pre-dose PK samples collected for each dose* ***Day 10****: PK samples will be collected pre-dose and at the following time points post first-dose: 10min, 30min, 1hr, 1.5hr, 2hr, 2.5hr, 3hr, 4hr, 5hr, 6hr, 8hr, 10hr, and 12hr.* *The time points stated may be modified depending on emerging SAD PK profiles. If a different dosing regimen is used, refer to Appendix 5 for alternative PK blood sampling time-points.* *Blood volumes to be collected include:* • *2 mL for post first-dose 0-11 hrs, and* • *5 mL for post first-dose 12-24 hrs (Days 1 and 10).*
Urine Sampling (metabolism)													X	X			*A urine sample will be taken pre-dose (approx. 20mL).* All urine from each participant will be collected from 0-24 hrs post dosing. 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** (14-21 days post last dose) / **Early Withdrawal**	**Notes**
		-2	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	
Meals		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	***If on fed regimen:*** *On Day 1 through to D10, participants will receive an adapted standard meal 30 mins prior to dosing.* ***If on fasted regimen:*** *On Day 1 through to D10, participants will have fasted 8hr overnight prior to dose 1. A breakfast will be served approximately 2hr after dose 1. Dinner will be served at least 2hr prior to dose 2. A snack may be consumed approximately 2hr after dose 2.* *Participants will receive standardized meals scheduled at the same time in each period. If a different dosing regimen is used, refer to Appendix 5 for alternative meal times.* *Meals will be served as per the site schedule on Days -1 and Days 11-13.* *Water 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.* *At least 8 fl oz (240ml) to be taken 1 hour after dosing No water to be taken in the hour after dosing except for the rinse of the dose.*
AE review		←==========X==========→														X	

Procedure	**Screening** (Up to 28 days before Day 1)	**Study Period** (Days)														**Follow-up** (14-21 days post last dose) / **Early Withdrawal**	**Notes**
		-2	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	
SAE review	X	←==========X==========→															X	
Concomitant medication review	X	←==========X==========→															X	

- The timing and number of planned study assessments, including safety, pharmacokinetic or other assessments may be altered during the course of the study based on newly available data (e.g., to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.
- Any changes in the timing or addition of time points for any planned study assessments 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 IRB/IEC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the informed consent form (ICF).

3. INTRODUCTION

3.1. 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 programme will comprise a First Time in Human (FTIH) study of single and repeat ascending doses in healthy participants, incorporating a food effect component to investigate the influence of food on the pharmacokinetics (PK) of GSK3186899. The study will evaluate the safety, tolerability and PK profile of single and repeat ascending doses of GSK3186899. Results of this study are intended to be used to identify appropriate and well tolerated doses of GSK3186899 to be used in further studies. This study will be conducted at a single centre.

3.2. 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, GSK3186899 was identified through a phenotypic screening approach. Subsequently detailed mode of action studies utilising a variety of approaches, including genomics and chemical proteomics, have been undertaken which indicate that GSK3186899 acts principally by inhibiting the parasite complex of the cyclin dependent kinase; cdc 2 related kinase 12 (CRK12) with CYC9 as the definitive partner cyclin for CRK12.

More detailed information relating to non-clinical pharmacology, safety pharmacology, PK and metabolism, toxicology and other pre-clinical data can be found in the GSK3186899 Investigators Brochure [GlaxoSmithKline Document Number 2018N372131_00].

3.3. Benefit/Risk Assessment

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

To date, GSK3186899 has not been administered to human participants; therefore, no clinical data are available. This is the first single and repeat dose study proposed in human participants with GSK3186899. GlaxoSmithKline (GSK) is not aware of any compound targeting this pathway having previously been administered in humans.

The risk assessment of GSK3186899 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). Non-adverse vacuolation in the female rat adrenal glands

and ovaries was observed at the NOAEL and above, as a result some adrenal function monitoring has been added to this study. However, by observing the safety margin for renal findings of 3 to 5-fold below the female rat NOAEL (AUC: 434 µg.h/mL, C_{max}: 46.2 µg/mL), this should reduce the risk of adrenal and ovary effects in humans. Details of the risks and the proposed strategy to mitigate/monitor these risks are detailed in Section 3.3.1.

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 (CHMP)/SWP/28367/07]. GSK has assessed this study for any risks that may be posed to participants taking part. Only healthy male and female participants of non-child bearing potential 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 treatment period and will only be discharged from the unit at the end of each treatment period, if the investigator deems it safe to do so.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of GSK3186899 may be found in the IB [GlaxoSmithKline Document Number 2018N372131_00].

3.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data / Rationale for Risk	Mitigation Strategy
Investigational Medicinal Product (IMP) GSK3186899		
Kidney	• Kidney tubule dilatation, which involved tubular epithelial cell loss, was noted in female rats given 400 mg/kg/day as spray dried dispersion (SDD), for 28 days (mean AUC 1290 µg.h/mL, mean C_{max} 74.2 µg/mL on Day 28). This lesion is considered adverse in rats. • These findings were associated with lower urine volume, with accompanying higher urine-specific gravity and lower urine pH, in females given 400 mg/kg/day. • This lesion was not seen in 7-day rat studies nor in monkey toxicology studies of ≤21 days duration.	Inclusion/exclusion criteria: • History of current or past significant renal diseases to be excluded. • Screening eGFR (CKD-EPI) > 90 ml / min • Urinary analysis at screening to be free of blood and protein. If trace protein is found, a repeat test will be performed within 24 hours Monitoring: • Serum Renal function and urinary analysis monitoring • By observing the PK safety margin for renal findings of up to 3-fold (during the SAD part of the study) and up to 5-fold (during the MAD part of the study) for the total daily AUC and C_{max} to be below the female rat NOAEL (AUC: 434 µg.h/mL, C_{max}: 46.2 µg/mL). Participant withdrawal • New onset of any clinically significant and persistent haematuria / proteinuria (Spot Urine Protein Creatinine (UPC) ratio > 0.5) in the absence of another clinical explanation e.g. calculus / infection.

Potential Risk of Clinical Significance	Summary of Data / Rationale for Risk	Mitigation Strategy
		• 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 hours. If confirmed, the participant will be withdrawn. If a participant meets the withdrawal criteria for serum creatinine, then further investigations will be performed. • Hypophosphataemia (less than 0.8mmol/L). If confirmed, the participant will be withdrawn. If a participant meets the withdrawal criteria for hypophosphataemia, then further investigations will be performed. Study Stopping criteria • The study will be temporarily halted if 2 or more participants <u>across all study parts</u> develop any of the above withdrawal criteria.
Stomach	• Stomach erosion/ulceration in the glandular region, was noted in female rats given 400 mg/kg/day (dose conc 40 mg/mL), as SDD, for 28 days (mean AUC 1290 µg.h/mL, mean C_{max} 74.2 µg/mL on Day 28). This lesion is considered adverse in rats. • Erosion/ulceration was not seen in NHPs given ≤150 mg/kg/day (dose conc 30 mg/mL), as SDD, for 21 days (AUC range across all doses 3.34 to	• Contact time with stomach in humans are likely to be short (less than 2 hours) and concentrations considered in the human study are much lower than in the Rat study. • Participants with current or past history of clinically significant gastritis or gastroduodenal ulcers or regular NSAID use, will be excluded from the study based on medical history at screening. • Participants will be monitored for GI symptoms

Potential Risk of Clinical Significance	Summary of Data / Rationale for Risk	Mitigation Strategy
	187 µg.h/mL on Day 21) nor in male rats given ≤1000 mg/kg/day (dose conc 100 mg/mL), as free base, for 7 days (AUC range across all doses 26.8 to 273 µg.h/mL on Day 7). • Localized erosion of the pyloric gastric mucosa was noted in the male monkey given 500 mg/kg/day (dose conc 100 mg/mL), as free base, for 7 days (mean AUC 896 µg.h/mL on Day 7) and focal ulceration of the mucosa at the gastro-duodenal junction and in the colon in the female given 150 mg/kg/day (dose con 30 mg/mL), as free base, for 7 days (mean AUC 613 µg.h/mL on Day 7). Erosion in the stomach and ulceration of the duodenum was noted in 1 female monkey given 500 mg/kg/day (dose con 100 mg/mL), as free base, for 14 days (mean AUC 545 µg.h/mL on Day 14). • Due to the localised nature and low incidence, these lesions are considered to be local, dose concentration-related, effects rather than due to systemic exposure.	reported as adverse events. 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).
Adrenal gland	• Adrenal cortex vacuolation was noted in male and female rats given ≥100 mg/kg/day, as SDD, for 28 days (≥mean AUC 316 µg.h/mL, mean C_{max} 44.0 µg/mL on Day 28). • Adrenal cortex vacuolar degeneration was noted in male rats given 1000 mg/kg/day, as free base,	• These adrenal findings are considered not adverse and did not have any secondary effects in the rats. However, these findings were consistently observed in rats at all tested doses. The potential risk to healthy volunteers is expected to be low especially when administered as a single dose.

Potential Risk of Clinical Significance	Summary of Data / Rationale for Risk	Mitigation Strategy
	for 7 days (mean AUC 204 μg.h/mL on Day 7). • This test article-related, non-adverse finding correlated with increased adrenal weight following 28 days dosing in male rats given ≥100 mg/kg/day, as SDD, and female rats given ≥25 mg/kg/day, as SDD.	Therefore, no specific monitoring, other than standard clinical and laboratory parameters, will be implemented for healthy volunteers during SAD part of the study. However, for the MAD cohorts, adrenal function will be assessed prior to first dose and on completion of 10 days dosing. Also, by observing the safety margin for renal findings of up to 3-fold (during the SAD part of the study) and up to 5-fold (during the MAD part of the study) for the total daily AUC and C_{max} to be below the female rat NOAEL (AUC: 434 μg.h/mL, C_{max}: 46.2 μg/mL), should reduce the risk of adrenal and ovary effects in humans. Exclusion criteria (Part B only): • Participants with borderline adrenal glucocorticoid function (early morning serum cortisol < 420nmol/L) will only be included in the study if after an adrenocorticotropic hormone (ACTH) stimulation test, there is a rise in cortisol level from baseline of at least 250nmol/L Monitoring: • Participants will be monitored clinically for any symptoms of adrenal insufficiency, (nausea, vomiting, dizziness) and objective assessments (supine/standing BP). Depending on the investigators clinical judgement, a ACTH

Potential Risk of Clinical Significance	Summary of Data / Rationale for Risk	Mitigation Strategy
		stimulation test may be done to exclude adrenal insufficiency. Day 11 (Part B only): • Early morning serum cortisol (+ ACTH stimulation test if levels < 420nmol/L) will be performed on all participants at Day 11. If during Day 11 early morning cortisol is < 420 nmol/L, volunteers will undergo a ACTH stimulation test the next day to rule out adrenal insufficiency. Participants with adrenal insufficiency will be withdrawn from the study, refer to Section 8.1.4. Stopping criteria: • A stopping criterion has been included if one or more volunteers in Part B develop adrenal insufficiency with clinical signs and symptoms.
Study Procedures		
Bile Sampling (Entero-test)	As the swallowed capsule is attached to string, participants may experience a gagging sensation when the string is being withdrawn or may swallow the whole string. Sometimes streaks of blood can be seen on the nylon string after it is retrieved from the mouth, due to local irritation. Rarely, participants may be unable to swallow the capsule because of gagging or will vomit after doing so.	• Participants will be informed of these study procedure risks in the Information and Consent Form. • To minimize the risk of swallowing the string, it will be securely taped to the side of the participants face. • In the event of swallowing the whole string, no ill effects are anticipated as the nylon string will pass out from the body through the faeces.

