Reporting and Analysis Plan

Study ID: 208436

Official Title of Study: Reporting and Analysis Plan for a randomised, 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

Date of Document: 21-Nov-2019

GSK Vaccines Controlled Document

Documentum Name : GSK3186899-208436 Statistical Analysis Plan Reporting and Analysis Plan Version 001 (18-Nov-2019)

Documentum Id : 090f45f689e7c46d

Documentum Version : 1.4

Date (UTC date)	Signed by
19-Nov-2019 10:47:00 AM	PPD
Justification	Sign as Approver
21-Nov-2019 10:29:17 AM	PPD
Justification	Sign as Approver
Justification	
Justification	
Justification	
Justification	
Justification	
Justification	
Justification	
Justification	

GSK Vaccines Controlled Document

Documentum Name : GSK3186899-208436 Statistical Analysis Plan Reporting and Analysis Plan Version 001 (18-Nov-2019)

Documentum Id : 090f45f689e7c46d

Documentum Version : 1.4

Date (UTC date)	Signed by
Justification	
Justification	
Justification	
Justification	
Justification	
Justification	
Justification	
Justification	
Justification	
Justification	

Division	:	Worldwide Development
Information Type	:	Reporting and Analysis Plan (RAP)
Title	:	Reporting and Analysis Plan for a randomised, 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
Compound Number	:	GSK3186899
Effective Date	:	[15-NOV-2019]

Description:

- The purpose of this reporting and analysis plan (RAP) is to describe the planned analyses and output to be included in the Clinical Study Report for Protocol 208436, which is a first time in human (FTiH) study comprising of a single and repeat ascending dose regimens in healthy participants, incorporating a food effect component.
- The key objective is to describe the safety, tolerability and pharmacokinetics of GSK3186899. Results from this study will also be used to identify appropriate and well tolerated doses of GSK3186899 and to investigate the influence of food on the PK of GSK3186899.
- This full RAP will be provided to the study team members to convey the content of the reporting efforts planned for the study informal interim analysis and final analysis deliverables for the Statistical Analysis Complete (SAC).
- All sections of the RAP have been populated in this version.

Author(s)

Author	Date
PPD Study Statistician (Statistics Manager, FPD Clinical Statistics)	15-Nov-2019
PPD Clinical Pharmacokineticist (Scientific Director, Quantitative Clinical Development (QCD), PAREXEL International)	16-Oct-2019

RAP Team Review Confirmations (Method: E-mail)

Reviewer	Date
PPD Project Statistician (Principal Statistician, FPD Clinical Statistics)	12-Nov-2019
PPD Operational Study Lead and Clinical Investigation Lead (Clinical Development Manager, R&D PCPS GCDO Clinical Unit Cambridge)	16-Oct-2019
PPD Medical Monitor (Head NCD Open Lab and Global Health Futures)	16-Oct-2019
PPD Safety and Medical Governance (SMG) Pharma Safety (formerly GCSP) representative (SERM Director, SMG Pharma Safety)	16-Oct-2019
PPD DQL (Principal Clinical Data Manager, R&D PCPS GCDO DM FPD)	16-Oct-2019
PPD Clinical Pharmacokineticist (Scientific Director Quantitative Clinical Development (QCD), PAREXEL International)	16-Oct-2019
PPD Study Programmer (Principal Programmer, FPD Clinical Statistics)	16-Oct-2019

Clinical Statistics & Clinical Programming Line Approvals (Method: Pharma TMF eSignature)

Approver	Date
PPD Diseases of the Developing World (DDW) Statistical Lead (Statistics Director, FPD Clinical Statistics)	To be updated after esigning is completed
PPD Lead Programmers Line Manager (Programming Manager, FPD Clinical Programming)	To be updated after esigning is completed

TABLE OF CONTENTS

PAGE

1. INTRODUCTION

The purpose of this reporting and analysis plan (RAP) is to describe the analyses to be included in the Clinical Study Report for Protocol 208436:

Protocol Revision Chronology:		
Original Document Number: 2018N385133_00	Dated: 09-JAN-2019	Version: Original
Original Document Number: 2018N385133_01	Dated: 19-MAR-2019	Version: Amendment 01

2. SUMMARY OF KEY PROTOCOL INFORMATION

2.1. Changes to the Protocol Defined Statistical Analysis Plan

There were no major changes or deviations to the originally planned statistical analysis specified in the Original Protocol 208436 (Dated: 09-Jan-2019) and the Amendment 01 (Dated: 19-Mar-2019).

A minor change is made to the first secondary objective where trough plasma concentration (Ctau) is removed from the SAD part and added to the MAD part after confirmation from the Study Pharmacokineticist.

2.2. Study Objective(s) and Endpoint(s)

Objectives	**Endpoints**
Primary Objectives	**Primary Endpoints**
• To evaluate the safety and tolerability of single and repeat doses of GSK3186899 in healthy participants	• Adverse event reporting, clinical laboratory safety data, physical examinations, vital signs, 12 lead ECGs, 24 hr telemetry
Secondary Objectives	**Secondary Endpoints**
• To evaluate the systemic pharmacokinetic (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}), and apparent terminal half-life ($T_{1/2}$) as data allow. Predicted accumulation Ratio (AR_{pred})# will be calculated. **For MAD part:** AUC(0-t), AUC(0-∞), AUC(0-tau), C_{max}, trough plasma concentration (C_{tau}), 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}

Objectives	Endpoints
	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}, RC_{tau}. Time-invariance ratio calculation as AUC(0-12) † on day 10 to AUC(0-∞) on day 1.
Exploratory Objectives	**Exploratory Endpoints**
• 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 detailed in a separate analysis plan.
• To collect bile sample for analysis of metabolites of GSK3186899 (Part A fed regimen only)	• Metabolites of GSK3186899 in bile. These analyses will be detailed in a separate analysis plan.

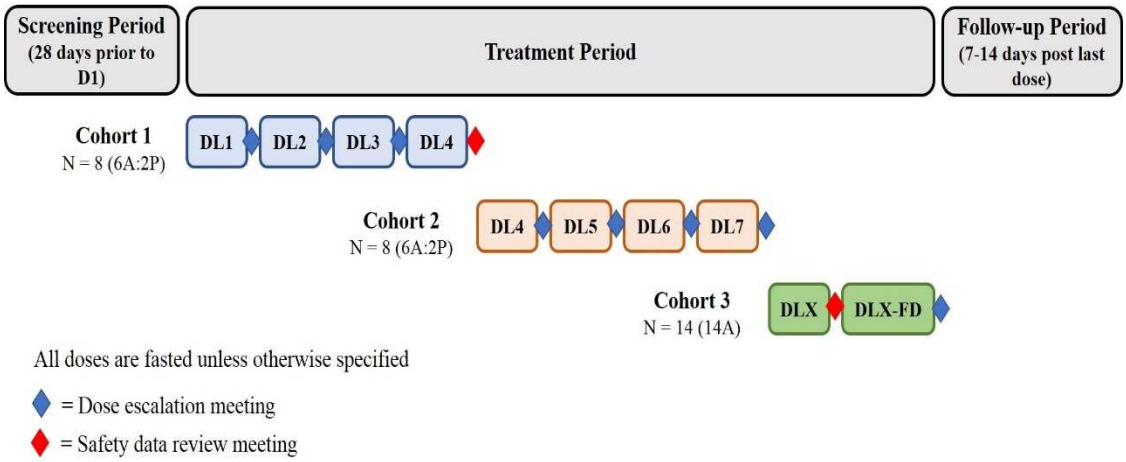
** Accumulation ratios calculated as the ratio of last dose to first dose PK parameters: $RAUC_{(0\text{-}tau)}$ = $AUC_{(0\text{-}tau)}$ on last dose to $AUC_{(0\text{-}tau)}$ on first dose, RCmax = Cmax on last dose to Cmax on first dose, RC_{tau}= C_{tau} on last dose to C_{tau} on first dose. # ARpred = 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.*

† *It is AUC(0-12) if dosing is BID, or, AUC(0-8) if dosing is TID.*

2.3. Study Design

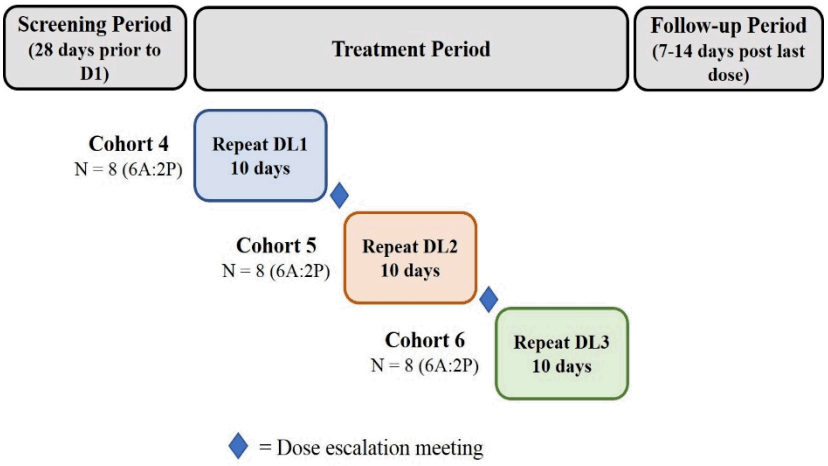
Overview of Study Design and Key Features

Figure 1 Study Design (Part A)



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

Figure 2 Study Design (Part B)



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

Note: DL7 was not dosed in the study due to higher than expected exposures.

Design Features	This study will be a randomized, double-blind (sponsor unblinded), placebo-controlled, 2-part study of the oral administration of GSK3186899A in healthy participants. Planned to include approximately 54 participants and will consist of 2 parts as below: • **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 period crossover which includes 4 dosing regimens under fasted conditions. Part A Cohort 3 will comprise of a 2 period crossover which includes 1 dosing regimen

Overview of Study Design and Key Features	
	under fasted conditions and 1 regimen under fed conditions. The fed conditions regimen will investigate the 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). 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.
Dosing	• **Part A (single ascending dose)** For Part A, the dose escalation phase, up to 3 cohorts may be used (Cohorts 1-3). Cohorts 1 and 2 will consist of 8 healthy participants each. If used, 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 above. - For Cohort 3, each participant will receive 1 oral dose of GSK3186899 selected based on the results from Cohorts 1 and 2, under both fasted and fed conditions. • 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. • **Part B (repeat dose)** For the repeat dose escalation phase in Part B, there will be up to 3 cohorts (Cohorts 4, 5 and 6), consisting of 8 healthy participants randomised 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. Based on emerging data in Part A, an alternate dosing regimen (OD or TID) may be selected if deemed suitable. • The first 2 participants in each cohort in Part B 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) the remaining 6 participants will be randomized to dosing.
Time & Events	• Refer to Appendix 2: Schedule of Activities
Treatment Assignment	• Part A consists of up to 30 participants in up to 3 cohorts (excluding possible replacements): o Cohort 1 and 2 will each have 6 participants in active versus 2 participants in placebo (i.e., in a 3:1 ratio)

Overview of Study Design and Key Features	
	○ Cohort 3 will contain up to 14 participants in a 1:1 ratio for (fed and active) versus (fasted and active) • Part B consists of up to 24 participants in up to 3 cohorts: ○ Cohorts 4, 5 and 6 will each have 6 participants in active versus 2 participants in placebo (i.e., in a 3:1 ratio)
Interim Analysis	No formal interim analyses (IA) 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 to progress to Part B.

2.4. Statistical Analyses

Given that this is a FTiH study, statistical analyses planned will be mainly descriptive in nature involving frequencies and percentages for categorical variables and number of subjects (n), mean, standard deviation, median, minimum and maximum for continuous variables.

Where appropriate (for e.g., evaluation of dose proportionality, drug accumulation, food effect) statistical modelling will be performed and point estimates with 90% confidence intervals (CIs) will be constructed.

3. PLANNED ANALYSES

3.1. Interim Analyses

No formal interim analyses (IA) are planned for this study. However, regular dose escalation meetings, an informal IA and safety review meetings are planned to be performed at different time points described below.

- Dose escalation meetings are planned to review the safety, tolerability, and PK data prior to:
    - each dose escalation in Part A (single dose) – Cohorts 1 and 2,
    - initiation of the food effect Cohort 3, and
    - each dose escalation in Part B (repeat dose) – prior to initiation of Cohorts 5 and 6.
- An informal IA to review the safety, tolerability, and PK data from Part A is planned prior to:
    - progression to Part B.

- Additional instream safety review meetings including all safety and tolerability data only are planned prior to:
    - progression to Cohort 2 in Part A
    - progression to Period 2 in the food effect Cohort 3.

There will not be a formal database freeze performed for this informal IA. Data included for these analyses will be as complete and clean as possible based on continuous data review and monitoring activities.

The final study analysis post- database freeze will include all data captured in the study database.

3.1.1.1. Dose escalation meetings

Statistical displays will not be produced by Biostatistics for the dose escalation meetings. During the meeting, safety data (presented by the CUC Principal Investigator or delegate) and PK data (presented by Study Pharmacokineticist or delegate) will be reviewed by the committee.

The meeting will discuss blinded data in an open forum with the GSK Study team members and Principal Investigator (or their delegate) in attendance. If required, the data may be reviewed in an unblinded fashion by the unblinded members including the SMG (formally GCSP) Safety representative and Study Pharmacokineticist.

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 individuals (including AEs, laboratory safety tests, telemetry, ECGs and vital signs) from a minimum of 48 hours post-dose (10 days for repeat dose) from a minimum of 4 or more participants who have received GSK3186899 at the current dose level

- all available safety and tolerability data accumulated from preceding single/repeat dose levels and available PK data from current (minimum of 4 or more participants) and preceding single/repeat dose levels.

Further details of the DEC membership, data to be reviewed and stopping criteria are outlined in the DEC charter.

3.1.1.2. Informal interim analysis

An informal interim analysis (IA) after completion of Part A will be conducted prior to initiation of Part B. This analysis will support the decision to progress, or, not progress to Part B and will consist of the following statistical displays on blinded safety and blinded PK data. Safety tables will therefore be presented by period rather than treatment to maintain the blind of the study.

