Division	:	Worldwide Development
Information Type	:	Statistical Analysis Plan (SAP)
Title	:	Statistical Analysis Plan for a randomized, double-blind, placebo-controlled, first time in human study to evaluate the safety, tolerability, and pharmacokinetics of single (in both fed and fasted states) and repeat doses of GSK3494245 in healthy participants.
Compound Number	:	GSK3494245
Effective Date	:	23 May 2024

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Version History

SAP version	Approval Date	Protocol version Date on which SAP is based	Change	Rationale
SAP	04 Sep 2020	14-Aug-2020	Not applicable	Original Version
SAP amendment1	27 Nov 2023	Protocol Amendment 5: 20-Aug-2022 Protocol Amendment 6 :21-Jun-2023	In this version, Cohorts from 3-8 have been added	The food effect design has been changed, and the MAD Part has been added to Protocol Amendment 05 and Protocol Amendment 06
SAP Amendment2	23 May 2024	Protocol Amendment 5: 20-Aug-2022 Protocol Amendment 6 :21-Jun-2023	In this version, Section 7 has been updated	Alternative model for dose proportionality is added and dose normalized pk parameters have been added.

SAP Biostatistics Line Approval (Vault TMF approval):

Approver	Date
PPD Senior Manager- Statistics, Dev Biostats India Stats	23 May 2024

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1. INTRODUCTION

The purpose of this SAP is to describe the planned analyses to be included in the Clinical Study Report for Protocol 208441.

Descriptive study population analyses such as summary of demography and baseline characteristics and additional detail with regards to data handling conventions and the specification of data displays will be provided in the Output and Programming Specification (OPS) document.

1.1. Objectives, Estimands and Endpoints

1.1.1. Objectives and Endpoints

Objectives	Endpoints
Primary Objectives	**Primary Endpoints**
• To evaluate the safety and tolerability of single and repeat doses of GSK3494245 in healthy participants.	Adverse event reporting, treatment emergent, clinically significant changes from baseline in clinical laboratory, safety data, physical examinations*, vital signs, 12 lead electrocardiograms (ECGs) and telemetry.
Secondary Objectives	**Secondary Endpoints**
• To evaluate the PK profile of single (fasted and fed) and repeat doses of GSK3494245 in healthy participants.	• SAD Part: Derived PK parameters for GSK3494245 following single dose (fasted and fed) including area under the plasma drug concentration versus time curve (AUC(0-t), AUC (0-∞), maximum observed plasma drug concentration (Cmax), time to maximum observed plasma drug concentration (Tmax), and apparent terminal half-life (t1/2) as data allow. • MAD part: as appropriate: o Day 1 AUC(0-t), AUC (0-∞), AUC(0-tau), Cmax, Tmax, t1/2 o Day 4-7 morning trough plasma concentration (Ctau) o Day 7 AUC(0-t), AUC(0-tau), Cmax, Tmax, t1/2, CLss o Additionally, for TID regimen if conducted): Day 6 evening dose AUC (0-t), AUC(0-tau), Cmax, Tmax, •

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

* Physical examination is not captured in the study CRF but documented only at the site. However, all clinically significant findings on physical examination will be reported as adverse events.

1.1.2. Estimands

Primary estimands:

The primary clinical question of interest is*:*

To evaluate the safety and tolerability of single doses of GSK3494245 in healthy participants.

The primary estimand is described by the following attributes:

- **Population***:* Healthy participants of age 18 to ≤ 55 years.

- **Treatment condition***:*
  - The SAD part will consist of a single-dose escalation phase in up to 3 cohorts and a food effect cohort. On completion of Cohort 3, Cohort 3a will assess single ascending doses of GSK3494245 taken with food.

  - The MAD part will be a twice-daily (BID) or three times daily TID 7-day repeat dose design in up to 5 cohorts of participants (Cohorts 4, 5, 6, 7 and 8).

- **Endpoints***:*

  Adverse event reporting, treatment emergent, clinically significant changes from baseline in clinical laboratory including hematological tests, safety data, physical examinations, vital signs, 12 lead electrocardiograms (ECGs) and telemetry.