3.3.2. Benefit Assessment

The proposed study with GSK3186899 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.

3.3.3. Overall Benefit: Risk Conclusion

The known risks associated with GSK3186899 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, 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 2) will allow for continuous medical monitoring for all participants following the first dose in each treatment group. Participants will only be discharged from the unit 48 hours 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 GSK3186899 are justified by the anticipated benefits that may be afforded by the future development of a new therapy in an area of unmet need.

4. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To evaluate the safety and tolerability of single and repeat doses of GSK3186899 in healthy participants	• Adverse event reporting, clinical laboratory safety data, vital signs, 12 lead ECGs, 24 hr telemetry.
Secondary	
• To evaluate the systemic PK profile of single (fasted and fed) and repeat doses of GSK3186899 in healthy participants	• Plasma concentrations of GSK3186899 plus derived parameters, as data allow. **For SAD part**: Derived PK parameters for GSK3186899 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 (C_{max}), time to maximum observed plasma drug concentration (T_{max}),trough plasma concentration (C_{tau}) and apparent terminal half-life ($T_{1/2}$) as data allow. Predicted

Objectives	Endpoints
	accumulation Ratio (AR_{pred})# will be calculated. **For MAD part**: AUC(0-t), AUC(0-∞), AUC(0-tau), C_{max}, T_{max} and $T_{1/2}$.
• To examine dose proportionality following single and multiple doses of GSK3186899	• Dose-proportionality assessment using derived PK parameters, as data allow: **For SAD part:** AUC(0-∞), C_{max} **For MAD part:** AUC(0-tau), C_{max}, C_{tau}
• To assess accumulation and time-invariance ratios of GSK3186899 after multiple doses	• Accumulation ratios assessment*, where data allow: $RAUC_{(0\text{-}tau)}$, RC_{max}, RC_{tau}. • Time-invariance ratio calculation as AUC(0-12) on day 10 to AUC(0-∞) on day 1.
Exploratory	
• To collect residual plasma following GSK3186899 analysis, and urine samples, for analysis of metabolites of GSK3186899	• Metabolites of GSK3186899 in plasma and urine. These analyses will be run and reported separately from this protocol.
• To collect bile samples for analysis of metabolites of GSK3186899 (Part A Cohort 3 only)	• Metabolites of GSK3186899 in bile. These analyses will be run and reported separately from this protocol.

** Accumulation ratios calculated as the ratio of last dose to first dose PK parameters: $RAUC_{(0\text{-}tau)}$ = $AUC_{(0\text{-}tau)}$ on last dose to $AUC_{(0\text{-}tau)}$ on first dose, RCmax = Cmax on last dose to Cmax on first dose, RC_{tau}= C_{tau} on last dose to C_{tau} on first dose. # ARpred = 1/(1-e^(k*tau)) where k is elimination rate constant following the single dose and tau is the dosing interval for the intended repeat dosing.*

5. STUDY DESIGN

5.1. Overall Design

This study will be a randomized, double-blind (sponsor unblinded), placebo-controlled, 2-part study of the oral administration of GSK3186899 in healthy participants. As this will be the first time GSK3186899 is administered to humans, the study design may change based on emerging data as the study progresses.

This study is planned to include approximately 54 participants and will consist of 2 parts:

- Part A will include a single-ascending, sequential crossover design in up to 3 cohorts of participants (Cohorts 1, 2 and 3). Part A Cohorts 1-2 will comprise of a 4-way crossover which includes 4 dosing regimens under fasted conditions. Part A Cohort 3 will comprise of a 2-way crossover which includes 1 dosing regimen under fasted conditions and 1 regimen under fed conditions. The fed conditions regimen will

investigate the effect of safety, tolerability and PK of a single dose of GSK3186899 following food administration.

- Part B will be a twice-daily (BID) repeat dose design in up to 3 parallel cohorts of participants (Cohorts 4, 5 and 6), although the dosing regimen may be altered depending on emerging data (Appendix 5). Part B may include drug administration after either fed or fasted conditions, this will be dependent on the interim results from Part A. If under fasted conditions, participants will be required to fast at least 2 hours before and after drug administration.

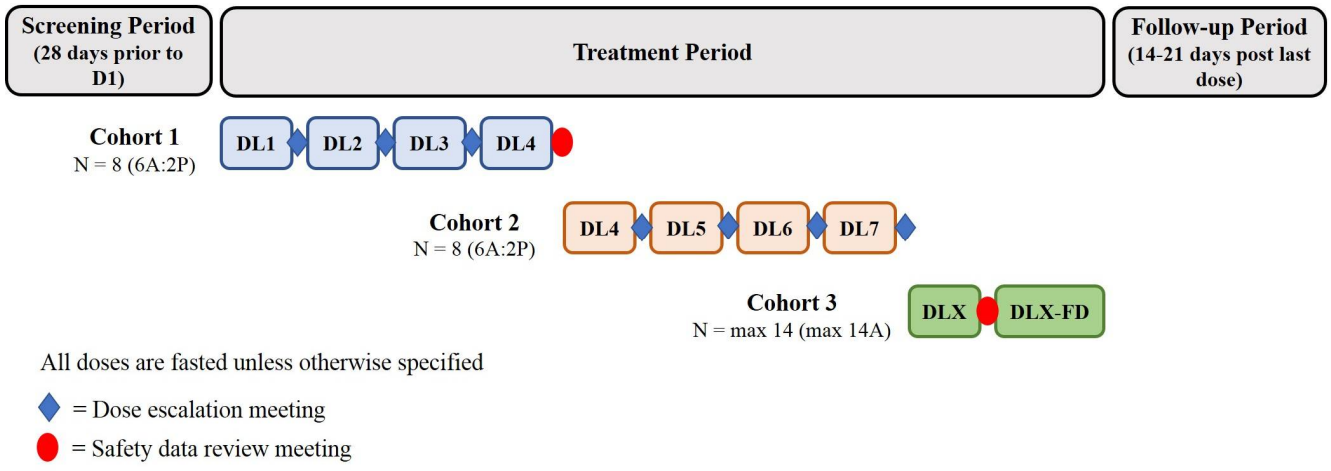
All participants in the study will attend a screening visit within 28 days prior to their first dose and a follow-up visit within 14-21 days after their final dose. If required, additional follow-up visits may be scheduled. Participants that take part in Part A of the study cannot participate in Part B.

Part A

For the dose escalation phase in Part A, up to 3 cohorts may be used (Cohorts 1-3). Cohorts 1 and 2 will consist of 8 healthy participants each. Cohort 3 will consist of up to 14 healthy participants.

For Cohorts 1 and 2, each participant will receive a maximum of 3 ascending oral doses of GSK3186899 and 1 placebo dose under fasted conditions. At each dose level, GSK3186899 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 7 dose levels will be studied in Part A as illustrated in Figure 1.

Figure 1 Study Design (Part A)



DL = Dose level; DLX = Dose level to be determined; FD = Fed Conditions; A = Active; P = Placebo

For further information on the dose escalation and safety review meetings refer to Section 5.6.2.

Initiation of food effect phase: The selected dose level (DLX) to investigate the effect of food on the safety, tolerability and PK of a single dose of GSK3186899 will be one

already evaluated from a previous treatment period. Dose selection will be based on *in silico* modelling, where the maximum exposure would not be exceeded following fed administration. The decision on the dose level of GSK3186899 to be administered will be made by the dose escalation committee (DEC). Bile samples will be collected under both fed and fasted conditions for the analysis of GSK3186899 and any metabolites.

Sentinel Dosing: For each cohort and within each treatment 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 24hr post-dose safety data (e.g. vital signs, ECGs and AEs), the remaining 6 participants can then be randomized to dosing.

Table 1 Study Duration of Cohorts 1-3

Screening	All screening assessments to be completed within 28 days prior to first-dose.
Treatment Period	Cohorts 1 and 2 will comprise of 4 treatment periods, investigating 4 dosing regimens under fasted conditions. Cohort 3 will comprise of 2 treatment periods, investigating 2 dosing regimens under fasted and fed conditions. 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 10 days between each dose for an individual participant.
Follow-up	At least 14 days and no greater than 21 days after last study drug administration. If warranted, additional follow-up visits may be scheduled.
Total duration	Cohorts 1 and 2 will be approximately 11-12 weeks each Cohort 3 will be approximately 8-9 weeks

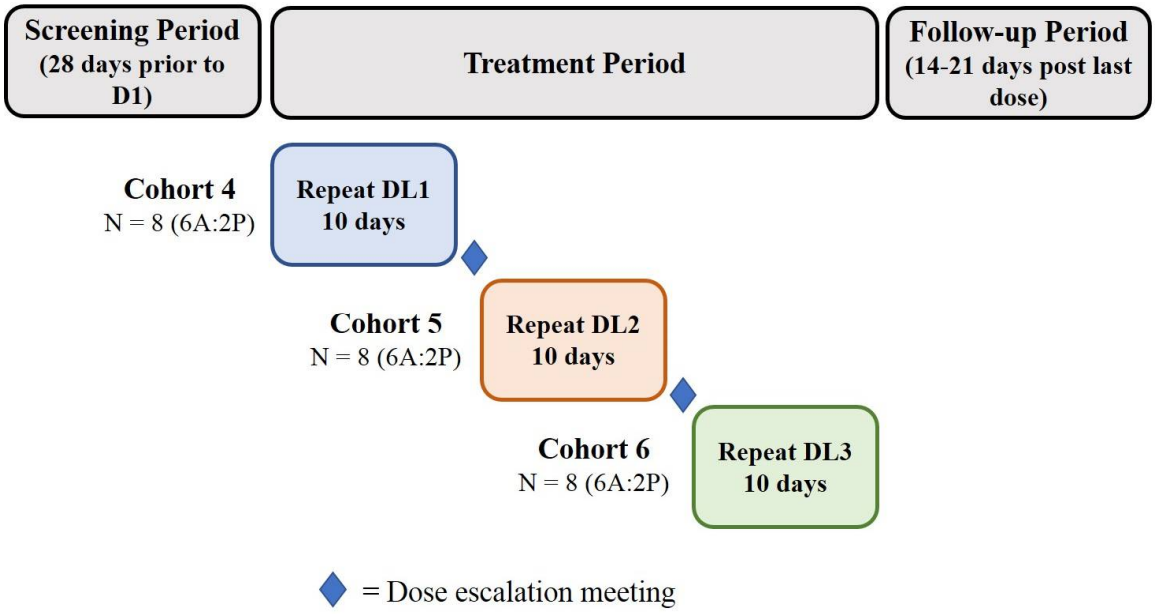
Part B

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

For the repeat dose escalation phase in Part B, there will be up to 3 cohorts (Cohorts 4, 5 and 6), each cohort will consist of 8 healthy participants. Participants will only participate in one cohort. In each cohort, participants will be randomized to receive repeat doses of either GSK3186899 or placebo, administered in a 3:1 ratio according to the randomization schedule in a blinded manner. For BID dosing, GSK3186899 or placebo will be administered using a 12hr dosing interval. If another dosing regimen is selected for Part B based on emerging data, the interval between doses is outlined in Appendix 5.