Table 1: Planned Statistical Displays for the Interim analysis

Sl. No.	Population	IDSL / Example Shell	Title	Responsible function
1	Safety	ES1A	Summary of Participant Disposition for the Participant Conclusion Record – Part A (Cohort 1 and Cohort 2 only)	Biostatistics
2	Safety	ES3	Listing of Reasons for Study Withdrawal – Part A (Cohort 1 and Cohort 2 only)	Biostatistics
3	Safety	SD3	Listing of Reasons for Study Treatment Discontinuation – Part A (Cohort 1 and Cohort 2 only)	Biostatistics
4	Safety	DM3	Summary of Demographic Characteristics – Part A (Cohort 1 and Cohort 2 only)	Biostatistics
5	Safety	DM4	Listing of Demographic Characteristics - Part A (Cohort 1 and Cohort 2 only)	Biostatistics
6	Safety	EX1	Summary of Exposure to Study Treatment - Part A (Cohort 1 and Cohort 2 only)	Biostatistics
7	Safety	EX4	Listing of Exposure Data – Part A (Cohort 1 and Cohort 2 only)	Biostatistics
8	Safety	AE1CP	Summary of All Adverse Events by System Organ Class and Preferred Term - Part A (Cohort 1 and Cohort 2 only)	Biostatistics
9	Safety	AE9	Listing of All Adverse Events - Part A (Cohort 1 and Cohort 2 only)	Biostatistics
10	Safety	EG4	Listing of All ECG Values for Subjects with Any Value of Potential Clinical Importance - Part A (Cohort 1 and Cohort 2 only)	Biostatistics
11	Safety	EG6	Listing of All ECG Findings for Subjects with an Abnormal Finding - Part A (Cohort 1 and Cohort 2 only)	Biostatistics
12	Safety	LB6	Listing of All Laboratory Data for Participants with Any Value of Potential Clinical	Biostatistics

			Importance – Part A (Cohort 1 and Cohort 2 only)	
13	Safety	UR2B	Listing of All Urinalysis Data for Subjects with Any Value of Potential Clinical Importance - Part A (Cohort 1 and Cohort 2 only)	Biostatistics
14	Safety	VS5	Listing of All Vital Signs for Subjects with values Potential Clinical Importance - Part A (Cohort 1 and Cohort 2 only)	Biostatistics
15	Safety	EG6 (to be modified for telemetry data)	Listing of Telemetry findings - Part A (Cohort 1 and Cohort 2 only)	Biostatistics
16	Safety	DV2	Listing of Important Protocol Deviations – Part A (Cohort 1 and Cohort 2 only)	Biostatistics
17	PK	Non standard shell	Summary of Untransformed Derived GSK3186899 Plasma Pharmacokinetic Parameters by dose and fed status - Part A (All Cohorts)	CPMS
18	PK	Non standard shell	Summary of the ratio of fed versus fasted on AUC(0-∞) and Cmax – Part A Cohort 3	CPMS
19	PK	Non standard shell	Geo Mean (+ SD) GSK3186899 Plasma Concentration-Time Plot (Linear and Semi-Log) – Part A (Cohort 1 and Cohort 2 only)	CPMS
20	PK	Non standard shell	Box Plot of AUC(0-∞) and Cmax versus dose (Linear) – Part A (Cohort 1 and Cohort 2 only)	CPMS
21	PK	Non standard shell	Box Plot of dose normalised AUC(0-∞) and Cmax versus dose (Linear) – Part A (Cohort 1 and Cohort 2 only)	CPMS
22	PK	Non standard shell	Geo Mean (+ SD) GSK3186899 Plasma Concentration-Time Plot (Linear and Semi-Log) grouped by fed and fasted status – Part A Cohort 3	CPMS
23	PK	Non standard shell	Box Plot of AUC (0-∞) and Cmax (Linear) grouped by fed and fasted status – Part A Cohort 3	CPMS
24	PK	Non standard shell	Listing of GSK3186899 Plasma Pharmacokinetic Concentrations (log_e-transformed) -Time Data by dose - Part A (All Cohorts)	CPMS

The PK related displays will be prepared by/under the auspices of the CPMS function and the safety related displays will be prepared by/under the auspices of the Biostatistics function.

The safety related IA displays will include data from Cohort 1 and Cohort 2 only. This is because all the doses will be investigated for safety and tolerability during these two cohorts and Cohort 3 will provide further information on the fed or fasted regimen to be applied in the Part B, for multiple ascending doses.

The actual treatment information will not be presented in any displays. Aggregated data will be reported in the tables of safety endpoints. The PK data will be presented without subject IDs. Blinded listings of safety and PK data will be provided.

A blinded dry run will be performed prior to the informal IA. The dry run displays will be reviewed by the study team including SMG Pharma Safety representative.

If required and/or requested by the DEC, an independent statistician and programmer(s) may be deployed to create unblinded displays.

However, a support pharmacokineticist in GSK will have access to extract scrambled PK data from SMS2000 to PKHARP and transfer the data via secured email to the Study pharmacokineticist (in PAREXEL International) for their reviews and analyses during study.

In case, there are any serious adverse events requiring further investigation, the unblinded SMG Pharma Safety representative and unblinded Study Pharmacokineticist can support further investigation.

3.1.1.3. Safety review meetings

The decision to proceed from Cohort 1 Period 4 to Cohort 2 Period 1 and similarly progress from 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 also be reviewed. PK data will not be included in these reviews.

The study team will remain blinded until the database freeze, except for the unblinded site Pharmacist, unblinded study Pharmacokineticist and SMG Pharma Safety representative.

3.2. Final Analyses

The final planned analyses will be performed after the completion of the following sequential steps:

1. All participants have completed the study as defined in the protocol.
2. All required database cleaning activities have been completed and final database release (DBR) and database freeze (DBF) have been declared by Data Management.
3. All criteria for unblinding the randomization codes have been met.
4. Randomization codes have been distributed according to RandAll NG procedures.

A final blinded dry run will be performed prior to the database lock for review by the study team.

4. ANALYSIS POPULATIONS

For purposes of analysis, the following populations are defined:

Population	Description	Analyses Evaluated
Screened	• All participants who were screened for eligibility	• Screen Failure
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.*	• Study Population
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.*	• Study Population • Safety
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).	• PK

Refer to **Error! Reference source not found.**: List of Data Displays which details the population used for each display.
* PK assessments refer to the plasma concentrations and not the PK parameters.

4.1. Protocol Deviations

Important protocol deviations (PDs), including deviations related to study inclusion/exclusion criteria, conduct of the trial, patient management or patient assessment) will be summarised and listed.

Protocol deviations will be tracked by the study team throughout the conduct of the study in accordance with the Protocol Deviation Management Plan [Version 1.0 dated 10 April 2019 or later].

Exclusion from the analysis sets due to a deviation will be determined programmatically using the criteria described in the table of Analysis populations above. These deviations will not be included in the SDTM dataset but will be programmed in the protocol deviation analysis (ADaM) dataset. This dataset will be the basis for the summaries and listings of protocol deviations.

Data will be reviewed prior to unblinding and freezing the database to ensure all important deviations and deviations which may lead to exclusion from the analysis are captured and categorised.

A separate summary and listing of all inclusion/exclusion criteria deviations will also be provided. This summary will be based on data as recorded on the inclusion/exclusion page of the eCRF.

5. CONSIDERATIONS FOR DATA ANALYSES AND DATA HANDLING CONVENTIONS

5.1. Study Treatment & Sub-group Display Descriptors

Treatment Group Descriptions			
RandAll NG		Data Displays for Reporting	
Code	Description	Description	Order in TLF
PART A			
P1 / P2	Placebo cohort 1 / Placebo cohort 2	Placebo Part A	1
D1	GSK3186899 Dose Level 1	GSK 30 mg	2
D2	GSK3186899 Dose Level 2	GSK 60 mg	3
D3	GSK3186899 Dose Level 3	GSK 120 mg	4
D4	GSK3186899 Dose Level 4	GSK 300 mg	5
D5	GSK3186899 Dose Level 5	GSK 600 mg	6
D6	GSK3186899 Dose Level 6	GSK 800 mg	7
D7	GSK3186899 Dose Level 7 (this dose was not investigated)	GSK X.X mg	8
DX-FA	GSK3186899 Dose Level X fasted	GSK X.X mg fasted	9
DX-FE	GSK3186899 Dose Level X fed	GSK X.X mg fed	10
PART B			
P4/ P5/ P6	Placebo cohort 4/ Placebo cohort 5/ Placebo cohort 6	Placebo Part B	1
R1	GSK3186899 Repeat Dose Level 1	GSK X.X mg BID	2
R2	GSK3186899 Repeat Dose Level 2	GSK X.X mg BID	3
R3	GSK3186899 Repeat Dose Level 3	GSK X.X mg BID	4

Note: Doses levels 1 to 6 were known at the time of RAP finalisation. The later doses were unknown, but will be known and detailed in the final study reporting.

For Part A, this order of the treatments will be considered for displays including all treatment groups from Cohorts 1, 2 and 3. However, for displays by Cohorts, only relevant treatment groups will be presented in the same ascending order mentioned above.

Treatment comparisons will be displayed using the descriptors as specified below:

- In general, comparison between 2 doses: GSK X.X mg vs GSK X.X mg
- In Cohort 3 (same dose different food regimen): GSK X.X mg - fed vs fasted.

5.2. Baseline Definitions

Baseline is defined as the last non-missing pre-dose assessment in each cohort. In general, assessments on Study day 1 taken prior to first dose are used as baseline. In some unlikely situations described below, the baseline will be defined as:

- when there are multiple assessments captured on Day 1, but the time of the first assessments is missing, then this first recorded assessment will be considered as the baseline
- when only one assessment is captured on Day 1 with time of assessment as missing, then conservatively the last available assessment from Day -1 or prior will be defined as the baseline
- when there are no assessments collected at Day 1, the last available data from either Day -1/ Day -2 or screening (as schedule of assessment in each Part/Cohort permits) will be defined as baseline
- when pre-dose data is completely missing for a subject, then no derivation will be performed, and the baseline will be set to missing

In Part A, for each period within a cohort, the period baseline is defined in a similar manner, by considering the last available non-missing pre-dose assessment in that period.

For some ECG and Vital Signs parameters, the pre-dose data is captured as triplicate. In these cases, the baseline will be defined as the mean of the assessments.

In addition, for some PK endpoint analyses, the adjusted baselines may be considered, if the pre-dose PK concentration value in a period is observed to be greater than 5% of the previous dose Cmax value:

- Subject level baseline is defined as the mean of baseline across periods for each subject. If a period baseline is missing, the mean of available period baselines will be considered as baseline.

- Period level baseline is defined as the difference between the baseline value and subject level baseline for each period and each subject.

5.2.1. Derivations and Handling of Missing Baseline Data

Definition	Reporting Details
Change from baseline in the study	
Change from Baseline	= Post-dose visit value – Baseline value
% Change from Baseline	= 100 x [(Post-dose visit value – Baseline value) / Baseline value]
Change from baseline within a period	
Change from Baseline in Period X	= Period X Post-dose value – Period X baseline value

% Change from Baseline in Period X	= 100 x [(Period X Post-dose value – Period X baseline value) / Period X baseline value]

NOTES:

- Unless otherwise specified, the baseline definitions specified in Section 5.2 Baseline Definitions (the baseline of the study and the baseline of each period (unadjusted)) will be used for derivations for endpoints / parameters and indicated on summaries. Unless otherwise stated, if baseline data is missing or post-dose data is missing no derivation will be performed and (%) change from baseline will be set to missing.
- The relevant baseline definition will be footnoted on all displays involving change from baseline.

5.3. Other Considerations for Data Analyses and Data Handling Conventions

Other considerations for data analyses and data handling conventions are outlined in the appendices:

Section	Component
10.1	Appendix 1: Protocol Deviation Management and Definitions for Per Protocol Population
10.2	Appendix 2: Schedule of Activities
10.3	Appendix 3: Assessment Windows
10.4	Appendix 4: Study Phases and Treatment Emergent Adverse Events
10.5	Appendix 5: Data Display Standards & Handling Conventions
10.5	Appendix 6: Derived and Transformed Data
10.7	Appendix 7: Reporting Standards for Missing Data
10.8	Appendix 8: Values of Potential Clinical Importance

6. STUDY POPULATION ANALYSES

6.1. Overview of Planned Study Population Analyses

The study population analyses will be based on the "Safety" population, unless otherwise specified.

Study population analyses including analyses of subject's disposition, protocol deviations, demographic and baseline characteristics, prior and concomitant medications, and exposure and treatment compliance will be based on GSK Core Data Standards. In this document, Appendix 12 contains a list of data displays and analysis sets planned for the informal interim analysis.

Details of the planned displays and analysis sets for final study reporting will be presented in **Error! Reference source not found.**: List of Data Displays.

7. SAFETY ANALYSES

The safety analyses will be based on the "Safety" population, consisting all subjects who had a dose (including those who had partial dose) of study treatment.

7.1. Adverse Events Analyses

Adverse events analyses including the analysis of adverse events (AEs), Serious (SAEs) and common (≥ 5%) AEs by overall frequency will be based on GSK Core Data Standards. The details of the planned displays are provided in **Error! Reference source not found.**: List of Data Displays.

7.2. Adverse Events of Special Interest Analyses

Adverse events of special interest are those considered possibly related to/associated with stomach erosion, adrenal insufficiency and renal impairment.

A comprehensive list of MedDRA terms based on clinical review will be used to identify each type of event. Changes to the MedDRA dictionary may occur between the start of the study and the time of reporting and/or emerging data from on-going studies may highlight additional adverse events of special interest, therefore the list of terms to be used for each event of interest and the specific events of interest will be based on the safety review team (SRT) agreements in place at the time of final reporting. The details of the planned displays are provided in **Error! Reference source not found.**: List of Data Displays.

7.3. Clinical Laboratory Analyses

Laboratory evaluations including the analyses of Chemistry laboratory tests, Hematology laboratory tests, Urinalysis, Renal and Liver function tests will be based on GSK Core Data Standards. The details of the planned displays are in **Error! Reference source not found.**: List of Data Displays.

7.4. Other Safety Analyses

The analyses of non-laboratory safety test results including vital signs, 12 lead ECG and 24-hour telemetry will be based on GSK Core Data Standards, unless otherwise specified. The details of the planned displays are presented in **Error! Reference source not found.**: List of Data Displays.

8. PHARMACOKINETIC ANALYSES

All PK analyses planned for the study are a part of the secondary objectives.

8.1. Statistical analyses of derived PK parameters

8.1.1. Endpoints / Variables

8.1.1.1. Drug Concentration Measures

Refer to Appendix 5: Data Display Standards & Handling Conventions (Section 10.5.3 Reporting Standards for Pharmacokinetic).

8.1.1.2. Derived Pharmacokinetic Parameters

Pharmacokinetic parameters will be calculated by standard non-compartmental analysis according to current working practices and using the currently supported version of WinNonlin version 8.0. All calculations of non-compartmental parameters will be based on actual sampling times.