- **Population Level Summary measure:**
  - Categorical variables: Frequency and percentages.

  - Continuous variables: mean, standard deviation, median, minimum, and maximum will be reported separately for each dose.

- **Intercurrent events:**

  Study treatment discontinuation due to any reason – treatment policy strategy will be applied for this intercurrent event.

- **Rationale for Estimand:**

  The rationale of treatment policy strategy is to use the actual values of the safety data regardless study treatment discontinuation. Safety data will be monitored

throughout the study after the start of treatment. There is interest in evaluating and reporting safety events regardless of whether participants discontinued treatment.

Secondary Estimands 1:

The clinical question of interest for the secondary objective is:

- To evaluate the PK profile of single (fasted and fed) doses of GSK3494245.

The estimand is described by the following attributes:

- **Population:** Healthy participants of age 18 to ≤ 55 years.

- **Treatment condition**:
  - The SAD part will consist of a single-dose escalation phase in up to 3 cohorts and a food effect cohort. On completion of Cohort 3, Cohort 3a will assess single ascending doses of GSK3494245 taken with food.

  - The MAD part will be a twice-daily (BID) or three times daily TID 7-day repeat dose design in up to 5 cohorts of participants (Cohorts 4, 5, 6, 7 and 8).

- **Endpoints:**

  SAD Part: Derived PK parameters will be collected for GSK3494245 following single dose (fasted and fed) including area under the plasma drug concentration versus time curve (AUC(0-t) AUC (0-∞)), maximum observed plasma drug concentration (Cmax), time to maximum observed plasma drug concentration (Tmax), and apparent terminal half-life (t1/2) as data allow.

  MAD part: as appropriate:

  - Day 1 AUC(0-t), AUC (0-∞), AUC(0-tau), Cmax, Tmax, t1/2
  - Day 4-7 morning trough plasma concentration (Ctau)
  - Day 7 AUC(0-t), AUC(0-tau), Cmax, Tmax, t1/2, CLss
  - Additionally, for TID regimen if conducted): Day 6 evening dose AUC(0-t), AUC(0-tau), Cmax, Tmax,

- **Population Level Summary measure:**

  Descriptive statistics for log transformed data and untransformed data will be presented with mean, median, standard deviation, minimum and maximum.

- **Intercurrent events:**
  a) Treatment discontinuation due to any reasons– While on treatment policy strategy will be used.
  b) Use of concomitant/prohibited medication – Treatment policy strategy will be used.

- **Rationale for Estimand:**
  a) Interest lies in the treatment effect prior to the withdrawal- all available data up until the withdrawal of the consent will be reported.
  b) Interest lies in the overall treatment effect- The data post consumption of concomitant/prohibited medications (intercurrent event) will be analyzed as collected.

Secondary Estimands 2:

The clinical question of interest for the secondary objective is:

To examine dose proportionality for the following single doses of GSK3494245 for fasted and fed cohorts separately.

The estimand is described by the following attributes:

- **Population:** Healthy participants of age 18 to ≤ 55 years.

- **Treatment condition**:
  - The SAD part will consist of a single-dose escalation phase in up to 3 cohorts and a food effect cohort. On completion of Cohort 3, Cohort 3a will assess single ascending doses of GSK3494245 taken with food.

- **Endpoint:**

  Area under the plasma GSK3494245 concentration by time curve AUC (0-∞), Maximum observed plasma drug concentration (Cmax).

- **Population Level Summary measure:**

  Estimate of slope and corresponding 90% Confidence Interval (CI).

- **Intercurrent events:**
  a) Treatment discontinuation due to any reasons–Hypothetical strategy will be used.
  b) Use of concomitant/prohibited medication – Treatment policy strategy will be used.

- **Rationale for Estimand:**
  a) Interest lies in the dose proportionality (i.e., slope) in the hypothetical situation where the treatment discontinuation had not occurred.
  b) Interest lies in the overall treatment effect- The data post consumption of concomitant/prohibited medications (intercurrent event) will be analyzed as collected.