Participants will receive each dose after either fed or fasted conditions, dependent upon the interim results from Part A. If under fasted conditions, participants will be required to fast at least 2 hours before and after drug administration. Up to a maximum of 3 dose levels will be studied in Part B as illustrated below:

Figure 2 Study Design (Part B)



DL = Dose level; A = Active; P = Placebo

Sentinel Dosing: We will stagger each new dose level in Part B so that the first 2 participants will act as sentinels. On Day 1 until Day 10, 1 of the 2 sentinel participants will receive the active dose twice daily and the other will receive placebo twice daily. Once these participants have completed their first 5-days of dosing, the safety and tolerability data will be reviewed by the Principal Investigator. If there are no clinically relevant safety or tolerability concerns (e.g. vital signs, ECGs and AEs) in the judgement of the Principal Investigator, the remaining 6 participants can then be randomized to dosing.

Table 2 Study Duration of Cohorts 4-6

Screening	All screening assessments to be completed within 28 days prior to first-dose.
Treatment Period	Each Cohort will consist of a 10-day treatment duration (Days 1-10), with participants in-house for 14 nights and 15 days. Participants will be admitted to the unit the day before dosing (Day -2) and will remain in the unit overnight until Day 13, when they will be discharged after completion of all assessments.
Follow-up	At least 14 days and no greater than 21 days after last study drug administration. If warranted, additional follow-up visits may be scheduled.
Total duration	Approximately 8-9 weeks

5.2. Number of Participants

A sufficient number of participants will be screened to ensure that a planned minimum of 54 are eligible to be randomized (Part A: 8 participants into each of Cohorts 1-2 and up to 14 participants for Cohort 3; Part B: 8 participants into each of Cohorts 4-6). A participant is considered evaluable if they complete both screening and at least one treatment period in Part A, or the 10-day treatment period in Part B. Participants that take part in Part A of the study cannot participant in Part B.

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 Parts A and B.

5.3. End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study including the last scheduled procedure shown in the SoA (Section 2).

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 trial.

5.4. Scientific Rationale for Study Design

This study will be the first administration of GSK3186899 in human participants. The primary purpose of the current study is to characterise the safety and tolerability of GSK3186899 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 Part A, this study employs a randomized 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 allows for a shorter washout period between doses of an individual Cohort as the estimated half-life of GSK3186899 is ~1.3 hours.

- In Part A, the study employs a repeat of Dose Level 4 in Cohorts 1 and 2, the rationale for this is to understand potential variability of drug exposure between different cohorts of participants as the projected bioavailability for GSK3186899 varies between 4-100%.

- Further, a food-effect evaluation is planned to support progression into patient studies. An assessment of food effect on the exposure to GSK3186899 will be incorporated into the single dose part of the study (Part A). 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 10.2 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 14 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. In Part B, the 10-day BID dosing will enable assessment of exposure at PK steady state and will also be informative of the likely safety and tolerability in future longer studies.

- To characterize potential biliary elimination pathways, this study will also employ the Entero-Test for sampling of bile to conduct qualitative assessment of drug metabolites in this matrix (Part A, Cohort 3). The Entero-Test is an easy-to-use, well tolerated and minimally-invasive method for sampling small volumes of bile (ca. 1 mL) from the duodenum. Entero-Test is a FDA approved device for human non-invasive sampling of upper gastrointestinal content. Information on the biliary disposition of drug-related material derived in the current study may avoid the need for invasive methods of bile collection in future studies. Details of bile Entero-Test sample collection, processing, storage, and shipping procedures will be detailed in the SRM.

- Part B is designed to be a repeat dosing part of the study with an intention of 10-day dosing to support the proposed clinical duration of treatment. GSK3186899 is proposed for VL oral short therapy. This study design will provide exposure to PK steady state and will be informative for any future longer studies in humans. A flexibility is built into this part of the study to determine the required frequency of dosing (e.g. Twice-daily [BID] or Three-times daily [TID]) and alter the dosing regimen as appropriate based on emerging PK data from part A of the study.

5.5. Justification for Dose

5.5.1. Human Predicted Pharmacokinetics

The preclinical PK data (mouse, rat and dog) was used to predict human blood pharmacokinetic (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 detailed elsewhere [In Vitro to In Vivo Extrapolation (IVIVE), allometry, Physiologically Based Pharmacokinetics (PBPK) using CloePK and Wajima transform of *in vivo* profiles] (N26988-33).

An average clearance (CL) of 7.3mL/min/kg and steady state volume of distribution (VDSS) of 0.8L/kg are used as the human predicted final blood PK parameters from the overall predictions. A conservative value of 50% bioavailability (F) has been used for human PK calculations given a range of bioavailability values from 4 to 100% observed across the preclinical species [GlaxoSmithKline Document Number 2018N372131_00]. A first order absorption rate constant (KA) of $0.7h^{-1}$ was assumed based on data from formulations with immediate release profiles. CL and V are scaled to humans assuming a 70kg typical subject. The human PK profiles were simulated using a population PK analysis approach assuming relevant inter-individual variabilities (IIVs – log normal distribution) around the PK parameters as shown in Table 3. Briefly, 1600 participants (with varying body weight) were simulated 20 times resulting in 32000 participants with CL and V scaled to body weight using the allometric exponents of 0.75 and 1, respectively. Maximum blood concentration (C_{max}) was determined from the maximum simulated concentration and area under the blood concentration curve from time zero to 24h ($AUC_{0\text{-}24h}$) was calculated using the trapezoidal rule.

Table 3 Predicted human blood PK parameters for GSK3186899 that were employed for simulation of human PK profile

Parameter	Predicted Value	%CV[#]
Clearance (mL/hr/kg)	438	50
Vdss (mL/kg)	800	30
KA (hr-1)	0.7	10
F (%)	50	NA

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

5.5.1.1. Background on Pharmacology for Human Dose Selection

CRK12 is a key target for GSK3186899. In the in vitro whole cell intracellular amastigote assay, GSK3186899 showed a parasitic potency of 400 nM (197 ng/mL) and has similar activity to standard of care (SoC) miltefosine when tested in whole cell in vitro intracellular amastigote assay as stated in the IB [GlaxoSmithKline Document Number 2018N372131_00]. Further, GSK3186899 has shown comparable or more

potent activity to miltefosine against isolated clinical strains in mouse macrophages and ~9-fold more potent activity to miltefosine against a panel of strains in human macrophages as per the IB [GlaxoSmithKline Document Number 2018N372131_00]. In addition, when tested in the in vivo mouse efficacy models, GSK3186899 achieved similar potency to miltefosine (i.e. >95% reduction of parasite load at 25 mg/kg BID for 10 days). A whole blood concentration was used as surrogate marker of PK at bio-phase for human dose prediction. Thus, the desired whole blood concentration PK profile (in terms of AUC0-24h) that achieves >95% parasite reduction in BalbC mouse model will be leveraged for human dose selection. [Dorlo, 2012] and [Dorlo, 2014] have published a description of the clinical efficacy of miltefosine and its association with drug exposures which has been used to determine the relevance of mouse efficacy model for human translation as described elsewhere [GlaxoSmithKline Document Number 2018N372131_00]. No prior data exist for relevance of time over a minimum concentration (e.g. IC50) in BalbC mouse for drugs with similar target to GSK3186899 as the target is novel for visceral leishmaniasis (VL). Human PK projections were done assuming BID. dosing (12h) similar to the protocol utilized for the efficacy model in female BalbC mouse. Figure 3 shows the exposure (or dose)-response relationship between blood AUC0-8h and % reduction of parasitemia. From this relationship, a range of target AUC's can be derived for efficacy consideration as shown in Table 4. For simplicity, we approximated observed blood AUC(0-8h) values with blood AUC(0-12h) in the mouse to make it simpler to leverage to humans; and this is justifiable given the extrapolated AUC from 8-12h is negligible (~1%). Figure 4 shows human predicted blood AUC0-24h and Cmax values for a range of human doses from 5 mg to 2500 mg doses with anticipated variability assuming two scenarios of dose-independent F (F=0.5 across doses) and dose-dependent F [F=0.5-((0.3*dose)/(300+dose)) based on solubility limited decrease in absorption]. Dose selection for GSK3186899 will be based on blood target AUC0-24h values based on mouse efficacy data from minimal to maximum pharmacology (Figure 3). Table 4 shows the assumed mouse doses to predict target blood AUC0-24h values [using the relationship between doses (x) and AUC(0-12h)(y) as y=326.27*x-1057.9] and target blood AUC0-24h as 2XAUC0-12h with minimal to maximal pharmacology in terms of % suppression of parasitemia along with average steady state concentration (Css) values in relation to in vitro IC50 value (197 ng/mL).

Figure 3 **GSK3186899 dose (or blood exposure [AUC_{0-8h}])-response relationship in *in vivo* efficacy evaluation of parasitic reduction using female BalbC mouse model.**