For dose escalation meeting and interim analysis planned sampling times may be used if actual timepoints are not available.

Pharmacokinetic parameters listed will be determined from the plasma concentration-time data, provided there is enough evaluable data available for the calculations. If the concentration data is available partially, then based on scientific judgement the data will be assessed for inclusion or exclusion from the analysis.

Parameter	Parameter Description
Plasma PK Parameters:	
Cmax	Maximum observed concentration, determined directly from the concentration-time data.
RCmax	Ratio of Cmax on last dose to Cmax on first dose, i.e., $$RCmax = \frac{Cmax\ on\ the\ last\ dose}{Cmax\ on\ the\ first\ dose}.$$
Ctau	Trough concentration determined directly from the concentration data (only for Part B of the study). It will be the concentrations at 12h or 8h after first dose (if BID or TID administration, respectively) and always concentration at pre-dose on the last dose.
RCtau	Ratio of Ctau on last dose to Ctau on first dose, i.e., $$RCtau = \frac{Ctau\ on\ the\ last\ dose}{Ctau\ on\ the\ first\ dose}$$
tmax	Time to reach Cmax, determined directly from the concentration-time data.
tlag*	Lag time before first observation of drug concentrations (after single dose only)

Parameter	Parameter Description
Tlast*	Time of last quantifiable concentration
$t_{½}$	Apparent terminal half-life will be calculated as: $$t_{1/2} = \frac{\ln 2}{\lambda_z}$$ (NOTE: λ_z is the terminal phase rate constant).
AUC(0-24h)	Area under the concentration-time curve from time zero to 24 hours post-dose (after single dose only).
AUC(0-t)	Area under the concentration-time curve from time zero to the time of the last quantifiable concentration (C(t)) will be calculated using the linear trapezoidal rule for each incremental trapezoid and the $\log_e$ trapezoidal rule for each decremental trapezoid.
AUC(0-tau)	Area under the concentration-time curve from time zero to the time of the trough concentration (C(tau)) will be calculated for Part 2 of the study only (repeat dose) using the linear trapezoidal rule for each incremental trapezoid.
RAUC(0-tau)	AUC(0-tau) on last dose to AUC(0-tau) on first dose $$RAUC(0-tau) = \frac{AUC(0-tau)\ on\ the\ last\ dose}{AUC(0-tau)\ on\ the\ first\ dose}$$
AUC(0-∞)	Area under the concentration-time curve extrapolated to infinity will be calculated (after single dose only) as: $$AUC(0-\infty) = AUC(0-t) + \frac{C(t)}{\lambda z}$$ (NOTE: λz is the terminal phase rate constant. % of the extrapolated area should not exceed 20%. Any value of AUC(0-∞) derived with more than 20% extrapolation should be flagged and excluded from summary statistics if >30%).
AR_{pred}	AR_{pred} is calculated as : $$ARpred = \frac{1}{1 - e^{k*tau}}$$ where k is elimination rate constant following the single dose and tau is the dosing interval for the intended repeat dosing.
R^2adjusted*	The goodness of fit statistic for the terminal elimination phase, adjusted for the number of points used in the estimation of λz.
λz	λ_z is the terminal phase rate constant. A minimum number of three data points in the terminal phase will be used starting at any post-Cmax data point. The adjusted correlation coefficient (R^2 adjusted) in general should be greater than 0.90. Any value < 0.90 but ≥0.8 will be flagged but may be used at the PK Scientist's best knowledge and judgment, any value <0.8 should be considered for exclusion from the statistical analysis. All the derived parameters that include λz in their calculation (i.e, t½, AUC(0-∞) will need to be flagged or excluded from statistical analysis accordingly. The interval used to determine λz should be equal or greater than 1.5-fold the estimated half-life or otherwise flagged and used at the PK Scientist's best knowledge and judgment.
λz upper limit*	The upper limit on time for values to be included in the calculation of λz.

Parameter	Parameter Description
λz lower limit*	The lower limit on time for values to be included in the calculation of λz
λz number of points*	The number of time points used in computing λz.
% AUCex*	Percent of AUC_{∞} that is extrapolated beyond last quantified concentration
CL/F*	The apparent clearance will be calculated only for Part 1 of the study (single dose) as Dose/ AUC(0-∞)
CLss*	The apparent clearance at steady state will be calculated only for day 10 Part 2 of the study (repeat dose) as Dose/ AUC(0-tau)
Urine PK Parameters:	
$Ae_{(t1-tz)}$*	Amount excreted in the urine at each interval collection (24 h)
$fe_{(0-tz)}$*	The fraction of unchanged drug excreted in urine will be calculated as $f_e = A_e$/Dose, up to tz hours, where tz is the last collection time
CL_R*	Renal Clearance calculated as $Ae_{(0-tz)}$ / $AUC_{(0-tz)}$.

NOTES:

- *Additional exploratory parameters have been included which will be listed only.

8.1.2. Summary Measure

All the derived PK parameters will be summarized descriptively.

Detail methods and displays of the summary measures are specified in Section 8.1.6 Statistical Analyses/ Methods.

Some of the parameters in the list above will be used for statistical modelling, as described in the subsequent analyses sections.

8.1.3. Population of Interest

These descriptive summaries will be based on the PK population.

8.1.4. Strategy for Intercurrent (Post-Randomization) Events

In Table 2 below, the possible intercurrent events and the rationale for relating them to treatment or otherwise is described. Once a subject discontinues from study treatment, they will proceed straight to follow up and no further data will be collected.

Individual subject data will be included in data listings regardless of the strategies followed for the analyses.

If feasible, subjects will be replaced until the desired sample size is attained.

Table 2 Strategies for Intercurrent events

Intercurrent events	Relation to treatment and rationale	Strategy, rationale and details of action taken
Subject withdraws study consent	Not related to treatment/ Subject drops out due to logistic reasons and not due to any event related to treatment	- The strategy will be a **While-on-Treatment strategy,** where we are interested in the treatment effects prior to the withdrawal only. - Subjects' data available up to the withdrawal will be included in the descriptive PK summaries. - If a subject withdraws consent during a period, the missing data post withdrawal will not be imputed. - The derived PK parameters for e.g., AUC, C_{max} etc. of that partially completed period will be calculated if data permits (See section 8.1.1.2 Derived Pharmacokinetic Parameters for details on derivation criteria).
Subject does not take the full treatment	Not related to treatment/ The treatment will be administered as a powder dissolved in diluent. To ensure all treatment is ingested, the bottle containing the dispersion will be rinsed three times and the subject will be expected to ingest this in addition to the initial dispersion. If three rinses are not all ingested, the subject may not take the full treatment dose.	In the current formulation, it is hard to measure the exact proportion of dose ingested if not all rinses are taken. It is also uncertain whether the formulation could change in future development. To account for this, we propose two different strategies described below. If this intercurrent event is not observed, then both strategies will provide the same results and only the hypothetical strategy will be presented for the final analysis. **Primary analysis** - The strategy will be a **Hypothetical strategy,** where we are interested in the treatment effects in a hypothetical scenario where all subjects have taken complete dose. - In this case, the data from a period in which an incomplete dose is taken would be considered as missing at random and excluded from analyses. - If the drug formulation is changed in the future studies, this estimate will provide the true relationship between the actual dose intake and its exposure under this strategy. **Supplementary analysis** - The strategy will be a **Treatment policy strategy,** where we are interested in the

		treatment effects regardless of the actual amount of dose taken. - The analysis will include PK parameters derived based on concentrations of both complete and partial doses (if data permits based on criteria described in Section 8.1.1.2) and will be analysed using the nominal or prescribed dose. - If the drug formulation remains unchanged in the future studies, this estimate will provide the true relationship between a nominal dose and its exposure under this strategy, i.e., a close to real-world situation.
Subject drops out due to Adverse events	Related to treatment/ If the adverse event is confirmed to be related to study treatment	- The primary strategy will be a **Hypothetical strategy,** where we are interested in the treatment effects in a hypothetical scenario where discontinuation due to an AE would not happen. - The missing data after discontinuation will assumed to be missing at random - The derived PK parameters of the last fully or partially completed period will be calculated if data permits (See section 8.1.1.2 Derived Pharmacokinetic Parameters for details on derivation criteria).

8.1.5. Statistical Analyses / Methods

For parameters tabulated in Section 8.1.2, data will be summarized using the following descriptive statistics.

- N, n, arithmetic mean, 95% confidence interval (CI) for the arithmetic mean, SD, median, minimum, maximum for the untransformed data
- Geometric mean, 95% CI for the geometric mean, SD of $\log_e$-transformed data and $\%CV_b$ or %CVw for the untransformed data (except Tmax and $T_{½}$)
- Based on the intercurrent events observed in the study, appropriate strategies from Table 2 in Section 8.1.4 will be considered for handling of missing data (if any) and interpretation of the analysis results. If multiple intercurrent events are observed (for e.g., if the subject does not take the full treatment as well he withdraws study consent), then the data will be handled using more than one strategy as described in Table 2 and interpretations of the results will be made accordingly.

Graphical presentations will be provided if appropriate. All data will be listed. Details of the planned displays are provided in **Error! Reference source not found.**: List of Data Displays and will be based on GSK Data Standards and statistical principles.

8.2. Statistical analysis for comparison of food effect – Single dose study part

8.2.1. Endpoints/Variables

To assess the food effect in Cohort 3, the statistical analysis will be based on AUC(0-t), AUC(0-∞) and Cmax, only.

8.2.2. Summary Measure

The summary measure will be the point estimates and 90% CIs of mean differences of GSK3186899 fed – GSK3186899 fasted, based on the $\log_e$-transformed data, and after back-transformation of this estimated differences, the geometric mean ratios of (GSK3186899 fed: GSK3186899 fasted) will be presented.

8.2.3. Population of Interest

These analyses will be based on the PK population.

8.2.4. Strategy for Intercurrent (Post-Randomization) Events

In the Table 3 below, the possible intercurrent events and the rationale for relating them to treatment or otherwise is described. Once a subject discontinues from study treatment, they will proceed straight to follow up and no further data will be collected.

All subjects' data will be included in data listings irrespective of the strategies followed for the analysis.

If feasible, subjects will be replaced until the desired sample size is attained.

Table 3 Strategies for Intercurrent events

Intercurrent events	**Relation to treatment and rationale**	**Strategy, rationale and details of action taken**
Subject withdraws study consent	Not related to treatment/ Subject drops out due to logistic reasons and not due to any event related to treatment	- The strategy will be a **While-on-Treatment strategy,** where we are interested in the treatment effects prior to the withdrawal only. - Subjects' data available up to the withdrawal will be included in the food effect analyses. - If a subject withdraws consent during a period, the missing data post withdrawal will not be imputed. - The derived PK parameters for e.g., AUC, C_{max} etc. of that partially completed period will be calculated if data permits (See section 8.1.1.2 Derived Pharmacokinetic Parameters for details on derivation criteria).

Subject does not take the full treatment	Not related to treatment/ The treatment will be administered as a powder dissolved in diluent. To ensure all treatment is ingested, the bottle containing the dispersion will be rinsed three times and the subject will be expected to ingest this in addition to the initial dispersion. If three rinses are not all ingested, the subject may not take the full treatment dose.	In the current formulation, it is hard to measure the exact proportion of dose ingested if not all rinses are taken. It is also uncertain whether the formulation could change in future development. To account for this, we propose two different strategies described below. If this intercurrent event is not observed, then both strategies will provide the same results and only the hypothetical strategy will be presented for the final analysis. **Primary analysis** - The strategy will be a **Hypothetical strategy,** where we are interested in the treatment effects in a hypothetical scenario where all subjects have taken complete dose. - In this case, the data from a period in which an incomplete dose is taken would be considered as missing at random and excluded from analyses. - If the drug formulation is changed in the future studies, this estimate will provide the true relationship between the actual dose intake and its exposure under this strategy. **Supplementary analysis** - The strategy will be a **Treatment policy strategy,** where we are interested in the treatment effects regardless of the actual amount of dose taken. - The analysis will include PK parameters derived based on concentrations of both complete and partial doses (if data permits based on criteria described in Section 8.1.1.2) and will be analysed using the nominal or prescribed dose. - If the drug formulation remains unchanged in the future studies, this estimate will provide the true relationship between a nominal dose and its exposure under this strategy, i.e., close to a real-world situation.
Subject drops out due to	Related to treatment/ If the adverse event is confirmed	- The primary strategy will be a **Hypothetical strategy,** where we are interested in the treatment effects in a hypothetical scenario where discontinuation due to an AE would not happen.

Adverse events	to be related to study treatment	- The missing data after discontinuation will assumed to be missing at random - The derived PK parameters of the last fully or partially completed period will be calculated if data permits (See section 8.1.1.2 Derived Pharmacokinetic Parameters for details on derivation criteria).

8.2.5. Statistical Analyses / Methods

Details of the planned displays are provided in **Error! Reference source not found.**: List of Data Displays and will be based on GSK Data Standards and statistical principles. Graphical presentations will be provided if appropriate. All data will be listed.

8.2.5.1. Statistical Methodology Specification

The following statistical analyses will only be performed if sufficient data is available (i.e. if subjects have well defined plasma profiles).

Pharmacokinetic analysis will be the responsibility of the Clinical Pharmacology Modelling and Simulation Department, (CPMS) and Statistical analyses of the pharmacokinetic parameters will be the responsibility of the Biostatistics Department.

(1) Statistical analysis for comparison of food effect – Single dose study part
Endpoint / Variables
• AUC (0-t) • AUC(0-∞) • Cmax
Model Specification

• Log_e-transformed data will be statistically analysed using a Mixed model.
• The mixed model will contain
  o Fixed effect: fed or fasted status, period and their interaction term (if tested as significant)
  o Random effect: subject
• Only data of subjects participating in Cohort 3 will be included in this analysis, all other dose level data from Cohorts 1 and 2 will be excluded from this analysis.
• The Kenward and Roger method for approximating the denominator degrees of freedom and correcting for bias in the estimated variance-covariance of the fixed effects will be used.
• An unstructured type of the covariance matrices R (accounting for the within subject variability) and G (accounting for the between subject variability) will be used.
• Based on the intercurrent events observed in the study, appropriate strategies from Table 3 in Section 8.2.4 will be considered for handling of missing data (if any) and interpretation of food effect analysis results. If multiple intercurrent events are observed (for e.g., if the

subject does not take the full treatment as well he withdraws study consent), then the data will be handled using more than one strategy as described in Table 3 and interpretations of the results will be made accordingly.
Model Checking & Diagnostics
• For the Mixed model, model assumptions will be checked, and appropriate adjustments may be applied based on the data. • Distributional assumptions underlying the model used for analysis will be examined by obtaining a normal probability plot of the residuals and a plot of the residuals versus the fitted values (i.e. checking the normality assumption and constant variance assumption of the model respectively) to gain confidence that the model assumptions are reasonable. • If there are any departures from the distributional assumptions, alternative transformations, such as data squared or square root of data, will be explored. • Non-parametric analyses will be conducted if the normality assumption does not hold for any of the alternative transformations. • If this model fails to converge, alternative covariance structures may be considered in the following order (1) Compound Symmetry (CS) and (2) Variance Components (VC).
Model Results Presentation
• Point estimates and corresponding 90% confidence intervals will be constructed for the comparisons of interest of GSK3186899 fed – GSK3186899 fasted, based on the log-transformed data. • These loge-transformed results will then be exponentially back-transformed to provide point estimates and corresponding 90% confidence intervals for the geometric mean ratios (GSK3186899 fed: GSK3186899 fasted).