Secondary Estimands 3:

The clinical question of interest for the secondary objective is:

1. To examine dose accumulation following repeat doses of GSK3494245.
2. To examine time-invariance ratios of GSK3494245 following repeat doses
3. To assess steady state following repeat doses of GSK3494245

The estimand is described by the following attributes:

- **Population**: Healthy participants of age 18 to ≤ 55 years

- **Treatment condition**:
  - The MAD part will be a twice-daily (BID) or three times daily TID 7-day repeat dose design in up to 5 cohorts of participants (Cohorts 4, 5, 6, 7 and 8).

- **Endpoint:**
  1. AUC ($RAUC_{(0\text{-}tau)}$), RCmax and Ctau (RCtau)
  2. Ratio of AUC(0-tau) on day 7 to AUC (0-∞) on day 1 or if TID is conducted, AUC(0-tau) on Day 6 evening dose to AUC (0-∞) on Day 1
  3. Ctau
- **Population Level Summary measure:**
  1. For each dose, point estimates and 90% confidence intervals for the differences "Day 7 - Day 1" (for BID) or "Day 6 evening dose - Day 1 morning dose" (for TID) and the geometric mean ratio and 90% CI for the ratios "Day 7: Day 1"

(for BID) or "Day 6- Day 1" (for TID) after back transformation for each active dose.

2. Point estimate and 90% CIs of mean difference of 'AUC(0-tau) at Day 7– 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 7: AUC (0-∞) at Day 1' and 90 % CI of ratio for each active dose.
3. Estimate of slope and corresponding 90% Confidence Interval CI for each active dose to assess steady state analysis.

- **Intercurrent events:**

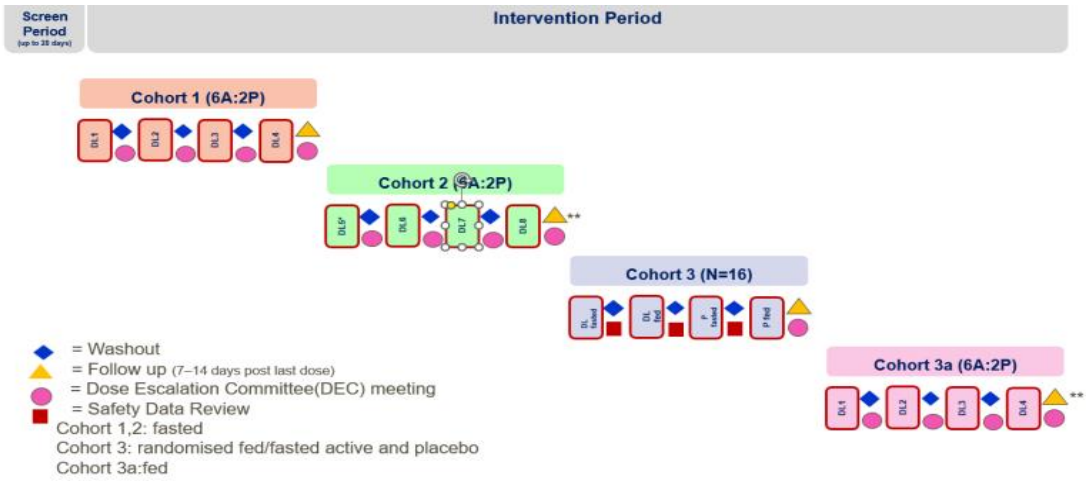
a) Treatment discontinuation due to any reasons–Hypothetical strategy will be used.
b) Use of concomitant/prohibited medication – Treatment policy strategy will be used.

- **Rationale for Estimand**:

a) Interest lies in the ratio between Day 7-Day 1 (for BID) or Day 6 – Day 1 (for TID) in the hypothetical situation where the treatment discontinuation had not occurred- The Day 1 data will be included even though Day 7 (for BID) or Day 6 (for TID) data is missing.
b) Interest lies in the overall treatment effect- The data post consumption of concomitant/prohibited medications (intercurrent event) will be analyzed as collected.