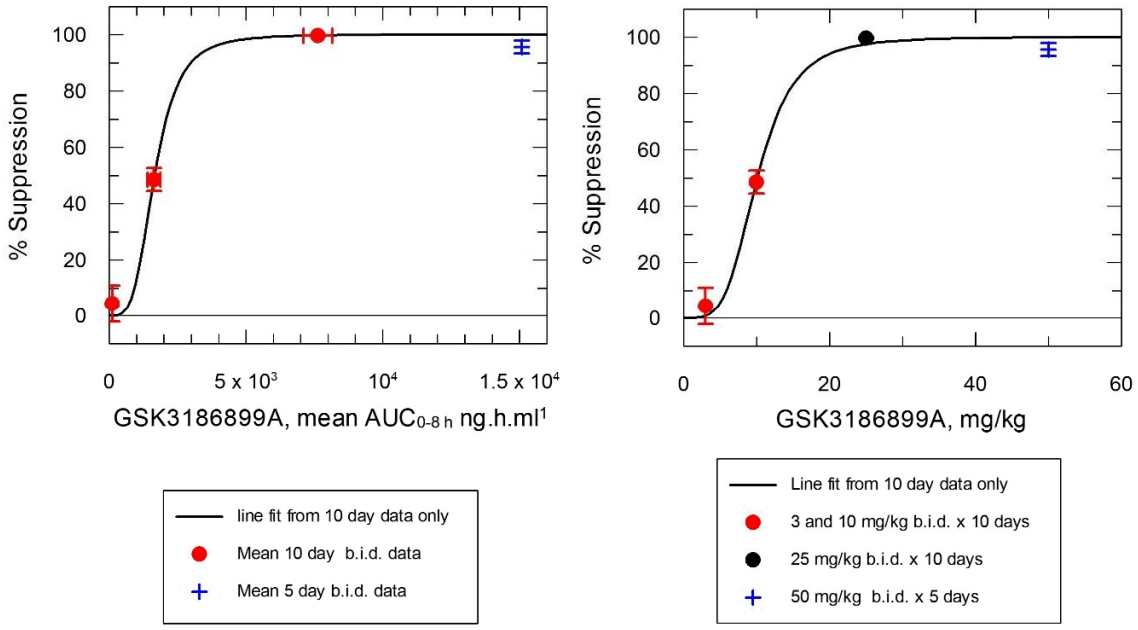
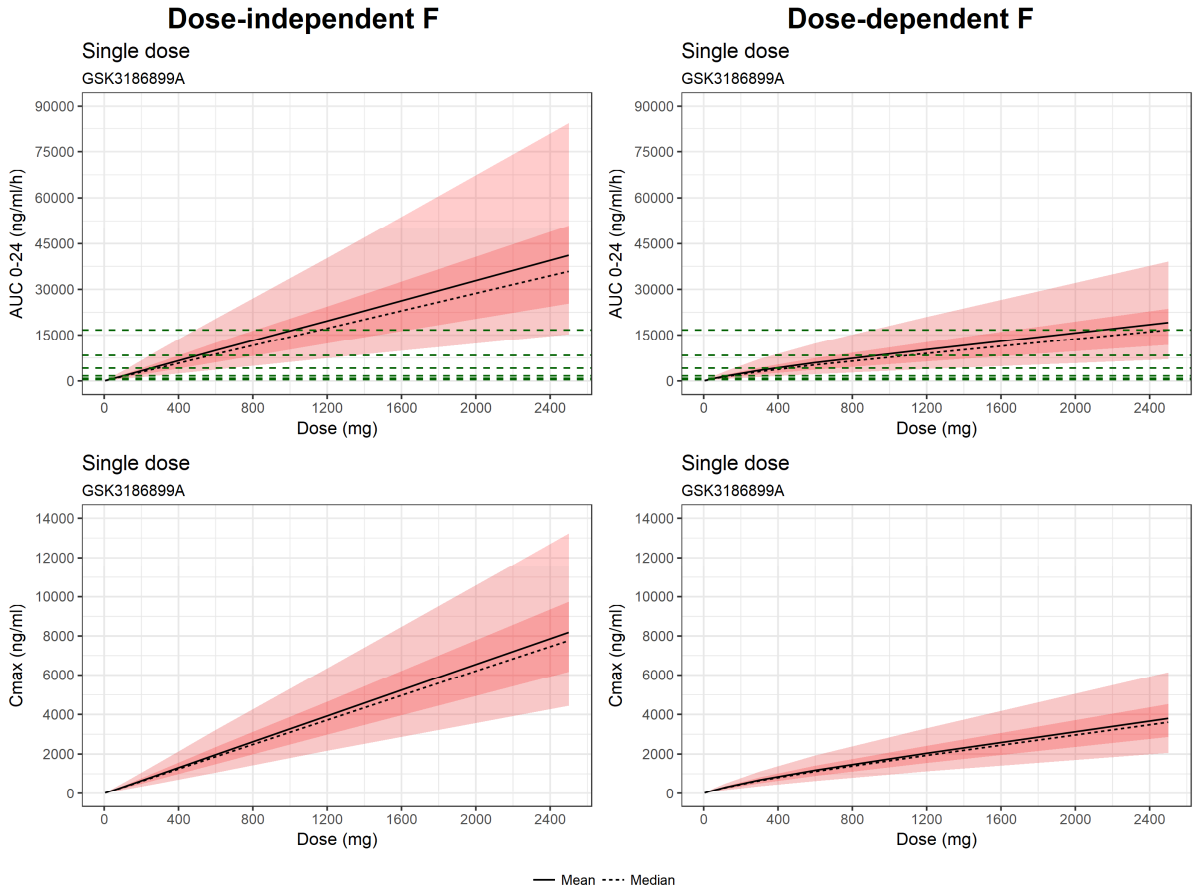


Table 4 **Target blood AUC's from the mouse efficacy model for achieving various levels of % parasite reduction and the associated steady state average (Css) concentrations in relation to IC50 value (197 ng/mL)**

Assumed Mouse Dose (mg/kg)	Target Blood $AUC_{(0-12\ h)}$ (ng.h/mL)	Target Blood $AUC_{(0-24\ h)}$ (ng.h/mL)	Css (ng/mL)	X IC50 (Css as fold of IC50)
4.5	417	833	35	0.18
5.8	833	1667	69	0.35
8.4	1667	3333	139	0.70
16.0	4167	8334	347	1.76
28.8	8333	16667	694	3.53
54.3	16667	33333	1389	7.05

Figure 4 **GSK3186899 predicted human systemic blood exposures (AUC_{0-24h} & Cmax) at various doses with anticipated variability assuming two scenarios of dose-independent and dose-dependent bioavailability (F)**



5.5.1.2. Human Starting Dose Determination

The proposed starting dose is based on anticipated minimum pharmacological activity looking at the derived blood AUC0-24h (~2XAUC0-12h) exposures on the exposure-response relationship from the BalbC mouse efficacy data with an additional consideration of uncertainty in assumed bioavailability given the preclinical bioavailability range of 4 – 100%. Based on the observed exposures from emergent clinical data for a starting dose of 30 mg, appropriate changes to the proposed nominal doses will be made during the dose escalation. There were considerable margins of safety to the NOAEL exposures (NOAEL dose is 100mg/kg/day based on 28-day GLP toxicological study evaluation in female rat) for the starting dose (528-fold for plasma AUC0-24h) with consideration of 50% bioavailability (264-fold margins of safety even with 100% assumption of bioavailability for 30 mg starting dose). Further, the reported off-target pharmacology [few kinase targets e.g. MAPK11(IC50=0.39µM), NLK (0.62µM), MAPK14 (1.2µM) and CDK7(2.4µM)] and hGABA inhibition was found to be of less concern at clinically relevant concentrations and further supported from general toxicology studies (antagonist of the human GABAA ($\alpha1\beta3\gamma2$) channel at 100 µM but not at 5 and 1.5 µM; no CNS-related effects in single and repeat dose in vivo rat and monkey studies). The p38/MAPK signalling pathway is known to participate in cell

proliferation, apoptosis, migration and differentiation. Additionally, knockout models for a number of these targets have highlighted the theoretic potential for embryolethality and/or teratogenicity. Due to the inconsistent in vitro activity data sets using GSK3186899 and lack of related findings in subsequent in vitro studies and animal in vivo studies using GSK3186899, these kinase data are considered unlikely to have human relevance. Given the wide margins of safety to NOAEL exposures and with appropriate safety mitigation plans in place, the currently proposed starting dose is robustly justifiable. In addition, the currently proposed starting dose is approx. 36-fold lower than human equivalent dose (HED) calculated for a 70kg human body weight as per (FDA Guidance, 2005) using the formula HED (mg/kg) = female rat NOAEL dose (100 mg/kg) X [Rat weight in kg (0.25kg) / human weight in kg (70kg)] ^0.33.

5.5.1.3. Human Anticipated Therapeutic Dose Determination

A target blood exposure of 7632 ng.h/mL [approx. $AUC_{(0\text{-}12h)}$], corresponding to plasma $AUC_{0\text{-}12h}$ of 12.745 µg.h/mL (i.e. plasma $AUC_{0\text{-}24h}$ of 25.49 µg.h/mL following a 25 mg/kg dose of GSK3186899 to BalbC mice [GlaxoSmithKline Document Number 2018N377947_00]) will be leveraged to select plausible therapeutic doses for humans. These estimates were determined from the data obtained after 10 days treatment of BalbC mouse, after which efficacy has been demonstrated. An estimated dose of 600mg b.i.d./day was predicted to provide a plasma $AUC_{0\text{-}24h}$ of 31.95 µg.h/mL) on day 10 (> mouse target plasma $AUC_{0\text{-}24h}$ of 25.49 µg.h/mL). Hence, a dose of ~600 mg b.i.d/day was considered as anticipated therapeutic dose (ATD) assuming a dose-independent bioavailability (F). However, if during dose escalation, clinical doses show a dose-dependent F, similar exposure are also expected to occur at a dose of 1200mg BID/day.

5.5.2. Maximum SAD Dose Determination

A nominal maximum SAD dose of 2500mg is proposed for this study to achieve >target plasma AUC0-24h for maximum pharmacology. This is based on the consideration that if a dose-dependent bioavailability decrease is observed as per the simulations presented, then a nominal dose of 1200 mg BID will be anticipated to produce desired therapeutic effect. If 1200 mg BID is ATD, then to support this dose in multiple ascending dose (MAD) study, exposures coverage from nominal SAD dose is desired. Hence, a maximum nominal SAD dose of 2500 mg is considered in this FTIH to support the development of GSK3186899. Accumulation following repeat dosing is not evident from simulations. The exposures from this dose have several-fold margins to the NOAELs from female rat (with dose independent F: 3-fold for Cmax & 7-fold for AUC0-24h; with dose dependent F: 7-fold for Cmax & 14-fold for AUC0-24h). The nonclinical data support the conduct of clinical studies in healthy volunteers up to 3 weeks duration up to 3-fold below the mean systemic exposure at the female NOAEL of 100 mg/kg/day in the rat 4-week study (AUC: 434 µg.h/mL, Cmax: 46.2 µg/mL) with appropriate monitoring in place. The dose escalation will proceed up to nominal top dose of 2500 mg in dose independent F scenario to provided PK stopping criteria is not met; considering the PKPD variability and translational uncertainty of the preclinical data to provide flexible dosing regimen option.

5.5.3. Dose Escalation Plan

The dose escalation will follow a scheme as shown in Table 5 with target plasma AUC_{0-24h} determined from the dose-response relationship from the BalbC mouse efficacy model. Based on the exposures from starting dose, appropriate modifications will be made to the subsequent proposed nominal doses. All available data will be evaluated for dose-escalation decisions. Based on emerging clinical data, appropriate changes to the dose-escalation step-size will be made. The decision to dose escalate, or to halt escalation, will be made by the DEC and will be guided by the safety and SAD PK stopping criteria as outlined below 'Dose escalation/stopping criteria'.