8.3. Statistical analysis for dose proportionality – Single and Repeat dose study parts

8.3.1. Endpoints/Variables

To assess the dose proportionality, the statistical analysis will be based on AUC, Cmax and Ctau variables, as appropriate in the single and repeat dose study part.

8.3.2. Summary Measure

The summary measure will be the point estimates and 90% CIs of mean slopes of $\log_e$(dose) in the single and repeat dose study part.

8.3.3. Population of Interest

These analyses will be based on the PK population.

8.3.4. Strategy for Intercurrent (Post-Randomization) Events

In the Table 4 below, the possible intercurrent events and the rationale for relating them to treatment or otherwise is described. Once a subject discontinues from study treatment, they will proceed straight to follow up and no further data will be collected.

All subjects' data will be included in data listings irrespective of the strategies followed for the analysis.

If feasible, subjects will be replaced until the desired sample size is attained.

Table 4 Strategies for Intercurrent events

Intercurrent events	**Relation to treatment and rationale**	**Strategy, rationale and details of action taken**
Subject withdraws study consent	Not related to treatment/ Subject drops out due to logistic reasons and not due to any event related to treatment	- The strategy will be a **While-on-Treatment strategy,** where we are interested in the treatment effects prior to the withdrawal only. - Subjects' data available up to the withdrawal will be included in the dose proportionality analyses. - If a subject withdraws consent during a period, the missing data post withdrawal will not be imputed. - The derived PK parameters for e.g., AUC, C_{max} etc. of that partially completed period will be calculated if data permits (See section

		8.1.1.2 Derived Pharmacokinetic Parameters for details on derivation criteria).
Subject does not take the full treatment	Not related to treatment/ The treatment will be administered as a powder dissolved in diluent. To ensure all treatment is ingested, the bottle containing the dispersion will be rinsed three times and the subject will be expected to ingest this in addition to the initial dispersion. If three rinses are not all ingested, the subject may not take the full treatment dose.	In the current formulation, it is hard to measure the exact proportion of dose ingested if not all rinses are taken. It is also uncertain whether the formulation could change in future development. To account for this, we propose two different strategies described below. If this intercurrent event is not observed, then both strategies will provide the same results and only the hypothetical strategy will be presented for the final analysis. **Primary analysis** - The strategy will be a **Hypothetical strategy,** where we are interested in the treatment effects in a hypothetical scenario where all subjects have taken complete dose. - In this case, the data from a period in which an incomplete dose is taken would be considered as missing at random and excluded from analyses. - If the drug formulation is changed in the future studies, this estimate will provide the true relationship between the actual dose intake and its exposure under this strategy. **Supplementary analysis** - The strategy will be a **Treatment policy strategy,** where we are interested in the treatment effects regardless of the actual amount of dose taken. - The analysis will include PK parameters derived based on concentrations of both complete and partial doses (if data permits based on criteria described in Section 8.1.1.2) and will be analysed using the nominal or prescribed dose. - If the drug formulation remains unchanged in the future studies, this estimate will provide the true relationship between a nominal dose and its exposure under this strategy, i.e., in a close to real-world setting
Subject drops out	Related to treatment/	- The primary strategy will be a **Hypothetical strategy,** where we are interested in the

due to Adverse events	If the adverse event is confirmed to be related to study treatment	treatment effects in a hypothetical scenario where discontinuation due to an AE would not happen. - The missing data after discontinuation will assumed to be missing at random - The derived PK parameters of the last fully or partially completed period will be calculated if data permits (See section 8.1.1.2 Derived Pharmacokinetic Parameters for details on derivation criteria).

8.3.5. Statistical Analyses / Methods

Details of the planned displays are provided in **Error! Reference source not found.**: List of Data Displays and will be based on GSK Data Standards and statistical principles. Graphical presentations will be provided if appropriate. All data will be listed.

8.3.5.1. Statistical Methodology Specification

The following statistical analyses will only be performed if sufficient data is available (i.e. if subjects have well defined plasma profiles).

Pharmacokinetic analysis will be the responsibility of the Clinical Pharmacology Modelling and Simulation Department, (CPMS) and Statistical analyses of the pharmacokinetic parameters will be the responsibility of the Biostatistics Department.

(2) Statistical analysis for dose proportionality – Single and Repeat dose study parts

Endpoint / Variables

- For SAD part: AUC(0-∞), Cmax
- For MAD part: AUC(0-tau), Cmax, Ctau

Model Specification

- Power model

$$y = \alpha * dose^{\beta}$$

where y denotes the PK parameter being analyzed, dose denotes the total dose administered to a subject. The α denotes random subject effect in the repeat dose Part B. In the crossover single ascending dose Part A, alpha depends upon random subject effect and period effect.

- Log_e transformed data will be analysed by fitting the following terms in the mixed effect model:
  - Fixed effect: log_e (dose), period (period will be included in SAD part only)
  - Random effect: Subject
- Data from all available doses in each part of the study will be considered (as described in Section 8.1.1.2).

• An unstructured covariance structure will be considered for the G matrix describing the between subject variability. • Based on the intercurrent events observed in the study, appropriate strategies from Table 4 in Section 8.3.4 will be considered for handling of missing data (if any) and interpretation of the analysis results. If multiple intercurrent events are observed (for e.g., if the subject does not take the full treatment as well he withdraws study consent), then the data will be handled using more than one strategy as described in Table 4 and interpretations of the results will be made accordingly.
Model Checking & Diagnostics
• For the Mixed Model, model assumptions will be checked, and appropriate adjustments may be applied based on the data. • Distributional assumptions underlying the model used for analysis will be examined by obtaining a normal probability plot of the residuals and a plot of the residuals versus the fitted values (i.e., checking the normality assumption and constant variance assumption of the model respectively) to gain confidence that the model assumptions are reasonable. • If there are any departures from the distributional assumptions, alternative transformations, such as data squared or square root of data, will be explored. • Non-parametric analyses will be conducted if the normality assumption does not hold for any of the alternative transformations.
Model Results Presentation
• Estimates of the mean slopes of $\log_e$(dose) will be reported along with corresponding 90% confidence intervals (slope ≈ 1 implied dose proportionality).

8.4. Statistical analysis for dose accumulation – Repeat dose study part

8.4.1. Endpoints/Variables

To assess the dose accumulation, the statistical analysis will be based on the ratios of RAUC(0-tau), RCmax and RCtau respectively.

8.4.2. Summary Measure

The summary measure will be the point estimates and 90% CIs of mean differences of 'Day 10 – Day 1' based on the log-transformed data and after back-transformation of this estimated differences, the geometric means of the ratio 'Day 10: Day 1' will be presented.

8.4.3. Population of Interest

These analyses will be based on the PK population.

8.4.4. Strategy for Intercurrent (Post-Randomization) Events

In the Table 5 below, the possible intercurrent events and the rationale for relating them to treatment or otherwise is described. Once a subject discontinues from study treatment, they will proceed straight to follow up and no further data will be collected.

All subjects' data will be included in data listings irrespective of the strategies followed for the analysis.

If feasible, subjects will be replaced until the desired sample size is attained.

Table 5 Strategies for Intercurrent events

Intercurrent events	**Relation to treatment and rationale**	**Strategy, rationale and details of action taken**
Subject withdraws study consent	Not related to treatment/ Subject drops out due to logistic reasons and not due to any event related to treatment	- The strategy will be a **While-on-Treatment strategy,** where we are interested in the treatment effects prior to the withdrawal only. - Subjects' data available up to the withdrawal will be included in the dose accumulation analyses. - If a subject withdraws consent during a period, the missing data post withdrawal will not be imputed. - The derived PK parameters for e.g., AUC, C_{max} etc. of that partially completed period will be calculated if data permits (See section

		8.1.1.2 Derived Pharmacokinetic Parameters for details on derivation criteria).
Subject does not take the full treatment	Not related to treatment/ The treatment will be administered as a powder dissolved in diluent. To ensure all treatment is ingested, the bottle containing the dispersion will be rinsed three times and the subject will be expected to ingest this in addition to the initial dispersion. If three rinses are not all ingested, the subject may not take the full treatment dose.	In the current formulation, it is hard to measure the exact proportion of dose ingested if not all rinses are taken. It is also uncertain whether the formulation could change in future development. To account for this, we propose two different strategies described below. If this intercurrent event is not observed, then both strategies will provide the same results and only the hypothetical strategy will be presented for the final analysis. **Primary analysis** - The strategy will be a **Hypothetical strategy,** where we are interested in the treatment effects in a hypothetical scenario where all subjects have taken complete dose. - In this case, the data from a period in which an incomplete dose is taken would be considered as missing at random and excluded from analyses. - If the drug formulation is changed in the future studies, this estimate will provide the true relationship between the actual dose intake and its exposure under this strategy. **Supplementary analysis** - The strategy will be a **Treatment policy strategy,** where we are interested in the treatment effects regardless of the actual amount of dose taken. - The analysis will include PK parameters derived based on concentrations of both complete and partial doses (if data permits based on criteria described in Section 8.1.1.2) and will be analysed using the nominal or prescribed dose. - If the drug formulation remains unchanged in the future studies, this estimate will provide the true relationship between a nominal dose and its exposure under this strategy, i.e., close to a real-world setting.
Subject drops out	Related to treatment/	- The primary strategy will be a **Hypothetical strategy,** where we are interested in the

due to Adverse events	If the adverse event is confirmed to be related to study treatment	treatment effects in a hypothetical scenario where discontinuation due to an AE would not happen. - The missing data after discontinuation will assumed to be missing at random - The derived PK parameters of the last fully or partially completed period will be calculated if data permits (See section 8.1.1.2 Derived Pharmacokinetic Parameters for details on derivation criteria).

8.4.5. Statistical Analyses / Methods

Details of the planned displays are provided in **Error! Reference source not found.**: List of Data Displays and will be based on GSK Data Standards and statistical principles. Graphical presentations will be provided if appropriate. All data will be listed.

8.4.5.1. Statistical Methodology Specification

The following statistical analyses will only be performed if sufficient data is available (i.e. if subjects have well defined plasma profiles).

Pharmacokinetic analysis will be the responsibility of the Clinical Pharmacology Modelling and Simulation Department, (CPMS) and Statistical analyses of the pharmacokinetic parameters will be the responsibility of the Biostatistics Department.

Statistical analysis for dose accumulation – Repeat dose study part
Endpoint / Variables
• RAUC(0-tau) • RCmax • RCtau
Model Specification
• Will be statistically analysed using a mixed model (MM) using a $\log_e$-transformation. The mixed model will contain: o Fixed effects: dose, day and dose*day o Random effect: Subject Here dose denotes the total dose administered per day to a subject. • The Kenward and Roger method for approximating the denominator degrees of freedom and correcting for bias in the estimated variance-covariance of the fixed effects will be used. • An unstructured type of the covariance matrices R (accounting for the within subject variability) and G (accounting for the between subject variability) will be used. • Based on the intercurrent events observed in the study, appropriate strategies from Table 5 in Section 8.4.4 will be considered for handling of missing data (if any) and interpretation of the analysis results. If multiple intercurrent events are observed (for e.g., if the subject does

not take the full treatment as well he withdraws study consent), then the data will be handled using more than one strategy as described in Table 5 and interpretations of the results will be made accordingly.
Model Checking & Diagnostics
• For the Mixed Model, model assumptions will be checked, and appropriate adjustments may be applied based on the data. • Distributional assumptions underlying the model used for analysis will be examined by obtaining a normal probability plot of the residuals and a plot of the residuals versus the fitted values (i.e. checking the normality assumption and constant variance assumption of the model respectively) to gain confidence that the model assumptions are reasonable. • If there are any departures from the distributional assumptions, alternative transformations, such as data squared or square root of data, will be explored. • Non-parametric analyses will be conducted if the normality assumption does not hold for any of the alternative transformations. • If this model fails to converge, alternative covariance structures may be considered in the following order (1) Compound Symmetry (CS) and (2) Variance Components (VC).
Model Results Presentation
• For each dose, point estimates and 90% confidence intervals for the differences “Day 10 - Day 1” will be presented based on the log-transformed data. • These 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, and only day effect is significant based on the data, then to evaluate the effect of day, a single point estimate and confidence interval pooled across all doses by day will be constructed.

8.5. Statistical analysis for time invariance ratio of GSK3186899 – Repeat dose study part

8.5.1. Endpoints/Variables

To assess the time invariance dose accumulation, the statistical analysis will be based on the ratio of AUC(0-tau) (i.e., AUC(0-12) if dosing is BID or, AUC(0-8) if dosing is TID) on day 10 to AUC(0-∞) on day 1, if data permits.

8.5.2. Summary Measure

The summary measure will be the point estimate and 90% CIs of mean difference of 'AUC(0-tau) at Day 10 – AUC(0-∞) at Day 1' based on the log-transformed data and after back-transformation of this estimated difference, the geometric mean of the ratio 'AUC(0-tau) at Day 10 : AUC(0-∞) at Day 1' will also be presented.

8.5.3. Population of Interest

This analysis will be based on the PK population.

8.5.4. Strategy for Intercurrent (Post-Randomization) Events

In the Table 6 below, the possible intercurrent events and the rationale for relating them to treatment or otherwise is described. Once a subject discontinues from study treatment, they will proceed straight to follow up and no further data will be collected.

All subjects' data will be included in data listings irrespective of the strategies followed for the analysis.

If feasible, subjects will be replaced until the desired sample size is attained.