5.5.4. Safety Margins

Table 5 below lists the predicted safety cover for GSK3186899 at various anticipated doses in the SAD FTIH study assuming dose independent and dose dependent bioavailability, respectively, and indicate that the anticipated doses have several-fold margins of safety to the NOAEL exposures from female rat:

Table 5 Projected mean plasma GSK3186899 AUC_{0-24h} and Cmax assuming dose-independent and dose-dependent bioavailability (F) scenarios following single oral doses of GSK3186899, with Fold Cover to preclinical NOAEL exposures alongside showing the nominal SAD doses with the fold dose-escalation

Dose Level	Dose# (mg)	Fold Escalation	Predicted Human Plasma Exposures*				Safety Margins (AUC_{0-24h})		Safety Margins (Cmax)	
			AUC_{0-24h} (µg.h/mL)		Cmax (µg/mL)					
			Dose IDP F	Dose DP F	Dose IDP F	Dose DP F	Dose IDP F	Dose DP F	Dose IDP F	Dose DP F
1	30	-	0.82	0.78	0.16	0.15	528	558	283	299
2	60	2	1.61	1.45	0.33	0.29	269	299	142	158
3	120	2	3.23	2.68	0.65	0.54	134	162	71	86
4	300	2.5	8.23	5.76	1.64	1.14	53	75	28	40
5	600	2	16.59	9.96	3.28	1.97	26	44	14	23
6	1200	2	32.77	17.04	6.55	3.41	13	25	7	14
7	2500	2.1	68.72	31.91	13.66	6.34	6	14	3	7

Key:

IDP = independent; DP = dependent; F = bioavailability

[#]Actual doses may be altered based on emerging PK data

[*]The predicted human exposures are in blood and the animal exposures are in plasma. Human Blood to plasma ratio (B/P ratio = 0.60) is used for conversion of predicted blood exposures (X1.67) to obtain human plasma exposures.

NOAEL exposures in Female rat: AUC = 434 µg.h/mL; C_{max} = 46.2 µg/mL. Safety margin = NOAEL exposure parameter value/predicted human plasma exposure parameter.

5.5.5. Multiple Ascending Dose (MAD)

Three dosing cohorts will be used for MAD. The selection of appropriate daily doses will be performed upon consideration of available safety, tolerability and PK data from SAD part and/or any preceding repeat dose cohorts in MAD and limiting exposure to be no less than 5-fold below the NOAEL of the rat 28-day toxicity study (AUC: 434 µg.h/mL, C_{max}: 46.2 µg/mL). Twice-daily (BID) dosing is currently planned for MAD, but other dosing options may be considered based upon the safety/tolerability and pharmacokinetics observed in SAD part. For MAD dose selection, three doses based on exposures from SAD that support single/repeated dosing will be chosen identifying maximum anticipated therapeutic dose. Once this dose is identified, three cohorts will be chosen for the MAD doses: cohort 1 (0.5X anticipated therapeutic dose), cohort 2 (0.75X maximum anticipated therapeutic dose) and cohort 3 (maximum anticipated therapeutic dose). It should be noted that calculated steady state plasma $AUC_{0\text{-}24h}$ exposure on day 10 will be used as part of PK stopping criteria following repeat dosing. PK sampling is proposed for 0-12h for BID dosing or 0-7h for TID dosing on day 10 at steady state; hence $AUC_{0\text{-}24h}$ (day 10) will be derived as 2XAUC0-12h or extrapolated AUC0-8hX3 for BID or TID dosing, respectively.

5.6. Dose Escalation

As part of this decision-making process, the DEC may decide to escalate or de-escalate the dose in Part A and/or B. 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.

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 clinical pharmacology modeling and simulation department (CPMS) pharmacokineticist and GCSP representative.

5.6.1. Dose Escalation Committee

The decision to proceed to the next dose level of GSK3186899 in each Cohort will be made by a DEC consisting of the Principal Investigator (or appropriate designee), Medical Monitor, GSK Clinical Investigational lead and/or Study Team Leader, GSK pharmacokineticist, a GSK GCSP representative and GSK Statistician. All GSK personnel will remain blinded throughout the course of the study, with the exception of the CPMS pharmacokineticist and GCSP representative. Additional internal GSK safety representatives may be consulted and included in the dose escalation decision making, as deemed necessary by the DEC.

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

5.6.2. Part A

Dose escalation meeting: The decision to proceed to the next dose level of GSK3186899 will be made at a DEC meeting based on:

- all available safety and tolerability data from a minimum of 48 hours post-dose from a minimum of 4 or more participants who have received GSK3186899 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.

Safety review meeting: The decision to proceed from Cohort 1 Period 4 (DL4) to Cohort 2 Period 1 (DL4), and Cohort 3 Period 1 (DLX) to Cohort 3 Period 2 (DLX-FD) will be made by the Principal Investigator and Medical Monitor based on:

- all available safety and tolerability data from a minimum of 48 hours post-dose from a minimum of 4 or more participants who have received GSK3186899 at the current dose level. Individual safety data (AEs, laboratory safety tests, telemetry, ECGs and vital signs) will be reviewed.

5.6.3. Part B

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

- The progression to Part B
- The starting dose level of Cohort 4
- The dosing regimen of Part B
- Whether dosing will be in a fed or fasted state

The decision for the next repeat dose level Cohorts (Cohort 5 onwards) will be made at a DEC meeting following completion of a minimum 10 days dosing in no fewer than 4 or more participants from the previous repeat dose cohort and will be based on:

- assessment of safety, plasma GSK3186899 PK concentrations obtained from a minimum of 4 or more participants from the previous repeat dose cohort. Individual safety data (AEs, laboratory safety tests, ECGs and vital signs) will be reviewed.
- evaluation of all available safety, tolerability and PK data accumulated from the previous repeat dose cohort.

6. STUDY POPULATION

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

6.1. Inclusion Criteria

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

AGE
1. Participant must be 18 to 55 years of age inclusive, 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. A subject 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 subjects 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 and/or Female Subjects **a. Male participants:** 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 treatment period and for at least 90 days after the last dose of study treatment and refrain from donating sperm during this period. **b. Female participants:** A female participant is eligible to participate if she is not a woman of childbearing potential (WONCBP) as defined in Appendix 4.

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.

6.2. Exclusion Criteria

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

MEDICAL CONDITIONS
1. History or presence of or current 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. Previous history of leishmaniasis 3. Alanine transaminase (ALT) >1.5x upper limit of normal (ULN). 4. Bilirubin >1.5xULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%). 5. Current or chronic history of liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones) 6. Current or past history of clinically significant gastritis or gastroduodenal ulcers or regular use of non-steroidal anti-inflammatory drugs (NSAID) 7. QTc >450 msec 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

MEDICAL CONDITIONS
discontinuation for an individual subject should be determined prior to initiation of the study. In other words, several different formulae cannot be used to calculate the QTc for an individual subject and then the lowest QTc value used to include or discontinue the subject 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).

PRIOR/CONCOMITANT THERAPY
8. 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.

PRIOR/CONCURRENT CLINICAL STUDY EXPERIENCE
9. Participation in the study would result in loss of blood or blood products in excess of 500 mL within a 56-day period. 10. Exposure to more than 4 new chemical entities within 12 months prior to the first dosing day. 11. The subject has participated in a clinical trial and has received an investigational product within the following time period prior to the first dosing day in the current study: 30 days, 5 half-lives or twice the duration of the biological effect of the investigational product (whichever is longer). 12. 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. 13. Regular use of known drugs of abuse.

DIAGNOSTIC ASSESSMENTS AND OTHER CRITERIA
14. Subjects with renal function defined as Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) with an age appropriate GFR $\leq$ 90 (ml/min/1.73m^2). 15. Presence of Hepatitis B surface antigen (HBsAg) or Positive Hepatitis C antibody test result at screening. 16. Positive human immunodeficiency virus (HIV) antibody test. 17. Positive pre-study drug/alcohol screen. 18. Presence of clinically significant haematuria and/or proteinuria.

19. Carbon monoxide levels indicative of smoking or history or regular use of tobacco- or nicotine-containing products within 3 months prior to screening.
20. Abnormally low blood pressure as determined by the Principal Investigator
21. **Part A (Food Effect) Cohort 3 only:** Participant must have no dietary restrictions (e.g., lactose intolerance) or inability to eat an adapted standard meal (includes 35-40% fat content).
22. **Part A (Food Effect) Cohort 3 only:** History of gall bladder surgery or gall bladder removal, or history of an acute disease state (e.g. cholelithiasis) within 14 days prior to receiving the study treatment.
23. **Part B only:** Early morning cortisol < 420 nmol/L and inadequate response (rise of <250mmol/L from baseline) to ACTH stimulation test at Day -1.

6.3. Lifestyle Considerations

6.3.1. 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 Part A up until discharge from the unit. In Part B, participants must 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 the first dose of study treatment until after the final dose.

- For cohort 3 of Part A, after an overnight fast of at least 8 hours, participants should start eating their breakfast 30 minutes prior to the dose of study drug and should consume the entire breakfast within 25 minutes. The study drug should be administered within 5 minutes of the completion of the meal. Participants will receive an adapted standard breakfast. 8 fl oz (240ml) of water is to be taken at the time of dosing. Water is allowed ad libitum up to 1 hour before dosing and from 1 hour after dosing.

6.3.2. 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 hours before the start of dosing until after collection of the final PK sample.
- During each dosing session, participants will abstain from alcohol for 24 hours before the start of dosing until after collection of the final PK sample.
- Use of tobacco products will not be allowed from 3 months prior to screening until after the final follow-up visit.

6.3.3. Activity and Travel

- Participants will abstain from strenuous exercise for 48 hours 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.

6.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are 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 should be assigned a new participant number.

7. STUDY TREATMENT

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

7.1. Study Treatment(s) Administered

	Study Treatment	
Product name:	GSK3186899	Placebo
Formulation description	Spray dried powder	Blend
Dosage form:	Powder in bottle (Extemporaneous Compounding)	Powder in bottle (Extemporaneous Compounding)
Unit dose strength(s)/Dosage level(s):	full dose per bottle	NA
Route of administration:	For oral use only	For oral use only
Dosing instructions:	Suspend in diluent and dose.	Suspend in diluent and dose.
Physical description:	White to slightly coloured powder	White to slightly coloured powder
Diluent description:	A mixture of propylene glycol and water	A mixture of propylene glycol and water
Source of procurement	Study medication is supplied by GlaxoSmithKline	Study medication is supplied by GlaxoSmithKline
Method for individualizing dosage:	Site to assemble	Site to assemble

7.2. Preparation/Handling/Storage/Accountability

- 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. Only unblinded pharmacy site staff (or designees) may prepare the 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 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.

7.3. Measures to Minimize Bias: Randomization and Blinding

7.3.1. 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 GSK3186899 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 centrally randomized using an Interactive Voice/Web Response System (IVRS/IWRS). Before the study is initiated, the telephone number and call-in directions for the IVRS and/or the log in information & directions for the IWRS will be provided to the site.

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

In Part A (Cohorts 1 and 2) and Part B (Cohorts 4-6), participants will be randomized in a 3:1 ratio to either GSK3186899 or placebo. In Part A Cohort 3, although all participants will receive GSK3186899, they will be randomized to either a fasted or fed regimen. The participants will be unblinded in this part of the study only.

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

Currently, there is no indication as to the taste of GSK3186899 administered as a solution. For this reason, participants receiving GSK3186899 or placebo as a solution (in any part of this study) may also need to consume a flavoured sweet (for example a hard boiled sweet) prior to and/or immediately following dosing, provided this does not interfere with ongoing monitoring or study procedures. The need for ongoing taste masking will be determined by the DEC.

7.3.2. Blinding

This will be a double blind (sponsor unblind) study with respect to allocation of GSK3186899 or placebo to participants. The food effect part of the study will be open label.

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 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 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 Clinical Safety and Pharmacovigilance (GCSP) 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.
- All GSK personnel will remain blinded throughout the course of the study, with the exception of the CPMS pharmacokineticist, GCSP representative and pharmacy site staff.

7.4. 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 study site staff.
- When participants are dosed at the site, they will receive the 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 the 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 personnel will examine the bottle to ensure there is no remaining study treatment and will examine each participant's mouth to ensure that the study treatment was ingested.

7.5. Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrolment or receives 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 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 may be considered on a case-by-case basis by the investigator, in consultation with the Medical Monitor if required.

7.6. Treatment after the End of the Study

Participants will not receive any additional treatment from GSK, or with GSK3186899, after completion of the study because only healthy volunteers are eligible for study participation.

8. DISCONTINUATION OF STUDY TREATMENT AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

8.1. Discontinuation of Study Treatment

Discontinuation of study treatment is considered "permanent". Once a participant is discontinued, they shall not be allowed to restart treatment.

8.1.1. Dose Adjustment/Stopping Pharmacokinetic Criteria

The following dose adjustment / PK stopping criteria will apply:

- A maximum C_{max} of 15.4µg/mL or 9.24µg/mL and a total daily AUC of 145 µg.h/mL or 86.8 µg.h/mL for SAD or MAD part, respectively, will not be intentionally exceeded and will be used as safety threshold exposures for PK stopping criteria as per GSK renal safety panel recommendations. These exposures are 3-fold or 5-fold below the NOAEL exposures of 46.2 µg/mL for C_{max} and 434 µg.h/mL for total daily AUC in the 28-day female rat study for SAD or MAD part, respectively.
- Dose escalation will be stopped if any single participant reaches exposures greater than PK stopping criteria threshold exposures. 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 dose vs. exposures ($AUC_{0\text{-}24h}$ & C_{max}) 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 mean $AUC_{0\text{-}24h}$ and C_{max} for the next dose level.
- If mean group exposure from the maximum total daily dose is predicted to reach the PK stopping criteria exposures, dose escalation will be stopped, or dose adjustment will be planned, as appropriate. For any dose adjustments for the next dose, an increase or decrease in the nominal dose will occur if the projected exposure for the

next dose deviates by more than 30% of the initial projected mean systemic exposure. The GSK study team 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.

8.1.2. Dose Escalation / Study Progression 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 is met:

- Two or more participants in the same cohort experience a severe non-serious adverse reaction (i.e. severe non-serious adverse events considered as, at least, possibly related to the IMP administration), independent of within or not within the same system-organ-class.
- One or more participants in Part B develop clinical signs/symptoms compatible with adrenal insufficiency and meets the adrenal withdrawal criterion defined below (Section 8.1.4).
- Two or more participants across all study parts develop an adverse renal event as defined in the renal withdrawal criteria below (Section 8.1.3).
- One or more participants from any dose level experiences a serious adverse event which has a reasonable possibility of relation to study drug.

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.

8.1.3. Renal Withdrawal Criteria

A participant that meets any of the following bulleted criteria will be withdrawn from the study:

- New onset of any clinically significant and persistent haematuria / proteinuria (Spot Urine Protein Creatinine (UPC) ratio >0.5) in the absence of another clinical explanation e.g. calculus / infection. If trace proteins are detected, repeat test should be performed within 24 hours.
- 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 hours. If confirmed, the participant will be withdrawn, and further investigations will be performed.
- Persistent hypophosphataemia (less than 0.8mmol/L) confirmed by repeat testing. If a participant meets the withdrawal criteria for hypophosphataemia, then further investigations will be performed.

8.1.4. Adrenal Withdrawal Criteria (Part B only)

- A participant that develops adrenal insufficiency will be withdrawn from the study. Adrenal insufficiency is defined by an early morning serum cortisol < 420 nmol/L and following an ACTH stimulation test, serum cortisol does not rise by >250 nmol/L from baseline. Any case of adrenal insufficiency will be referred to an endocrinologist for confirmation.

8.1.5. Liver Chemistry Stopping Criteria

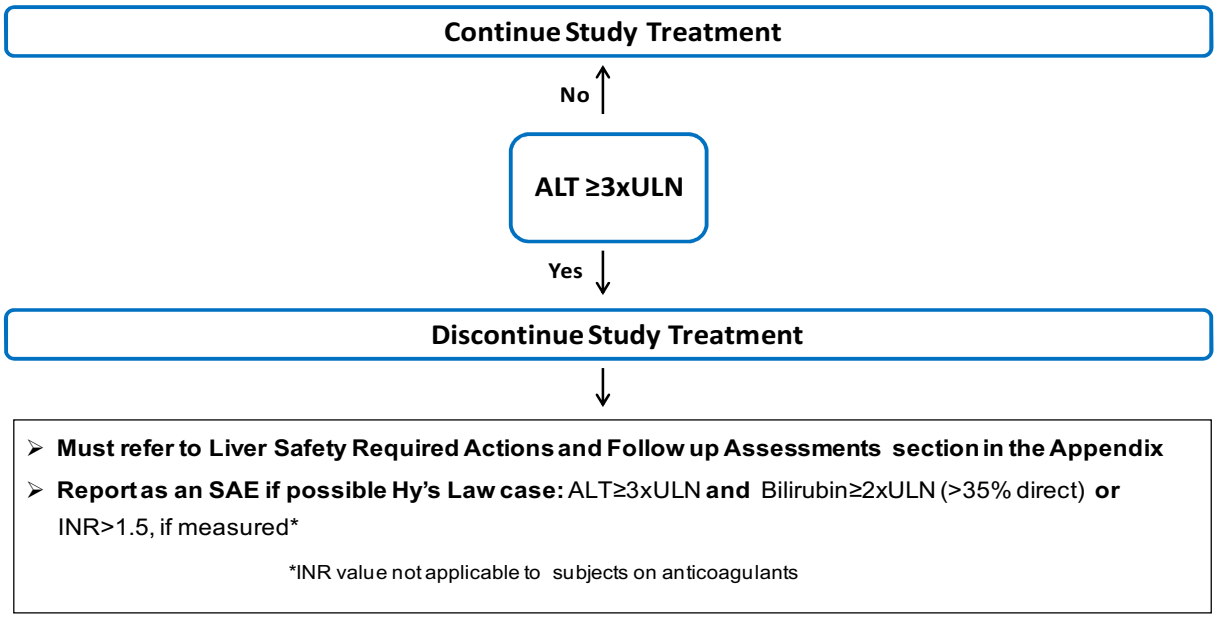
Liver chemistry stopping and increased monitoring criteria have been designed to assure participant safety and evaluate liver event etiology.

Discontinuation of study 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, the investigator believes study treatment discontinuation is in the best interest of the participant.

Refer to Appendix 6 for follow-up assessments in the event of a participant meeting the liver stopping criteria.

Phase I Liver Chemistry Stopping Criteria – Liver Stopping Event Algorithm



8.1.6. QTc Stopping Criteria

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

  - QTcF > 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.

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.

8.1.7. Individual Safety Stopping / Withdrawal Criteria

- If a participant experiences a serious or severe clinically significant AE that in the clinical judgement of the Investigator, after consultation with the medical monitor, is possibly, probably or definitely related to investigational product.
- The participant becomes pregnant.
- The participant initiates treatment with any prohibited medications.
- If any of the liver chemistry, QTc, renal and/or adrenal stopping criteria are met (See Section 8.1.3 -Section 8.1.6).
- The participant develops stomach erosion as confirmed clinically and following a gastro enterology specialist's opinion for further management, and endoscopy (if required).

8.1.8. 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 subject safety. Any changes to the study due to safety reasons will be promptly communicated to the appropriate Regulatory Authorities and Independent Research Ethics Committee.

8.1.9. 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.

8.2. Participant Discontinuation/Withdrawal from the Study

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

8.3. Lost to Follow Up

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

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

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

9. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA.
- Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and was performed within the time frame defined in the SoA.
    - The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed 500 mL.
    - Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

9.1. Safety Assessments

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

9.1.1. Physical Examinations

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

9.1.2. 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).
- In Part A and B 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 blood pressure readings will be recorded on the CRF.

9.1.3. Electrocardiograms

- Triplicate 12-lead ECG will be obtained as outlined in the SoA (see Section 2) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. Refer to Section 8 for QTc withdrawal criteria and additional QTc readings that may be necessary.
- At each time point at which triplicate ECG 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 be performed in supine position after at least 5 minutes rest at the time points indicated in the SoA (Section 2). Full disclosures will be reviewed in detail and the review maintained as part of the subject's source documents.

9.1.4. Holter Monitoring

Holter monitoring will be performed at screening only. This 48-hour Holter ECG will be performed to eliminate participants with non-clinically overt cardiac arrhythmias. 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.

9.1.5. Clinical Safety Laboratory Assessments

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

- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or baseline or are no longer considered significantly abnormal by the investigator or medical monitor.

- If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified, and the sponsor notified.
- All protocol-required laboratory assessments (including tests for urine trace proteins and safety biomarkers), as defined in Appendix 2, must be conducted in accordance with the SRM and the SoA.

9.2. Adverse Events and Serious Adverse Events

The definitions of an AE or SAE can be found in Appendix 3.

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 8).

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

- All SAEs will be collected from the signing of the ICF until the follow-up visit at the time points specified in the SoA (Section 2). However, any SAEs assessed as related to study participation (e.g., study treatment, protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product will be recorded from the time a participant consents to participate in the study.
- All AEs will be collected from the start of treatment until the follow-up visit at the time points specified in the SoA (Section 2).
- Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the case report form (CRF) not the AE section.
- All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.
- Investigators are not obligated to actively seek AEs or SAEs after the conclusion of the study participation. However, if the investigator learns of any SAE, 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.

9.2.2. Method of Detecting AEs and SAEs

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

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

9.2.3. 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, adrenal insufficiency or renal impairment as defined under the stopping and withdrawal criteria above), will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up (as defined in Section 8.3). Further information on follow-up procedures is given in Appendix 3.

9.2.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study 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 (IRB)/Independent Ethics Committees (IEC), and investigators.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information e.g., summary or listing of SAE) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

9.2.5. Pregnancy

- Details of all pregnancies in female participants and, if indicated, female partners of male participants will be collected after the start of study treatment and until the final follow-up visit.
- If a pregnancy is reported, the investigator should inform GSK within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 4.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAE.

9.3. 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 or treating physician should:

1. Contact the Medical Monitor immediately.
2. Closely monitor the participant for AE/SAE and laboratory abnormalities until GSK3186899 can no longer be detected systemically (at least 2 days).
3. Obtain a plasma sample for PK analysis if requested by the Medical Monitor (determined on a case-by-case basis).
4. Document the quantity of the excess dose as well as the duration of the overdosing in the CRF.