Table 6 Strategies for Intercurrent events

Intercurrent events	**Relation to treatment and rationale**	**Strategy, rationale and details of action taken**
Subject withdraws study consent	Not related to treatment/ Subject drops out due to logistic reasons and not due to any event related to treatment	- The strategy will be a **While-on-Treatment strategy,** where we are interested in the treatment effects prior to the withdrawal only. - Subjects' data available up to the withdrawal will be included in the time invariance accumulation rate analyses. - If a subject withdraws consent during a period, the missing data post withdrawal will not be imputed. - The derived PK parameters for e.g., AUC, C_{max} etc. of that partially completed period

		will be calculated if data permits (See section 8.1.1.2 Derived Pharmacokinetic Parameters for details on derivation criteria).
Subject does not take the full treatment	Not related to treatment/ The treatment will be administered as a powder dissolved in diluent. To ensure all treatment is ingested, the bottle containing the dispersion will be rinsed three times and the subject will be expected to ingest this in addition to the initial dispersion. If three rinses are not all ingested, the subject may not take the full treatment dose.	In the current formulation, it is hard to measure the exact proportion of dose ingested if not all rinses are taken. It is also uncertain whether the formulation could change in future development. To account for this, we propose two different strategies described below. If this intercurrent event is not observed, then both strategies will provide the same results and only the hypothetical strategy will be presented for the final analysis. **Primary analysis** - The strategy will be a **Hypothetical strategy,** where we are interested in the treatment effects in a hypothetical scenario where all subjects have taken complete dose. - In this case, the data from a period in which an incomplete dose is taken would be considered as missing at random and excluded from analyses. - If the drug formulation is changed in the future studies, this estimate will provide the true relationship between the actual dose intake and its exposure under this strategy. **Supplementary analysis** - The strategy will be a **Treatment policy strategy,** where we are interested in the treatment effects regardless of the actual amount of dose taken. - The analysis will include PK parameters derived based on concentrations of both complete and partial doses (if data permits based on criteria described in Section 8.1.1.2) and will be analysed using the nominal or prescribed dose. - If the drug formulation remains unchanged in the future studies, this estimate will provide the true relationship between a nominal dose and its exposure under this strategy, i.e. close to a real-world setting.

Subject drops out due to Adverse events	Related to treatment/ If the adverse event is confirmed to be related to study treatment	- The primary strategy will be a **Hypothetical strategy,** where we are interested in the treatment effects in a hypothetical scenario where discontinuation due to an AE would not happen. - The missing data after discontinuation will assumed to be missing at random - The derived PK parameters of the last fully or partially completed period will be calculated if data permits (See section 8.1.1.2 Derived Pharmacokinetic Parameters for details on derivation criteria).

8.5.5. Statistical Analyses / Methods

Details of the planned displays are provided in **Error! Reference source not found.**: List of Data Displays and will be based on GSK Data Standards and statistical principles. Graphical presentations will be provided if appropriate. All data will be listed.

8.5.5.1. Statistical Methodology Specification

The following statistical analyses will only be performed if sufficient data is available (i.e. if subjects have well defined plasma profiles).

Pharmacokinetic analysis will be the responsibility of the Clinical Pharmacology Modelling and Simulation Department, (CPMS) and Statistical analyses of the pharmacokinetic parameters will be the responsibility of the Biostatistics Department.

Statistical analysis for time invariance ratio of GSK3186899 – Repeat dose study part
Endpoint / Variables
• Ratio of AUC(0-tau) on day 10 to AUC(0-∞) on day 1 (This will be calculated only if AUC(0-∞) on day 1 is appropriately estimated)
Model Specification
• Will be statistically analysed using a mixed model (MM) using a $\log_e$-transformation. The mixed model will contain: o Fixed effects: day o Random effect: Subject • AUC(0-∞) on day 1 will be the reference phase in the analysis, while AUC(0-tau) on day 10 will be the test phase for BID (or, TID) regimen respectively, using loge-transformed AUC. • The Kenward and Roger method for approximating the denominator degrees of freedom and correcting for bias in the estimated variance-covariance of the fixed effects will be used. • An unstructured type of the covariance matrices G (accounting for the between subject variability) will be used.

• Based on the intercurrent events observed in the study, appropriate strategies from Table 6 in Section 8.5.4 will be considered for handling of missing data (if any) and interpretation of the analysis results. If multiple intercurrent events are observed (for e.g., if the subject does not take the full treatment as well he withdraws study consent), then the data will be handled using more than one strategy as described in Table 6 and interpretations of the results will be made accordingly.
Model Checking & Diagnostics
• For the Mixed Model, model assumptions will be checked, and appropriate adjustments may be applied based on the data. • Distributional assumptions underlying the model used for analysis will be examined by obtaining a normal probability plot of the residuals and a plot of the residuals versus the fitted values (i.e. checking the normality assumption and constant variance assumption of the model respectively) to gain confidence that the model assumptions are reasonable. • If there are any departures from the distributional assumptions, alternative transformations, such as data squared or square root of data, will be explored. • Non-parametric analyses will be conducted if the normality assumption does not hold for any of the alternative transformations. • If this model fails to converge, alternative covariance structures may be considered in the following order (1) Compound Symmetry (CS) and (2) Variance Components (VC).
Model Results Presentation
• The summary measure will be the point estimate and 90% CIs of mean difference of 'AUC(0-tau) at Day 10 – AUC(0-∞) at Day 1' based on the log-transformed data and after back-transformation of this estimated difference, the geometric mean of the ratio 'AUC(0-tau) at Day 10 : AUC(0-∞) at Day 1' will also be presented.

9. REFERENCES

- Alves F, Bilbe G, Blesson S et al. Recent development of visceral leishmaniasis treatments: success, pitfalls and perspectives. *Clin Microbiol Rev*. 2018 Aug 29; 31(4):e00048-18.
- Committee for Human Medicinal Products. ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials, Step 2b. London: European Medicines Evaluation Agency, August 2017.
- Dorlo TP, Rijal S, Ostyn B, de Vries PJ, Singh R, Bhattarai N, Uranw S, Dujardin JC, Boelaert M, Beijnen JH, Huitema AD. Failure of miltefosine in visceral leishmaniasis is associated with low drug exposure. *J Infect Dis.* 2014 Jul 1;210(1):146-53.
- Dorlo TP1, Huitema AD, Beijnen JH, de Vries PJ. Optimal dosing of miltefosine in children and adults with visceral leishmaniasis. *Antimicrob Agents Chemother*. 2012 Jul;56(7):3864-72.
- FDA Guidance for industry: Estimating the maximum safe dose in initial clinical trials for therapeutics in adult healthy volunteers. 2005 http://www.fda.gov/downloads/Drugs/Guidances/UCM078932.pdf

10. APPENDICES

10.1. Appendix 1: Protocol Deviation Management and Definitions for Per Protocol Population

10.1.1. Exclusions from Analysis Population

Per protocol population is not defined in this protocol.

Important protocol deviations and violations of the inclusion and exclusion criteria will be listed.

10.2. Appendix 2: Schedule of Activities

10.2.1. Protocol Defined Schedule of Events in 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 made full exams, by the Investigator, as deemed necessary (e.g. where safety or laboratory findings indicate). Tests will be conducted within site specified standards.*
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							
HIV, Hepatitis B and C Screening	X							
FSH + Oestradiol	X							*Females only, if required*
Holter Monitoring (48 hours)	X							
Haem/Chem/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 10 hrs, and 5 mL for time-points 12hr and 24 hr.*
12-Lead ECG	X	X	T	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 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, 1 hr, 1.5hr, 2hr, 2.5hr, 4hr, 8hs, 12hr, 24 hr, 48 hr* *Timings will be reviewed as cohorts progress and may be adjusted to ensure appropriate measurements relative to peak concentrations for subsequent cohorts.* *T = Triplicate (for all assessments, except temperature and respiratory rate).* *If any abnormal ECG reading is recorded, refer to Section* ***Error! Reference source not found.*** *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 3 hours after dosing.* ***Fed regimen:*** *On Day 1, participants will fast 8hr overnight and an adapted standard breakfast will be served approximately 30 minutes 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 1 hour 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 2 hr post-dose, after 5 hr the bile string will be removed.*
Randomization			X					
Study Treatment			X					
AE Review		←=======X=======→					X	
SAE Review	X	←=======X=======→					X	
Concomitant Medication Review	X	←=======X=======→					X	

10.2.2. Protocol Defined Schedule of Events in 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 made full exams, by the Investigator, as deemed necessary (e.g. where safety or laboratory findings indicate). Tests will be conducted within site specified standards.*
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	
Haem/Chem/ Urinalysis Test (Include Liver Chemistries)	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 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 of Protocol.*

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 **Error! Reference source***
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	
																	not found. *of protocol for appropriate action.*
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 of Protocol for alternative PK blood sampling time-points.* *Blood volumes to be collected include:* • *2 mL for post-dose 0-11 hrs, and* • *5 mL for post-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).

10.3. Appendix 3: Assessment Windows

10.3.1. Definitions of Assessment Windows for Analyses

Nominal time will be used for all analysis except PK analysis where planned and actual time will be used.

10.4. Appendix 4: Study Phases and Treatment Emergent Adverse Events

10.4.1. Study Phases

For each period in Part A Cohorts 1, 2 and 3, assessments and events will be classified according to the following phases:

Study Phase	Definition
Pre-Treatment	Date and time < Study Treatment Start Date and time of each period
Treatment	Study Treatment Start Date and time ≤ Date and time ≤ Study Treatment End Date and time + 24 hours, in each period
Post-Treatment	Date and time > Study Treatment End Date and time + 24 hours, within each period

Note: Estimated half-life of GSK3186899 is approx. 1.3 hours. The maximum of (5 half-lives (~ 6.5 hours) and 24 hours) after the Study Treatment End Date and time have been considered to define the end of treatment phase. If half-life is longer than 5 hours, then the definition will be revised accordingly.

Post-treatment phase will additionally include any events occurring in the washout period before start of the next treatment dose.

For the interim, the start of the period will be defined from the first dose of the period and then the end of the period is just before the first dose in the next period. For the final period the end date is just before the withdrawal/follow up visit.

For Part B Cohorts 4, 5 and 6, assessments and events will be classified according to the following:

Study Phase	Definition
Pre-Treatment	Date < Study Treatment Start Date of each Cohort
Treatment	Study Treatment Start Date and time ≤ Date and time ≤ Study Treatment End Date and time + 24 hours, in each cohort
Post-Treatment	Date and time > Study Treatment End Date and time 24 hours, in each cohort

Note: Estimated half-life of GSK3186899 is approx. 1.3 hours. The maximum of (5 half-lives (~ 6.5 hours) and 24 hours) after the Study Treatment End Date and time have been considered to define the end of treatment phase. If half-life is longer than 5 hours, then the definition will be revised accordingly.

10.4.1.1. Study Phases for Concomitant Medication

Study Phase	Definition
Prior	If medication end date is not missing and is before to the screening visit
Concomitant	Any medication that is not a prior

NOTES:

- Please refer to Appendix 7: Reporting Standards for Missing Data for handling of missing and partial dates for concomitant medication. Use the rules in this table if concomitant medication date is completely missing.

10.4.2. Treatment Emergent Flag for Adverse Events

Flag	Definition

Treatment Emergent	• If AE onset date is on or after treatment start date and time, it is considered as treatment emergent
	• For Part A, if AE onset is during one period and worsens during a later period it would be counted in both periods.
	  ○ For the initial period the logic would be as above.
	  ○ For the later period the logic would use the treatment dates associated with the later period:
	  Treatment Period Start Date ≤ AE Worsening Date ≤ Study Treatment Stop Date

NOTES:

- If the study treatment stop date is missing, then the AE will be considered as On-Treatment.
- Time of study treatment dosing and start/stop time of AEs should be considered, if collected.

10.5. Appendix 5: Data Display Standards & Handling Conventions

10.5.1. Reporting Process

Software	
• The currently supported versions of SAS software will be used.	
Reporting Area	
HARP Server	: \\UK1SALX00175.corpnet2.com\
HARP Compound	: \arprod\gsk3186899\mid208436\
Analysis Datasets	
• Analysis datasets will be created according to CDISC standards (SDTM IG Version 3.2 & ADaM IG Version 1.1]	
Generation of RTF Files	
• RTF files will be generated for SAC.	

10.5.2. Reporting Standards

General

- The current GSK Integrated Data Standards Library (IDSL) will be applied for reporting, unless otherwise stated (IDSL Standards Location: https://spope.gsk.com/sites/IDSLLibrary/SitePages/Home.aspx):
  - 4.03 to 4.23: General Principles
  - 5.01 to 5.08: Principles Related to Data Listings
  - 6.01 to 6.11: Principles Related to Summary Tables
  - 7.01 to 7.13: Principles Related to Graphics
- Do not include subject level listings in the main body of the GSK Clinical Study Report. All subject level listings should be located in the modular appendices as ICH or non-ICH listings

Formats

- GSK IDSL Statistical Principles (5.03 & 6.06.3) for decimal places (DP's) will be adopted for reporting of data based on the raw data collected, unless otherwise stated.
- Numeric data will be reported at the precision collected on the eCRF.
- The reported precision from non eCRF sources will follow the IDSL statistical principles as indicated below but may be adjusted to a clinically interpretable number of DP's.
  - Display all numeric variables with the same number of decimal places as the collected precision.
  - Display minimum and maximum values with the same number of decimal places as the collected precision.
  - Display the mean and percentiles (e.g. median, Q1, and Q3) with one additional decimal place.
  - Display the standard deviation and standard error with two additional decimal places.
  - Within a column, align all data values or summary statistics along the decimal point.

The reported precision for PK concentration data will be 1 decimal place but may be altered by parameter depending on the significant digits.
Planned and Actual Time

• Reporting for tables, figures and formal statistical analyses:
  • Planned time relative to dosing will be used in figures, summaries, statistical analyses and calculation of any derived parameters, unless otherwise stated.
  • The impact of any major deviation from the planned assessment times and/or scheduled visit days on the analyses and interpretation of the results will be assessed as appropriate.
• Reporting for Data Listings:
  • Planned and actual time relative to study drug dosing will be shown in listings (Refer to IDSL Statistical Principle 5.05.1).
  • Unscheduled or unplanned readings will be presented within the subject's listings.

Unscheduled Visits
• Unscheduled visits will not be included in summary tables and figures. • All unscheduled visits will be included in listings.

Descriptive Summary Statistics	
Continuous Data	Refer to IDSL Statistical Principle 6.06.1
Categorical Data	N, n, frequency, %

Graphical Displays
• Refer to IDSL Statistical Principals 7.01 to 7.13.