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

9.4. Pharmacokinetics

9.4.1. Blood Sample Collection

- Plasma samples of approximately 1 mL (from 2 mL of blood) will be collected for measurement of plasma concentrations of GSK3186899 as specified in the SoA. Plasma samples of approximately 2.5 mL (from 5 mL of blood) will be collected from time-points 12 hours and 24 hours post-dose in Part A.
- 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 collected for analyses of GSK3186899 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 GSK3186899 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 investigative sites or blinded personnel until the study has been unblinded.

9.4.2. Urine Sample Collection

- Urine samples for analysis of GSK3186899 and its metabolites, or for safety biomarkers 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.

9.4.3. Entero-test: Bile Sample Collection

Bile samples will be collected on Day 1 for the analysis of GSK3186899 and any metabolites for participants in Part A Cohort 3 only.

Bile fluid is recovered on a highly absorbent nylon line which is contained within a weighted gelatin capsule. The 140cm line unwinds after capsule swallowing, the capsule dissolves in the stomach and the line then passes into the duodenum. During withdrawal, the weighted section of the capsule separates from the line and passes in the stool. Additional details of the bile Entero-test sample collection, processing, storage and shipping procedures will be provided in the SRM.

9.5. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

9.6. Genetics

Genetics are not evaluated in this study.

9.7. Pharmacological Biomarkers

Biomarkers are not evaluated in this study.

9.8. Health Economics / Medical Resource Utilization and Health Economics

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

10. STATISTICAL CONSIDERATIONS

Statistical analyses will be performed by, or under the direct auspices of, Biostatistics, GlaxoSmithKline.

Reporting of study data will be performed in accordance with applicable GSK and/or contract research organization (CRO) standards.

Complete details of the planned statistical analyses will be provided in the Reporting and Analysis Plan (RAP).

10.1. Statistical Hypotheses

The focus of this FTIH study, both single and repeat dose phases, is to evaluate the safety, tolerability and PK of GSK3186899. As such no formal statistical hypotheses will be tested.

Where appropriate, an estimation approach will be taken, and point estimates and confidence intervals (CIs) will be constructed.

10.2. Sample Size Determination

The planned sample size is up to 30 subjects for Part A of this study (8 subjects each for Cohorts 1-2 and up to 14 subjects for Cohort 3) and up to 24 subjects for Part B (8 subjects per cohort). Additional subjects may be recruited as replacement for withdrawn subjects.

No statistical techniques were used to calculate the sample size for all cohorts except Part A Cohort 3, which was calculated based on the precision estimate for fed versus fasted and considering feasibility.

The objective of Part A Cohort 3 is to determine if GSK3186899 has a food effect and to inform the dosing regimen for Part B. A precision estimate was therefore used to determine the sample size, based on assumed within subject coefficients of variation (CVw) for AUC and C_{max} (20% and 30% respectively). A maximum of 14 subjects will be recruited with the aim of getting evaluable data from 12 subjects. If the estimates for the CVw decrease following review of the data from Cohorts 1 and 2, then less subjects may be recruited, with the aim of obtaining as few as 10 evaluable subjects. The number of planned evaluable subjects will not be less than 10, nor will the number of recruited subjects be greater than 14.

Assuming a point estimate for (fed versus fasted) of 1 (i.e. no food effect), under the variability assumptions described above, and a sample of 12 evaluable subjects, the precision estimates and 90% confidence intervals (CI) for AUC and C_{max} 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)

10.3. Sample Size Sensitivity

For the assumed variability of AUC and C_{max} respectively, the impact of different numbers of evaluable subjects on the precision estimates and 90% confidence intervals were assessed. Results are presented in Table 6.

Table 6 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)
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)

* Based on a CVw of 30%, it is estimated that for a sample size of 6 subjects, the lower bound of the 90% CI will be within approximately 41% of the point estimate and the upper bound of the CI within 68%, i.e. assuming a point estimate of 1 (i.e, no difference) the CI would be as **wide** as (0.59, 1.69).

10.4. 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 subject 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).

10.5. Statistical Analyses

10.5.1. Safety Analyses

The primary analyses are to evaluate safety and tolerability of single and repeat doses of GSK3186899.

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 safety data • vital signs • 12 lead ECGs • 24 hr telemetry will be presented in tabular and/or graphical format and summarized descriptively according to GSK's Integrated Data Standards Library (IDSL) standards by part.

10.5.2. 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 GSK3186899 concentration-time data will be analyzed by non-compartmental methods with WinNonlin 5.2 or higher. From the plasma concentration-time data, the following PK parameters will be determined, as data permit: • maximum observed plasma concentration (C_{max}) • time to C_{max} (T_{max}) • area under the plasma concentration time curve [AUC(0-t), AUC(0-tau), and AUC(0-∞)] • apparent terminal phase half-life (t1/2) • trough concentration (C_{tau}). Trough concentration (Ct_{au}) samples collected on the specified days may be used

Endpoint	Statistical Analysis Methods
	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. 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). **Food Effect (SAD part)** The effect of food on the pharmacokinetics of GSK3186899 will be examined. AUC(0-t), AUC(0-∞) and C_{max} of GSK3186899 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 subject as a random effect. Point estimates and corresponding 90% confidence intervals will be constructed for the comparisons of interest of GSK3186899 fed – GSK3186899 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. **Dose Proportionality (SAD and MAD parts)** Dose proportionality will be assessed following single doses of GSK3186899 (SAD part) via analyses of AUC(0-∞) and C_{max}. Dose proportionality following repeated dosing (MAD part) will be assessed using AUC(0-tau), C_{max} and Ctau. 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 subject 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 GSK3186899 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 GSK3186899. 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

Endpoint	Statistical Analysis Methods
	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 10 - Day 1" 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 10: Day 1" 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.

10.6. 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 Part A (single dose) and Part B (repeat dose), prior to the investigation of the food effect and between Part A and Part B.

An informal interim analysis for Part A will be conducted prior to initiating Part B. This analysis will support the decision to progress or not progress to Part B and will consist of the following displays. Further details, including the function responsible for each analysis, will be detailed in the final RAP. The data in this analysis will include:

- Listing and table to summarise demography, study disposition, and exposure
- Listings for vital signs, ECG, lab, telemetry and AEs including vital signs and ECGs of Potential Clinical Importance
- Table summarising AEs by SOC and PT
- Listings for PK concentration-time data and PK parameters (log transformed and untransformed)
- Figures for PK concentration-time data
- Tables summarising PK parameters (log transformed and untransformed)
- Analysis to determine the food effect of Part A Cohort 3

The Reporting and Analysis Plan will describe the planned informal interim analyses in greater detail.

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

10.7.1. Regulatory and Ethical Considerations

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

10.7.2. 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.

10.7.3. Informed Consent Process

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

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

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

10.7.4. Data Protection

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

10.7.5. Publication Policy

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

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

10.7.6. 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 the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study participants, as appropriate.
- GSK will provide the investigator with the randomization codes for their site only after completion of the full statistical analysis.
- A manuscript will be progressed for publication in the scientific literature if the results provide important scientific or medical knowledge.

10.7.7. 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.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (e.g., Contract Research Organizations).

- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 25 years from the issue of the final Clinical Study Report (CSR)/ equivalent summary unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.7.8. Source Documents

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

10.7.9. Study and Site Closure

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

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

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

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

10.7.10. 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.

10.8. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 7 will be performed by The Doctor's laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 6 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.

Table 7 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	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[1]	BUN	Potassium	Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total and direct bilirubin
	Creatinine	Sodium	Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT), Gamma GT	Total Protein
	Glucose (Fasted[2])	Calcium	Alkaline phosphatase	Albumin
	Magnesium	Phosphate	Creatine phosphokinase (CPK)	C-reactive protein (CRP)
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones by dipstick • Microscopic examination (if blood or protein is abnormal) • Urine Protein : Creatinine ratio, if trace urine protein is identified by dipstick • Urine creatinine			

Laboratory Assessments	Parameters
	• Urine phosphate
Safety Biomarkers[4]	• Kidney injury molecule 1 (KIM1) • Neutrophil gelatinase-associated lipocalin (NGAL) • Urine albumin
ACTH test[5]	• Cortisol
Other Tests	• Follicle-stimulating hormone and oestradiol (as needed in women of non-childbearing potential only) • Alcohol breath test and urine drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines) • 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 CKD-EPI formula The results of each test must be entered into the CRF.

NOTES :

1. Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 8.1.5. and Appendix 6.
2. 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. Non-fasted samples can be collected on Day -1 and at the Follow-up visit (All Parts).
4. Safety biomarkers will be collected as urine samples.
5. Cortisol test will be performed in Part B only

Laboratory results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

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

10.9.1. 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 <u>Meeting</u> the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study 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 <u>NOT</u> Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or

convenience admission to a hospital).

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

10.9.2. Definition of SAE

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

A SAE is defined as any untoward medical occurrence that, at any dose:

- Results in death
- Is life-threatening

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

Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AE. If a complication prolongs hospitalization or 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.

Results in persistent disability/incapacity

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

Is a congenital anomaly/birth defect

Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may

jeopardize the participant or may require medical or surgical treatment to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.9.3. 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 in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to GSK in lieu of completion of the GSK /AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by GSK. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to GSK.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AE and SAE can be assessed as severe.

  An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study treatment and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study 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 hours of receipt of the information.

10.9.4. 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) in order to report the event within 24 hours. • The site will enter the SAE data into the electronic system as soon as it becomes available. • The investigator or medically-qualified sub-investigator must show evidence within the eCRF (e.g., check review box, signature, etc.) of review and verification of the relationship of each SAE to IP/study participation (causality) within 72 hours of SAE entry into the eCRF. • After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data. • If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information 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 the SRM.

SAE Reporting to GSK via Paper CRF
• Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the medical monitor 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. • Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames. • Contacts for SAE reporting can be found in the SRM.

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

10.10.1. Definitions:

Woman of Childbearing Potential (WOCBP)

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

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

Women in the following categories are not considered WOCBP

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

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

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

10.10.2. Contraception Guidance:

Male participants

- Male participants with female partners of child-bearing potential are eligible to participate if they agree to ONE of the following during the treatment phase and until at least 90 days after the last administration of study drug:
    - Are abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent
    - Agree to use a male condom with an additional method of contraception with a failure rate of <1% (see below) per year when having penile-vaginal intercourse with a woman of childbearing potential
- Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse
- In addition, male participants must refrain from donating sperm for duration of study and for 90 days after study completion.

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
Highly Effective Methods[b] That Have Low User Dependency
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)[c]
• Bilateral tubal occlusion
• Vasectomized partner *Note: Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.*
Highly Effective Methods[b] That Are User Dependent
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c] • oral • intravaginal • transdermal • injectable
Progestogen-only hormone contraception associated with inhibition of ovulation[c] • oral

• injectable
Sexual abstinence *Note: Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. 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. Note: Periodic abstinence (calendar, sympto-thermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception for this study. Male condom and female condom should not be used together (due to risk of failure with friction)

10.10.3. Collection of Pregnancy Information:

Male participants with partners who become pregnant

- Investigator will attempt to collect pregnancy information on any male participant's female partner of a male study participant who becomes pregnant while participating in this study. This applies only to 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 hours 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 fetal status (presence or absence of anomalies) or indication for procedure.

Female Participants who become pregnant

- Investigator will collect pregnancy information on any female participant, who becomes pregnant while participating in this study.
- Information will be recorded on the appropriate form and submitted to GSK within 24 hours of learning of a participant's pregnancy.
- Participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow up information on participant and neonate, which will be forwarded to GSK Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.
- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.

- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the investigator, will be reported to GSK as described in Appendix 3. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Any female participant who becomes pregnant while participating will discontinue study treatment or be withdrawn from the study.

10.11. Appendix 5: Part B Assessments Based on an Alternative Dosing Regimen

If an alternative dosing regimen to BID dosing is selected for Part B (i.e. once-daily or three-times daily), the following assessment timings will be used to align with the alternative dosing intervals. All other assessments for Part B will be conducted as scheduled in the SOA (Section 2.2).

Procedure	**Screening** (Up to 28 days before Day 1)	**Study Period** (Days)														**Follow-up** (14-21 days post last dose) **/Early Withdrawal**	**Notes**
		-2	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	
12-Lead ECG	X		X	T	X		X		X		X		X		X	X	X	*Vital signs to include HR, BP, temperature and respiration rate. BP will be conducted in both a supine and standing position if participant develops any signs/symptoms which in the investigators opinion are suggestive of adrenal insufficiency.* *12-Lead ECG and Vital Signs to be conducted on Day-1 and pre-dose Day 1 and then at the subsequent time points post first-dose:* ***If, Once-daily dosing:*** ***Day 1:*** *pre-dose 30min, 1hr, 1.5hr, 2 hr, 2.5 hr, 4hr, 6 hr, 24 hr,* ***Days 3-10:*** *pre-dose samples only.* ***If, Three-times daily (TID) dosing:*** ***Day 1:*** *pre-dose, the post-first dose at 30min, 1hr, 1.5hr, 2 hr, 2.5hr, 4hr, 6hr* *Then post second-dose: 1hr, 2hr* *And post third-dose at:1hr, 2hr* ***Days 3-10:*** *pre-dose samples only.* *T = Triplicate (for all assessments except temperature and respiratory rate).*
Vital signs	X		X	T	X	X	X	X	X	X	X	X	X	X	X	X	X	

Procedure	**Screening** (Up to 28 days before Day 1)	**Study Period** (Days)														**Follow-up** (14-21 days post last dose) **/Early Withdrawal**	**Notes**
		-2	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	
																	If any abnormal ECG reading is recorded, refer to Section 8.1.6 for appropriate action.
PK Blood sampling				X													*PK samples will be collected at the following time points:* ***Once-daily dosing:*** ***Day 1****: Pre-dose, 10min, 30min, 1hr, 1.5hr, 2hr, 2.5hr, 3hr, 4hr, 5hr, 6hr, 8hr, 10hr, 12hr* ***Days 2 – 9:*** *Pre-dose PK samples collected* ***Day 10****: Pre-dose, 10min, 30min, 1hr, 1.5hr, 2hr, 2.5hr, 3hr, 4hr, 5hr, 6hr, 8hr, 10hr, 12hr* ***Day 11****: 24hr sample post-dose from Day 10.* ***TID dosing:*** ***Day 1****: Pre-dose, 10min, 30min, 1hr, 1.5hr, 2hr, 2.5hr, 3hr, 4hr, 5hr, 6hr, 7hr (pre-2nd dose)* ***Days 2 – 9:*** *Pre-dose PK samples collected prior to the first-dose and second-dose* ***Day 10****: pre-dose, then post first-dose at 10min, 30min, 1hr, 1.5hr, 2hr, 2.5hr, 3hr, 4hr, 5hr, 6hr, 7hr (pre-2nd dose).* *The time points stated may be modified depending on emerging SAD PK profiles.* *Blood volumes to be collected include 2 mL for post-dose 0-11 hrs, and 5 mL for post-dose 12-24 hrs.*
Study Treatment				X	X	X	X	X	X	X	X	X	X				***Once daily dosing:*** *GSK3186899 or placebo will be administered.*

Procedure	**Screening** (Up to 28 days before Day 1)	**Study Period** (Days)															**Follow-up** (14-21 days post last dose) **/Early Withdrawal**	**Notes**
		-2	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**		
																		TID dosing: *GSK3186899 or placebo will be administered using a 7 hr dosing interval between each dose.*
Meals		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		***If on fed regimen (both once daily and TID dosing):*** *On Day 1 through to D10, participants will receive an adapted standard meal 30 mins prior to dosing.* ***If on fasted regimen (once daily dosing):*** *On Day 1 through to D10, participants will have fasted 8hr overnight prior to dose 1. A breakfast will be served approximately 2hr after dose 1. Lunch, dinner and other snacks may be served as per the site schedule.* ***If on fasted regimen (TID dosing):*** *On Day 1 through to D10, participants will have fasted 8hr overnight prior to dose 1. A breakfast will be served approximately 2hr after dose 1. Lunch and dinner will be served between 2 hr prior to dose 2 and 3, respectively.* *Participants will receive standardized meals scheduled at the same time in each period. Meals will be served as per the site schedule on Days -1 and Days 11-13.* *8 fl oz (240mL) of water to be taken after dosing and permitted on an ad lib basis 1hr before and 1hr after dosing.*

10.12. Appendix 6: Liver Safety: Required Actions and Follow-up Assessments

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 bilirubin[1,2] ≥ 2xULN (>35% direct bilirubin) or INR >1.5, Report as an SAE.

See additional Actions and Follow Up Assessments listed below</td></tr>
<tr><th colspan="2">Required Actions 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 hours
• Complete the liver event CRF, and complete an SAE data collection tool if the event also meets the criteria for an SAE[2]
• Perform liver event follow up assessments
• Monitor the subject until liver chemistries resolve, stabilise, or return to within baseline (see MONITORING below)

MONITORING:

If ALT≥3xULN AND bilirubin ≥ 2xULN or INR >1.5

• Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within 24 hr
• Monitor subjects twice weekly until liver chemistries resolve, stabilise or return to within baseline
• A specialist or hepatology consultation is recommended

If ALT≥3xULN AND bilirubin < 2xULN and INR ≤1.5:

• Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform</td><td>• Viral hepatitis serology[3]
• Obtain INR and recheck with each liver chemistry assessment until the transaminases values show downward trend
• Obtain blood sample for pharmacokinetic (PK) analysis, obtained within 12 hours of last dose[4]
• Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).
• Fractionate bilirubin, if total bilirubin≥2xULN
• Obtain complete blood count with differential to assess eosinophilia
• Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form
• Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications.
• Record alcohol use on the liver event alcohol intake case report form

If ALT≥3xULN AND bilirubin ≥ 2xULN or INR >1.5:

• Anti-nuclear antibody, anti-smooth muscle</td></tr>
</table>

Liver Chemistry Stopping Criteria	
liver event follow up assessments within **24-72 hr** • Monitor subjects weekly until liver chemistries resolve, stabilize or return to within baseline	antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG) or gamma globulins. • Serum acetaminophen adduct high performance liquid chromatography (HPLC) assay (quantifies potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week James, 2009]. **NOTE: not required in China**. • Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy CRF forms.

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that subject if ALT ≥ 3xULN and bilirubin ≥ 2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, record presence of detectable urinary bilirubin on dipstick, indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT ≥ 3xULN and bilirubin ≥ 2xULN (>35% direct bilirubin) or ALT ≥ 3xULN and INR>1.5, if INR measured, which may indicate severe liver injury (possible 'Hy's Law'), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis); INR measurement is not required and the threshold value stated will not apply to subjects receiving anticoagulants
3. Includes: Hepatitis A IgM antibody; Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM); Hepatitis C RNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody
4. PK sample may not be required for subjects known to be receiving placebo or non-GSK comparator treatments. Record the date/time of the PK blood sample draw and the date/time of the last dose of study treatment prior to PK blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the subject'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.

10.13. Appendix 7: Abbreviations and Trademarks

Abbreviations

µg	Micrograms
µmol	Micromolar
ACTH	Adrenocorticotropic hormone
AE	Adverse Event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area Under the 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
BID	Twice-daily
BMI	Body Mass Index
BP	Blood Pressure
C_{max}	Maximum Observed Concentration
CHMP	Committee for Medicinal Products for Human Use
CONSORT	Consolidated Standards of Reporting Trials
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CPK	Creatine Phosphokinase
CPMS	Clinical Pharmacology Modelling and Simulation Department
CRK12	CDC-Related Kinase 12
CRP	C-Reactive Protein
DEC	Dose escalation committee
dL	Decilitre
DL	Dose Level
DLX	Dose Level to be determined
ECG	Electrocardiogram
eGFR	Estimated Glomerular Filtration Rate
EMA	European Medicines Agency
EMEA	European Medicines Evaluation Agency

FSH	Follicle Stimulating Hormone
FTIH	First Time in Human
GCP	Good Clinical Practice
GCSP	Global Clinical Safety and Pharmacovigilance
GFR	Glomerular Filtration Rate
hr	hour(s)
HBsAg	Hepatitis B Surface Antigen
HIV	Human Immunodeficiency Virus
HPA	Hypothalamic Pituitary Adrenal
HPLC	High Performance Liquid Chromatography
HR	Heart Rate
HRT	Hormone Replacement Therapy
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IDSL	Integrated Data Standards Library
IEC	Independent Ethics Committee
IgG	Immunoglobulin G
IP	Investigational Product
IRB	Institutional Review Board
KIM-1	Kidney Injury Molecule 1
kg	Kilograms
L	Litre
LDH	Lactate Dehydrogenase
MAD	Multiple Ascending Dose
MCH	Mean Corpuscular Haemoglobin
MCV	Mean Corpuscular Volume
mg	Milligrams
min	Minute(s)
mL	Millilitres
mmol	Millimolar
NGAL	Neutrophil gelatinase-associated lipocalin
NOAEL	No Observable Adverse Effect Limit
PK	Pharmacokinetics

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
RBC	Red Blood Cells
RAUC	Relative Area Under the Curve
SAD	Single Ascending dose
SAE	Serious Adverse Event
SDD	Spray Dried Dispersion
SGOT	Serum Glutamic-Oxaloacetic Transaminase
SGPT	Serum Glutamic-Pyruvic Transaminase
SOA	Schedule of Activities
SOP	Standard Operating Procedures
SRM	Study Reference Manual
SUSAR	Suspected Unexpected Serious Adverse Events
TID	Three-Times Daily
Tmax	Time Taken to Maximum Observed Plasma Drug Concentration
UK	United Kingdom
ULN	Upper Limit of Normal
VL	Visceral Leishmaniasis
WONCBP	Women of Non-Child Bearing Potential

Trademark Information

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SAS
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10.14. 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).

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