10.5.3. Reporting Standards for Pharmacokinetic

Pharmacokinetic Concentration Data	
PC Windows Non-Linear (WNL) File	PC WNL file (CSV format) for the non-compartmental analysis by Clinical Pharmacology Modelling and Simulation function will be created according to [SOP_514512]. Note: Concentration values will be imputed as per GUI_51487
Descriptive Summary Statistics, Graphical Displays and Listings	Refer to IDSL PK Display Standards. Refer to IDSL Statistical Principle 6.06.1. Note: Concentration values will be imputed as per GUI_51487 for descriptive summary statistics/analysis and summarized graphical displays only.
Pharmacokinetic Parameter Derivation	
PK Parameter to be Derived by Programmer	None. All PK parameters will be derived by the CPMS Pharmacokineticist.
Pharmacokinetic Parameter Data	
Is NQ impacted PK Parameters Rule Being Followed	Yes, refer to Standards for Handling NQ Impacted PK Parameters guidance.
Descriptive Summary Statistics, Graphical Displays and Listings	Refer to IDSL PK Display Standards. Log_e-transformed data: N, n, geometric mean, 95% CI of geometric mean, standard deviation (SD) of log_e transformed data and between subject

	geometric coefficient of variation (CV_b (%)) will be reported. CV_b (%) = $\sqrt{}$ (exp(SD^2) – 1) * 100 [NOTE: SD = SD of log_e transformed data] Parameters Not Being Log_e Transformed: Tmax and T1/2.

10.6. Appendix 6: Derived and Transformed Data

10.6.1. General

Multiple Measurements at One Analysis Time Point
• Mean of the measurements will be calculated and used in any derivation of summary statistics but if listed, all data will be presented. • Participants having both High and Low values for Normal Ranges at any post-baseline visit for safety parameters will be counted in both the High and Low categories of "Any visit post-baseline" row of related summary tables. This will also be applicable to relevant Potential Clinical Importance summary tables.
Study Day and Period Study Day

• **In PART A for each period**: Period Study day is calculated as the number of days from first Dose Date in the period for each subject as follows:
  • Ref Date = Missing → Period Study Day = Missing
  • Ref Date < First Dose Date in the period → Period Study Day = Ref Date – First Dose Date
  • Ref Data ≥ First Dose Date in the period→ Period Study Day = Ref Date – First Dose Date + 1
• **In Part A and Part B**: Study day is calculated as the number of days from First Dose Date in each Cohort for each subject as:
  • Ref Date = Missing → Study Day = Missing
  • Ref Date < First Dose Date → Study Day = Ref Date - First Dose Date
  • Ref Data ≥ First Dose Date → Study Day = Ref Date – (First Dose Date) + 1

10.6.2. Study Population

Treatment Exposure and Compliance
For Parts A and B: • Treatment compliance will be calculated based on the formula: **Treatment Compliance = Number of Doses taken/ (Planned Treatment Duration in Days * Frequency)** where Frequency will be 1 for OD, 2 for BID or 3 for TID. Treatment compliance could be greater than 100% if there are events of overdose. • Planned Treatment Duration is defined as 10 days, for each Cohort in Part B. As Part A is single dose this would be one day. • Number of days of exposure to study drug will be calculated based on the formula: **Duration of Exposure (in Days) = Treatment Stop Date – (Treatment Start Date) + 1** • Participants who were randomized but did not report a treatment start date will be categorised as having zero days of exposure. **For Part B:** • The cumulative dose will be based on the formula: **Cumulative Dose = Sum of (Number of Days x Total Daily Dose)**

Treatment Exposure and Compliance
• If there are any treatment breaks during the study, exposure data will be adjusted accordingly.

Demographics
Age
• GSK standard IDSL algorithms will be used for calculating age where birth date will be imputed as follows: o Any participant with a missing day will have this imputed as day '15'. o Any participant with a missing date and month will have this imputed as '30th June'. • Birth date will be presented in listings as 'YYYY'.
Body Mass Index (BMI)
• Calculated as Weight (kg) / [Height (m)]^2

10.6.3. Safety

Adverse Events
[AE'S OF Special Interest]
• Stomach erosion • Adrenal insufficiency • Renal impairment (Note: Protocol defines renal stopping and withdrawal criteria which are not "renal impairment" in the strict sense)

Laboratory Parameters
• If a laboratory value which is expected to have a numeric value for summary purposes, has a non-detectable level reported in the database, where the numeric value is missing, but typically a character value starting with '<x' or '>x' (or indicated as less than x or greater than x in the comment field) is present, the number of decimal places in the observed values will be used to determine how much to add or subtract in order to impute the corresponding numeric value. o Example 1: 2 Decimal Places = '< x' becomes x – 0.01 o Example 2: 1 Decimal Places = '> x' becomes x + 0.1 o Example 3: 0 Decimal Places = '< x' becomes x – 1 o For values '<=x' or '>=x' the value itself ('x') should be imputed as the numeric value.
• Renal biomarker data will be included in the final study analysis. The parameters will be corrected using the following formula, and the units are ng/mg Corrected KIM-1=8.8*Urine KIM-1(pG/mL)/Urine Creatinine (umol/L) Corrected NGAL=8800*Urine NGAL(nG/mL)/Urine Creatinine (umol/L)

10.6.4. Pharmacokinetic

PK parameters
• The PK Population will include all subjects who undergo PK sampling and have evaluable PK concentration results. • See Section 8.1 for derived Pharmacokinetic parameters

10.7. Appendix 7: Reporting Standards for Missing Data

10.7.1. Premature Withdrawals

Element	Reporting Detail
General	• Subject study completion (i.e. as specified in the protocol) was defined as the completion of all phases of the study including the last scheduled procedure shown in SoA (Appendix 2). The end of 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. • Withdrawn subjects may be replaced in the study. • All available data from participants who were withdrawn from the study will be listed and all available planned data will be included in summary tables and figures, unless otherwise specified.

10.7.2. Handling of Missing Data

Element	Reporting Detail
General	• Missing data occurs when any requested data is not provided, leading to blank fields on the collection instrument. Unless specified otherwise, o These data will be indicated by the use of a “blank” in subject listing displays. Unless all data for a specific visit are missing in which case the data is excluded from the table. o Answers such as “Not applicable” and “Not evaluable” are not considered to be missing data and should be displayed as such. Missing safety data (for e.g., lab, ECG, Vitals, etc.) will not be imputed. Missing PK data may be imputed (if required) by the Estimand strategy and will be outlined in the final RAP.
Outliers	• Any participants excluded from the summaries and/or statistical analyses will be documented along with the reason for exclusion in the clinical study report.

10.7.2.1. Handling of Missing and Partial Dates

Element	Reporting Detail
General	• Partial dates will be displayed as captured in subject listing displays.
Adverse Events	• Missing or Partial start/end date and time are not expected for Adverse events.
Concomitant Medications/ Medical History	Partial dates for any concomitant medications recorded in the CRF will be imputed using the following convention: • If the partial date is a start date, a '01' will be used for the day and 'Jan' will be used for the month • If the partial date is a stop date, a '28/29/30/31' will be used for the day (dependent on the month and year) and 'Dec' will be used for the month. The recorded partial date will be displayed in listings. • For assigning periods:

Element	Reporting Detail
	• If start date is completely missing, then we assume the medication has been taken from the beginning of the study • If stop date is completely missing, then we assume the medication has been taken until the end of the study If start and stop date are completely missing, then we assume the medication has been taken for the duration of the study

10.8. Appendix 8: Values of Potential Clinical Importance

The values of potential clinical importance for Laboratory, ECG and Vital signs are listed in this section.

10.8.1. Laboratory Values

Haematology				
Laboratory Parameter	**Units**	**Category**	**Clinical Concern Range**	
			Low Flag (< x)	**High Flag (>x)**
Hematocrit	%	Male	<37	>50
		Female	<33	>45
		Δ from BL	N/A	> 7.5%
Hemoglobin	g/L	Male	<130	>170
		Female	<115	>155
		Δ from BL	N/A	> 30 g/L
Lymphocytes	$x10^9$/ L		<1.2	>3.65
Neutrophils	$x10^9$/ L		<2	>7.5
Monocytes	$x10^9$/ L		<0.2	>1
Basophils	$x10^9$/ L		<0.0	>0.1
Platelet Count	$x10^9$/ L		<150	>400
While Blood Cell Count (WBC)	$x10^9$/ L		<3.0	>10
Red Blood Cell Count (RBC)	$x10^{12}$/L	Male	<4.4	>5.8
		Female	<3.95	>5.15

Clinical Chemistry				
Laboratory Parameter	**Units**	**Category**	**Clinical Concern Range**	
			Low Flag (< x)	**High Flag (>x)**
Albumin	g/L		< 34	> 50
Calcium	mmol/L		< 2.2	> 2.6
Creatinine	umol/L	Male	< 66	> 112
		Female	< 49	> 92
Glucose (Fasted)	mmol/L		< 3.9	> 5.8
Magnesium	mmol/L		< .6	> 1
Phosphate	mmol/L		< 0.87	> 1.45
Potassium	mmol/L		< 3.5	> 5.1
Sodium	mmol/L		< 135	> 145
Gamma GT	g/L		< 7.7	> 17.3

Liver Function				
Test Analyte	**Units**	**Category**	**Clinical Concern Range**	
			Low Flag (< x)	**High Flag (>x)**
Alkaline phosphatase	U/L	Female	< 35	> 104
		Male	< 40	> 129
AST/SGOT	U/L	Male	< 0	> 37
		Female	< 0	> 31
ALT/SGPT	U/L	Male	< 10	> 50
		Female	< 10	> 35
Total Bilirubin	µmol/L		< 0	> 20
Direct Bilirubin	µmol/L		< 0	> 20
Total Protein	g/L		< 63	> 83

10.8.2. ECG

ECG Parameter	**Units**	**Clinical Concern Range**	
		Lower	**Upper**
Absolute			
Absolute QTcF during the study (i.e. post dose)	msec		>500
Absolute PR Interval	msec	< 110	>220
Absolute QRS Interval	msec	< 75	>120
Change from Baseline			
Increase from Baseline QTc	msec		>60

10.8.3. Vital Signs

Vital Sign Parameter (Absolute)	**Units**	**Clinical Concern Range**	
		Lower	**Upper**
Systolic Blood Pressure	mmHg	<85	>160
Diastolic Blood Pressure	mmHg	<45	>100
Heart Rate	bpm	<40	>110
Tympanic temperature	°C	<35	>38
Respiratory rate	Breaths/min	<10	>25

10.9. Appendix 9: Population Pharmacokinetic (PopPK) Analyses

Not applicable.

10.10. Appendix 10: Pharmacokinetic / Pharmacodynamic Analyses

Not applicable.

10.11. Appendix 11: Abbreviations & Trade Marks

10.11.1. Abbreviations

Abbreviation	Description
ADaM	Analysis Data Model
AE	Adverse Event
AIC	Akaike's Information Criteria
AUC	Area under the concentration-time curve
A&R	Analysis and Reporting
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
Cmax	Maximum observed concentration
CPMS	Clinical Pharmacology Modelling & Simulation
CS	Clinical Statistics
CSR	Clinical Study Report
CTR	Clinical Trial Register
CV_b / CV_w	Coefficient of Variation (Between) / Coefficient of Variation (Within)
DBF	Database Freeze
DBR	Database Release
DEC	Dose escalation committee
DOB	Date of Birth
DP	Decimal Places
ECG	Electrocardiogram
eCRF	Electronic Case Record Form
EMA	European Medicines Agency
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Clinical Results Disclosure Requirements
FTIH	First Time in Human
GSK	GlaxoSmithKline
IA	Interim Analysis
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
IDSL	Integrated Data Standards Library
IMMS	International Modules Management System

Abbreviation	Description
IP	Investigational Product
LDH	Lactate Dehydrogenase
MAD	Multiple Ascending Dose
MCH	Mean Corpuscular Haemoglobin
MCV	Mean Corpuscular Volume
NGAL	Neutrophil gelatinase-associated lipocalin
NOAEL	No Observable Adverse Effect Limit
PCI	Potential Clinical Importance
PD	Pharmacodynamic
PDMP	Protocol Deviation Management Plan
PK	Pharmacokinetic
PP	Per Protocol
PopPK	Population PK
QC	Quality Control
QTc	Electrocardiogram QT interval corrected for heart rate
QTcF	Frederica's QT Interval Corrected for Heart Rate
QTcB	Bazett's QT Interval Corrected for Heart Rate
RAP	Reporting & Analysis Plan
RBC	Red Blood Cells
RAUC	Relative Area Under the Curve
RAMOS	Randomization & Medication Ordering System
SAC	Statistical Analysis Complete
SAD	Single Ascending dose
SAE	Serious Adverse Event
SDD	Spray Dried Dispersion
SDSP	Study Data Standardization Plan
SDTM	Study Data Tabulation Model
SGOT	Serum Glutamic-Oxaloacetic Transaminase
SGPT	Serum Glutamic-Pyruvic Transaminase
SOA	Schedule of Activities
SOP	Standard Operation Procedure
SRM	Study Reference Manual
SUSAR	Suspected Unexpected Serious Adverse Events
TA	Therapeutic Area
TFL	Tables, Figures & Listings
TID	Three-Times Daily
Tmax	Time Taken to Maximum Observed Plasma Drug Concentration
Tlag	Lag time before observation of drug concentrations
t1/2	Terminal phase half-life
τ	Dosing interval
UK	United Kingdom
ULN	Upper Limit of Normal
VL	Visceral Leishmaniasis

Abbreviation	Description
WONCBP	Women of Non-Child Bearing Potential

10.11.2. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies

Trademarks not owned by the GlaxoSmithKline Group of Companies
WinNonlin
SAS
NONMEM

10.12. Appendix 12: List of Data Displays

10.12.1. Data Display Numbering

The following numbering will be applied for RAP generated displays:

Section	Tables	Figures
Study Population	1.1 to 1.22	None
Efficacy	Not applicable	Not applicable
Safety	3.1 to 3.34	None
Pharmacokinetic	4.1 to 4.11	4.1 to 4.10
Section	**Listings**	
ICH Listings	1 to 65	
Other Listings	66 to 80	

10.12.2. Mock Example Shell Referencing

Non-integrated data standards library (IDSL) specifications will be referenced as indicated and if required example mock-up displays provided in

Appendix 11: Example Mock Shells for Data Displays.

Section	Figure	Table	Listing
Study Population	POP_Fn	POP_Tn	POP_Ln
Safety	SAFE_Fn	SAFE_Tn	SAFE_Ln
Pharmacokinetic	PK_Fn	PK_Tn	PK_Ln

NOTES:

- Non-Standard displays are indicated in the 'IDSL / Example Shell' column as '[Non-Standard] + Reference.'

10.12.3. Deliverables

Delivery	Description
IA	Informal Interim Analysis (displays to be prepared by Biostatistics function)
SAC	Final Statistical Analysis Complete

10.12.4. Study Population Tables

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition					
1.1.	Safety	ES1A	Summary of Participant Disposition for the Participant Conclusion Record – Part A	ICH E3, FDAAA, EudraCT	IA, SAC
1.2.	Safety	ES1	Summary of Participant Disposition for the Participant Conclusion Record – Part B	ICH E3, FDAAA, EudraCT	SAC
1.3.	Safety	SD1	Summary of Treatment Status and Reasons for Discontinuation of Study Treatment – Part B	ICH E3	SAC
1.4.	Safety	ES4	Summary of Participant Disposition at Each Study Epoch – Part A	ICH E3	SAC
1.5.	Safety	ES4	Summary of Participant Disposition at Each Study Epoch – Part B	ICH E3	SAC
1.6.	Screened	ES6	Summary of Screening Status and Reasons for Screen Failure – Part A		SAC
1.7.	Screened	ES6	Summary of Screening Status and Reasons for Screen Failure – Part B		SAC
Protocol Deviation					
1.8.	Safety	DV1	Summary of Important Protocol Deviations – Part A	ICH E3	SAC
1.9.	Safety	DV1	Summary of Important Protocol Deviations – Part B	ICH E3	SAC
Population Analysed					
1.10.	Enrolled	SP1	Summary of Study Populations – Part A		IA, SAC

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
1.11.	Enrolled	SP1	Summary of Study Populations – Part B		SAC
Demographic and Baseline Characteristics					
1.12.	Safety	DM3	Summary of Demographic Characteristics – Part A	ICH E3, FDAAA, EudraCT	IA, SAC
1.13.	Safety	DM1	Summary of Demographic Characteristics – Part B	ICH E3, FDAAA, EudraCT	SAC
1.14.	Enrolled	DM11	Summary of Age Ranges – Part A	EudraCT	SAC
1.15.	Enrolled	DM11	Summary of Age Ranges – Part B	EudraCT	SAC
1.16.	Safety	DM5	Summary of Race and Racial Combinations – Part A	ICH E3, FDA, FDAAA, EudraCT	SAC
1.17.	Safety	DM5	Summary of Race and Racial Combinations – Part B	ICH E3, FDA, FDAAA, EudraCT	SAC
Prior and Concomitant Medications					
1.18.	Safety	CM1	Summary of Concomitant Medications – Part A	ICH E3	SAC
1.19.	Safety	CM1	Summary of Concomitant Medications – Part B	ICH E3	SAC
Exposure and Treatment Compliance					
1.20.	Safety	EX1	Summary of Exposure to Study Treatment – Part A	ICH E3	IA, SAC
1.21.	Safety	EX1	Summary of Exposure to Study Treatment - Part B	ICH E3	SAC
1.22.	Safety	COMP1	Summary of Overall Compliance Based on Exposure –Part B		SAC

10.12.5. Safety Tables

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Adverse Events (AEs)					
3.1.	Safety	AE1CP	Summary of All Adverse Events by System Organ Class and Preferred Term – Part A	ICH E3	IA, SAC
3.2.	Safety	AE1	Summary of All Adverse Events by System Organ Class and Preferred Term – Part B	ICH E3	SAC
3.3.	Safety	AE3	Summary of Common (>=5%) Adverse Events by Overall Frequency – Part A	FDAAA, EudraCT	SAC
3.4.	Safety	AE3	Summary of Common (>=5%) Adverse Events by Overall Frequency – Part B	FDAAA, EudraCT	SAC
3.5.	Safety	AE1	Summary of All Drug Related Adverse Events by System Organ Class and Preferred Term – Part A	ICH E3	SAC
3.6.	Safety	AE1	Summary of All Drug Related Adverse Events by System Organ Class and Preferred Term – Part B	ICH E3	SAC
Serious and Other Significant Adverse Events					
3.7.	Safety	AE16	Summary of Serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences) – Part A	FDAAA, EudraCT	SAC
3.8.	Safety	AE16	Summary of Serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences) – Part B	FDAAA, EudraCT	SAC
Laboratory: Chemistry					
3.9.	Safety	LB1	Summary of Chemistry Changes from Baseline – Part A	ICH E3	SAC
3.10.	Safety	LB1	Summary of Chemistry Changes from Baseline – Part B	ICH E3	SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
3.11.	Safety	LB17	Summary of Worst-Case Chemistry Results by PCI Criteria Post-Baseline Relative to Baseline – Part A	ICH E3	SAC
3.12.	Safety	LB17	Summary of Worst-Case Chemistry Results by PCI Criteria Post-Baseline Relative to Baseline – Part B	ICH E3	SAC
Laboratory: Haematology					
3.13.	Safety	LB1	Summary of Haematology Changes from Baseline – Part A	ICH E3	SAC
3.14.	Safety	LB1	Summary of Haematology Changes from Baseline – Part B	ICH E3	SAC
3.15.	Safety	LB17	Summary of Worst-Case Haematology by PCI Criteria Post-Baseline Relative to Baseline – Part A	ICH E3	SAC
3.16.	Safety	LB17	Summary of Worst-Case Haematology by PCI Criteria Post-Baseline Relative to Baseline – Part B	ICH E3	SAC
Laboratory: Urinalysis					
3.17.	Safety	LB1	Summary of Urine Concentration Changes from Baseline – Part A	ICH E3 Includes Baseline values.	SAC
3.18.	Safety	LB1	Summary of Urine Concentration Changes from Baseline – Part B	ICH E3 Includes Baseline values.	SAC
3.19.	Safety	UR3a	Summary of Urinalysis Dipstick and Microscopy Results – Part A		SAC
3.20.	Safety	UR3a	Summary of Urinalysis Dipstick and Microscopy Results – Part B		SAC
3.21.	Safety	UR1	Summary of Worst-Case Urinalysis Results Post-Baseline Relative to Baseline – Part A	ICH E3	SAC
3.22.	Safety	UR1	Summary of Worst-Case Urinalysis Results Post-Baseline Relative to Baseline – Part B	ICH E3	SAC
Laboratory: Hepatobiliary (Liver)					

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
3.23.	Safety	LIVER1	Summary of Liver Monitoring/Stopping Event Reporting – Part A		SAC
3.24.	Safety	LIVER1	Summary of Liver Monitoring/Stopping Event Reporting – Part B		SAC
3.25.	Safety	LIVER10	Summary of Hepatobiliary Laboratory Abnormalities – Part A		SAC
3.26.	Safety	LIVER10	Summary of Hepatobiliary Laboratory Abnormalities – Part B		SAC
ECG					
3.27.	Safety	EG1	Summary of ECG Findings – Part A		SAC
3.28.	Safety	EG1	Summary of ECG Findings – Part B		SAC
3.29.	Safety	EG2	Summary of Change from Baseline in ECG Values by Visit – Part A	Includes Baseline values.	SAC
3.30.	Safety	EG2	Summary of Change from Baseline in ECG Values by Visit – Part B	Includes Baseline values.	SAC
Vital Signs					
3.31.	Safety	VS1	Summary of Change from Baseline in Vital Signs - Part A	ICH E3 Includes Baseline values.	SAC
3.32.	Safety	VS1	Summary of Change from Baseline in Vital Signs - Part B	ICH E3 Includes Baseline values.	SAC
3.33.	Safety	VS7	Summary of Worst-Case Vital Signs Results by PCI Criteria Post-Baseline Relative to Baseline – Part A		SAC
3.34.	Safety	VS7	Summary of Worst-Case Vital Signs Results by PCI Criteria Post-Baseline Relative to Baseline – Part B		SAC

10.12.6. Pharmacokinetic Tables

Pharmacokinetic: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Pharmacokinetic Concentration Data					
4.1.	PK	PK01	Summary of GSK3186899 Plasma Pharmacokinetic Concentration-Time Data - Part A		SAC
4.2.	PK	PK01	Summary of GSK3186899 Plasma Pharmacokinetic Concentration-Time Data - Part B		SAC
Derived Pharmacokinetic Parameters					
4.3.	PK	PK06	Summary of Non-transformed Derived GSK3186899 Plasma Pharmacokinetic Parameters by Dose - Part A		SAC
4.4.	PK	PK06	Summary of Non-transformed Derived GSK3186899 Plasma Pharmacokinetic Parameters by Dose - Part B		SAC
4.5.	PK	PK05	Summary of Log_e-Transformed Derived GSK3186899 Plasma Pharmacokinetic Parameters by Dose - Part A		SAC
4.6.	PK	PK05	Summary of Log_e-Transformed Derived GSK3186899 Plasma Pharmacokinetic Parameters by Dose - Part B		SAC
4.7.	PK	Non-standard PK_T1	Statistical analysis for comparison of food effect in Part A Cohort 3		SAC
4.8.	PK	Non-standard PK_T2	Statistical Analysis of Log Transformed Plasma GSK3186899 Pharmacokinetic Parameters Assessing Dose Proportionality (Power Model) – Part A		SAC
4.9.	PK	Non-standard PK_T3	Statistical Analysis of Log Transformed Plasma GSK3186899 Pharmacokinetic Parameters Assessing Dose Proportionality (Power Model) – Part B		SAC
4.10.	PK	Non-standard PK_T4	Statistical Analysis of Log-transformed Plasma GSK3186899 Parameters Assessing Steady-State – Part B		SAC

Pharmacokinetic: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
4.11.	PK	Non-standard PK_T4	Time invariance analysis of log-transformed Plasma GSK3186899 Parameters – Part B	Update the parameters for time invariance analysis	SAC

10.12.7. Pharmacokinetic Figures

Pharmacokinetic: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Pharmacokinetic Concentration Data					
4.1.	PK	PK16	Individual Plasma GSK3186899 Concentration-Time Plot (Linear and Semi-Log)– Part A		SAC
4.2.	PK	PK16	Individual Plasma GSK3186899 Concentration-Time Plot (Linear and Semi-Log)– Part B		SAC
4.3.	PK	PK19	Mean (+ SD) Plasma GSK3186899 Concentration-Time Plots (Linear and Semi-Log)- Part A		SAC
4.4.	PK	PK19	Mean (+ SD) Plasma GSK3186899 Concentration-Time Plots (Linear and Semi-Log)- Part B		SAC
4.5.	PK	PK20	Median (range) Plasma GSK3186899 Concentration-Time Plots (Linear and Semi-Log)- Part A		SAC
4.6.	PK	PK20	Median (range) Plasma GSK3186899 Concentration-Time Plots (Linear and Semi-Log)- Part B		SAC
Derived Pharmacokinetic Parameters					
4.7.	PK	Non-standard PK_F1	Box Plot of AUC(0-∞) and Cmax versus dose (Linear) – Part A		SAC
4.8.	PK	Non-standard PK_F1	Box Plot of AUC(0-∞) and Cmax versus dose (Linear) – Part B	AUC(0-tau) on day 10	SAC
4.9.	PK	Non-standard PK_F1	Box Plot of dose normalised AUC(0-∞) versus dose (Linear) – Part A		SAC
4.10.	PK	Non-standard PK_F1	Box Plot of dose normalised AUC(0-∞) and Cmax versus dose (Linear) - Part B	AUC(0-tau) on day 10	SAC

10.12.8. ICH Listings

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Subject Disposition					
1.	Screened	ES7	Listing of Reasons for Screen Failure – Part A		SAC
2.	Screened	ES7	Listing of Reasons for Screen Failure – Part B		SAC
3.	Screened	ES9	Listing of Subjects Who Were Rescreened by Cohort – Part A		SAC
4.	Screened	ES9	Listing of Subjects Who Were Rescreened in Part B by Cohort – Part B		SAC
5.	Safety	ES3	Listing of Reasons for Study Withdrawal – Part A	ICH E3	IA, SAC
6.	Safety	ES2	Listing of Reasons for Study Withdrawal – Part B	ICH E3	SAC
7.	Safety	SD3	Listing of Reasons for Study Treatment Discontinuation – Part A	ICH E3	IA, SAC
8.	Safety	SD2	Listing of Reasons for Study Treatment Discontinuation – Part B	ICH E3	SAC
9.	Enrolled	BL1	Listing of Participants for Whom the Treatment Blind was Broken – Part A	ICH E3	SAC
10.	Enrolled	BL1	Listing of Participants for Whom the Treatment Blind was Broken – Part B	ICH E3	SAC
11.	Enrolled	TA1	Listing of Planned and Actual Treatments - Part A		SAC
12.	Enrolled	TA1	Listing of Planned and Actual Treatments - Part B		SAC
Protocol Deviations					
13.	Safety	DV2	Listing of Important Protocol Deviations – Part A	ICH E3	IA, SAC
14.	Safety	DV2	Listing of Important Protocol Deviations – Part B	ICH E3	SAC

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
15.	Safety	IE3	Listing of Subjects with Inclusion/Exclusion Criteria Deviations - Part A	ICH E3	SAC
16.	Safety	IE3	Listing of Subjects with Inclusion/Exclusion Criteria Deviations – Part B	ICH E3	SAC
Populations Analysed					
17.	Safety	SP3	Listing of Subjects Excluded from Any Population – Part A	ICH E3	SAC
18.	Safety	SP3	Listing of Subjects Excluded from Any Population – Part B	ICH E3	SAC
Demographic and Baseline Characteristics					
19.	Safety	DM4	Listing of Demographic Characteristics – Part A	ICH E3 Include BMI and smoking status.	IA, SAC
20.	Safety	DM2	Listing of Demographic Characteristics – Part B	ICH E3 Include BMI and smoking status.	SAC
21.	Safety	DM9	Listing of Race – Part A	ICH E3	SAC
22.	Safety	DM9	Listing of Race – Part B	ICH E3	SAC
Prior and Concomitant Medications					
23.	Safety	CP_CM3	Listing of Concomitant Medications– Part A	IDSL	SAC
24.	Safety	CP_CM3	Listing of Concomitant Medications– Part B	IDSL	SAC
Exposure and Treatment Compliance					
25.	Safety	EX4	Listing of Exposure Data - Part A	ICH E3	IA, SAC
26.	Safety	EX3	Listing of Exposure Data - Part B	ICH E3	SAC
27.	Safety	COMP2	Listing of Compliance Based on Exposure –Part B		
Adverse Events					
28.	Safety	AE9	Listing of All Adverse Events – Part A	ICH E3	IA, SAC

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
29.	Safety	AE8	Listing of All Adverse Events – Part B	ICH E3	SAC
30.	Safety	AE7	Listing of Subject Numbers for Individual Adverse Events – Part A	ICH E3	SAC
31.	Safety	AE7	Listing of Subject Numbers for Individual Adverse Events – Part B	ICH E3	SAC
Serious and Other Significant Adverse Events					
32.	Safety	AE8CP	Listing of Serious Adverse Events – Part A	ICH E3	SAC
33.	Safety	AE8CP	Listing of Serious Adverse Events – Part B	ICH E3	SAC
34.	Safety	AE14	Listing of Reasons for Considering as a Serious Adverse Event- Part A	ICH E3	SAC
35.	Safety	AE14	Listing of Reasons for Considering as a Serious Adverse Event- Part B	ICH E3	SAC
36.	Safety	AECP8	Listing of Adverse Events Leading to Withdrawal from Study – Part A	ICH E3	SAC
37.	Safety	AECP8	Listing of Adverse Events Leading to Withdrawal from Study – Part B	ICH E3	SAC
38.	Safety	AECP8	Listing of Adverse Events Leading to Permanent Discontinuation of Study Treatment – Part A	ICH E3	SAC
39.	Safety	AECP8	Listing of Adverse Events Leading to Permanent Discontinuation of Study Treatment – Part B	ICH E3	SAC
Hepatobiliary (Liver)					
40.	Safety	MH2	Listing of Medical Conditions for Subjects with Liver Stopping Events - Part A	IDSL	SAC

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
41.	Safety	MH2	Listing of Medical Conditions for Subjects with Liver Stopping Events - Part B	IDSL	SAC
42.	Safety	SU2	Listing of Substance Use for Subjects with Liver Stopping Events - Part A	IDSL	SAC
43.	Safety	SU2	Listing of Substance Use for Subjects with Liver Stopping Events - Part B	IDSL	SAC
All Laboratory					
44.	Safety	LB6	Listing of All Laboratory Data for Participants with Any Value of Potential Clinical Importance – Part A	ICH E3 Display ALL chemistry data for a subject who experienced a value of potential clinical importance.	IA, SAC
45.	Safety	LB5	Listing of All Laboratory Data for Participants with Any Value of Potential Clinical Importance – Part B	ICH E3 Display ALL chemistry data for a subject who experienced a value of potential clinical importance.	SAC
46.	Safety	LB6	Listing of Laboratory Values of Potential Clinical Importance – Part A		SAC
47.	Safety	LB5	Listing of Laboratory Values of Potential Clinical Importance – Part B		SAC
48.	Safety	LB14	Listing of Laboratory Data with Character Results – Part A	ICH E3	SAC
49.	Safety	LB14	Listing of Laboratory Data with Character Results – Part B	ICH E3	SAC
50.	Safety	UR2B	Listing of All Urinalysis Data for Subjects with Any Value of Potential Clinical Importance – Part A	ICH E3 Display ALL urinalysis data for a subject who experienced a value of potential clinical importance.	IA, SAC

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
51.	Safety	UR2A	Listing of All Urinalysis Data for Subjects with Any Value of Potential Clinical Importance – Part B	ICH E3 Display ALL urinalysis data for a subject who experienced a value of potential clinical importance.	SAC
52.	Safety	UR2B	Listing of Urine Biomarker data for all Subjects – Part A	Only present urine biomarker data	SAC
53.	Safety	UR2A	Listing of Urine Biomarker data for all Subjects – Part B	Only present urine biomarker data	SAC
ECG					
54.	Safety	EG4	Listing of All ECG Values for Subjects with Any Value of Potential Clinical Importance – Part A	IDSL Display ALL ECG data for a subject who experienced a value of potential clinical importance.	IA, SAC
55.	Safety	EG3	Listing of All ECG Values for Subjects with Any Value of Potential Clinical Importance – Part B	IDSL Display ALL ECG data for a subject who experienced a value of potential clinical importance.	SAC
56.	Safety	EG4	Listing of ECG Values of Potential Clinical Importance – Part A	IDSL	SAC
57.	Safety	EG3	Listing of ECG Values of Potential Clinical Importance – Part B	IDSL	SAC
58.	Safety	EG6	Listing of All ECG Findings for Subjects with an Abnormal ECG Finding – Part A	IDSL	IA, SAC
59.	Safety	EG5	Listing of All ECG Findings for Subjects with an Abnormal ECG Finding – Part B	IDSL	SAC
Vital Signs					

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
60.	Safety	VS5	Listing of All Vital Signs Data for Subjects with Any Value of Potential Clinical Importance – Part A	IDSL Display ALL vital signs data for a subject who experienced a value of potential clinical importance.	IA, SAC
61.	Safety	VS4	Listing of All Vital Signs Data for Subjects with Any Value of Potential Clinical Importance – Part B	IDSL Display ALL vital signs data for a subject who experienced a value of potential clinical importance.	SAC
62.	Safety	VS5	Listing of Vital Signs of Potential Clinical Importance – Part A	IDSL	SAC
63.	Safety	VS4	Listing of Vital Signs of Potential Clinical Importance – Part B	IDSL	SAC
64.	Safety	EG6	Listing of Telemetry findings - Part A	Example shell to be modified for telemetry data	IA, SAC
65.	Safety	EG5	Listing of Telemetry findings - Part B	Example shell to be modified for telemetry data	SAC

10.12.9. Non-ICH Listings

Non-ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Safety					
66.	Safety	HM10	Listing of Clinically Significant Holter Abnormalities – Part A		SAC
67.	Safety	HM10	Listing of Clinically Significant Holter Abnormalities – Part B		SAC
68.	Safety	MH3	Listing of Medical conditions – Part A		SAC
69.	Safety	MH2	Listing of Medical conditions – Part B		SAC
Pharmacokinetic					
70.	PK	PK07	Listing of Plasma GSK3186899 Pharmacokinetic Concentration-Time Data – Part A		SAC
71.	PK	PK07	Listing of Plasma GSK3186899 Pharmacokinetic Concentration-Time Data – Part B		SAC
72.	PK	PK13	Listing of Derived Plasma GSK3186899 Pharmacokinetic Parameters – Part A		SAC
73.	PK	PK13	Listing of Derived Plasma GSK3186899 Pharmacokinetic Parameters – Part B		SAC
74.	PK	PK07	Listing of Urine GSK3186899 Pharmacokinetic Concentration-Time Data – Part A	Only include 3 Urine PK parameters: Ae(t1-tz), fe(0-tz), CLR	SAC
75.	PK	PK07	Listing of Urine GSK3186899 Pharmacokinetic Concentration-Time Data – Part B	Only include 3 Urine PK parameters: Ae(t1-tz), fe(0-tz), CLR	SAC
76.	PK	Non-standard	Raw SAS output of Statistical Analysis for Comparison of Food effect - Part A Cohort 3		SAC

Non-ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
77.	PK	Non-standard	Raw SAS output of Statistical Analysis of Log Transformed Plasma GSK3186899 Pharmacokinetic Parameters Assessing Dose Proportionality (Power Model) – Part A		SAC
78.	PK	Non-standard	Raw SAS output of Statistical Analysis of Log Transformed Plasma GSK3186899 Pharmacokinetic Parameters Assessing Dose Proportionality (Power Model) – Part B		SAC
79.	PK	Non-standard	Raw SAS output of Statistical Analysis of Log-transformed Plasma GSK3186899 Parameters Assessing Steady-State – Part B		SAC
80.	PK	Non-standard	Raw SAS output of Time invariance analysis of log-transformed Plasma GSK3186899 Parameters – Part B		SAC

10.13. Appendix 13: Example Mock Shells for Data Displays

Example : PK_T1
Population : Pharmacokinetic

Table 4.7
Statistical analysis for comparison of food effect in Part A Cohort 3

Parameter (Units)	Fed		Fasted		GSK X.X mg Fed vs Fasted (Difference)	90% CI of the difference	GSK X.X mg Fed vs Fasted (Ratio)	90% CI of the Ratio
	n	LS Mean	n	LS Mean				
AUC(0-t) (µg.h/mL)	x	xx.xx	x	xx.xx	x.xx	(x.xx, x.xx)	x.xx	(x.xx, x.xx)
Cmax (µg/mL)	x	xx.xx	x	xx.xx	x.xx	(x.xx, x.xx)	x.xx	(x.xx, x.xx)
……..								

Log-transformed parameter is modelled with fed or fasted status and period as fixed effects and subject as a random effect. Unstructured covariance structures are considered describing within and between subject variability.
A ratio of 1 indicates same PK response is seen in both the fed and fasted subjects. A ratio > 1 indicates a higher PK response was seen in the fed subjects.

USER ID:directory/program.sas 01JAN2002 12:01

Example : PK_T2
Population : Pharmacokinetic

Table 4.8
Statistical Analysis of Log Transformed Plasma GSK3186899 Pharmacokinetic Parameters Assessing Dose Proportionality (Power Model) – Part A

Parameter (Units)	Slope Log Parameter vs Log Dose	90% CI of the Slope
<AUC(0-t) (µg.h/mL)>	x.xx	(x.xx, x.xx)
Cmax (µg/mL)	x.xx	(x.xx, x.xx)
……		

A Power model is used to assess the dose proportionality.
Log_e(dose) and period are fitted as fixed effects and subject as a random effect. An unstructured covariance structure is considered describing between subject variability.
A slope of 1 indicates the pharmacokinetics are dose proportional. A slope greater than 1 indicates the increase in PK is greater than proportional to dose.

USER ID:directory/program.sas 01JAN2002 12:01

Example : PK_T3
Population : Pharmacokinetic

Table 4.9
Statistical Analysis of Log Transformed Plasma GSK3186899 Pharmacokinetic Parameters Assessing Dose Proportionality (Power Model) – Part B

Parameter (Units)	Timepoint	Slope Log Parameter vs Log Dose	90% CI of the Slope
<AUC(0-t) (µg.h/mL)>	Day 1	x.xx	(x.xx, x.xx)
	Day 10	x.xx	(x.xx, x.xx)
Cmax (µg/mL)	Day 1	x.xx	(x.xx, x.xx)
	Day 10	x.xx	(x.xx, x.xx)
……			

A Power model is used to assess the dose proportionality.
Log_e(dose) is fitted as a fixed effect and subject as a random effect. An unstructured covariance structure is considered describing between subject variability.
A slope of 1 indicates the pharmacokinetics are dose proportional. A slope greater than 1 indicates the increase in PK is greater than proportional to dose.

USER ID:directory/program.sas 01JAN2002 12:01

Example : PK_T4
Population : Pharmacokinetic

Table 4.10
Statistical Analysis of Log Transformed Plasma GSK3186899 Trough Concentration Assessing Steady-State – Part B

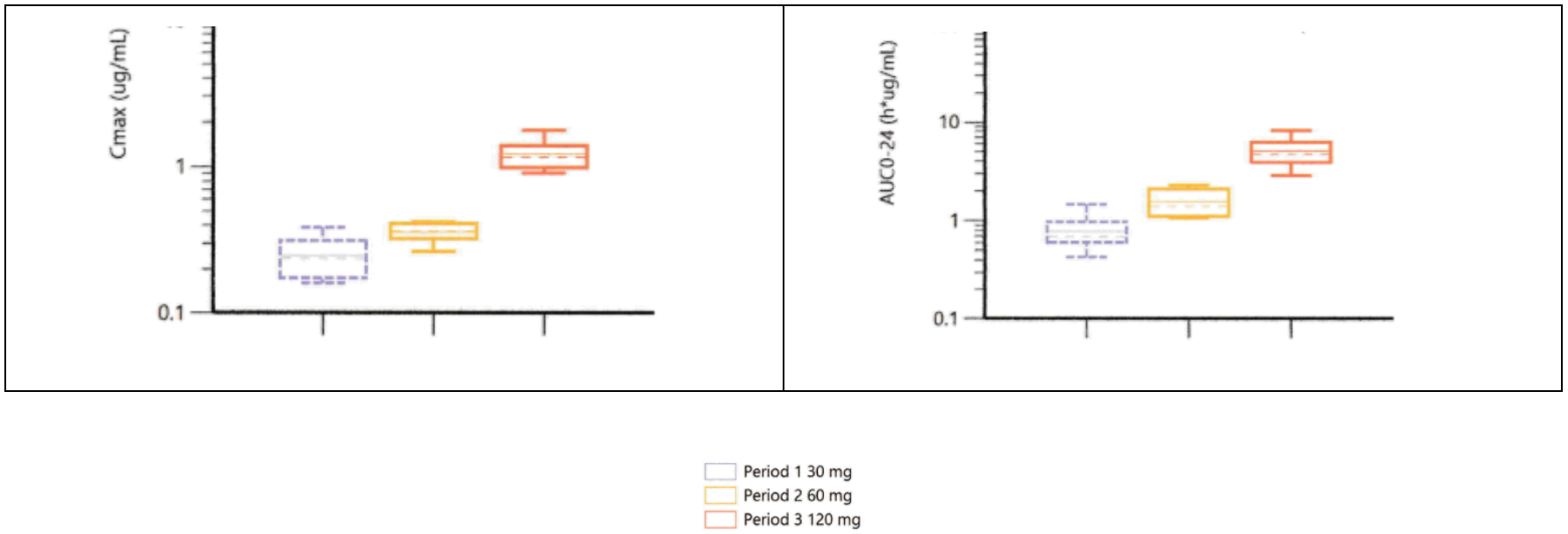
Parameter (Units)	Treatment	Day 10		Day 1		Log-transformed Day 10 – Day 1	90% Confidence Interval	Back-Transformed Ratios	90% Confidence Interval
		n	LS Mean	n	LS Mean				
Ctau (ug/mL)	<Dose 1>	x	xx.xx	x	xx.xx	x.xx	(x.xx, x.xx)	x.xx	(x.xx, x.xx)
	<Dose 2>	x	xx.xx	x	xx.xx	x.xx	(x.xx, x.xx)	x.xx	(x.xx, x.xx)
	<Dose 3>	x	xx.xx	x	xx.xx	x.xx	(x.xx, x.xx)	x.xx	(x.xx, x.xx)
……									

A Mixed effect model including dose, day and dose-by-day interaction as fixed effects and subject as a random effect is used to assess accumulation ratios. Unstructured covariance structures are used to describe within and between subject variabilities. A ratio of 1 indicates no accumulation. A ratio > 1 indicates drug accumulation.

USER ID:directory/program.sas 01JAN2002 12:01

Example : PK_F1
Population : Pharmacokinetic

Figure 4.7
Box Plot of AUC and Cmax versus doses (Linear) – Part A



Programming notes: this is an example shell to be updated to present each dose level.

USER ID:directory/program.sas 01JAN2002 12:01