1.2. Study Design

Overview of Study Design and Key Features



Overview of Study Design and Key Features

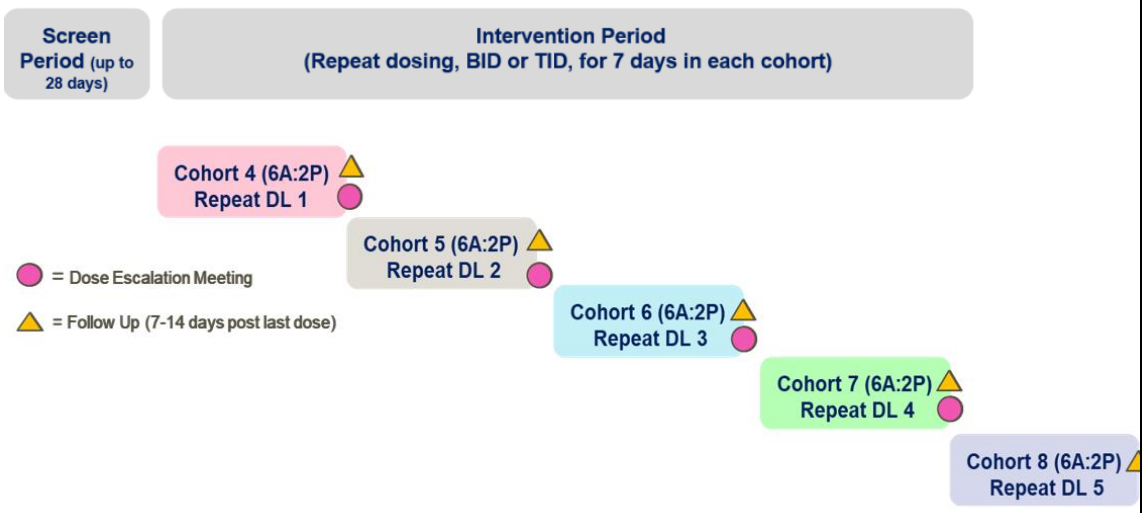
A = active drug; DL = dose level; DLX = dose level to be determined; Fed = fed conditions; P = placebo.

*Depending on the outcome of review of all available safety and PK data from Cohort 1, the DEC may repeat DL4 at the start of Cohort 2. Then escalate to DL5, DL6 and DL7 as needed.

Note: In Cohorts 1, 2 and 3a, the first two participants, within each intervention period, will act as sentinels. Cohorts 1, 2 and 3 comprise of a 4-way cross-over design.

The dosing schedule may be adjusted to add an additional cohort to further evaluate safety or PK findings at a given dose level, or to evaluate additional doses. The additional cohort will be up to 8 participants following the same design and dose escalation principles as Cohort 1 and 2.

Study Design (Multiple Ascending Dose)



A = active drug; BID = twice-daily; TID= three-times daily; DL = dose level; P = placebo. Day 7 is morning dose only.

Note: For each new dose level, the first two subjects in each cohort will act as sentinels.

Design Features	This is a randomized, double-blind, placebo-controlled, study of the oral administration of GSK3494245 in healthy participants. As this will be the first time GSK3494245 is administered to humans, the study design may change based on emerging data as the study progresses. **Dose Escalation (SAD):** For this part, 2 cohorts (Cohorts 1 and 2) will be considered, containing 8 participants each. In each cohort, the participants will be randomized to one of 4 sequences. Each participant will receive a maximum of 3 ascending oral doses of GSK3494245 and a placebo under fasted conditions.

Overview of Study Design and Key Features	
	In the event the DEC decide there is a need to address any concerns from a safety or PK point of view, the 4th dose level (DL4) may be repeated at the start of Cohort 2. Thereby allowing up to 7 dose levels to be studied, in this scenario. In addition, the DEC may decide, based on emergent safety and PK data to include an additional cohort of up to 8 participants following the same design as Cohorts 1 and 2. **Food Effect:** Cohort 3 will consist of up to 16 healthy participants and will comprise of a 4-way crossover in which participants will receive GSK3494245 and placebo in both fasted and fed conditions. The selected dose level (DLX) to investigate the effect of food on the safety, tolerability, and PK of a single dose of GSK3494245 will be one already evaluated from a previous intervention period. Cohort 3a will comprise of 4 intervention periods, investigating 4 dosing regimens under fed conditions. Participants will receive three doses of GSK3494245 and a randomised placebo dose, administered in the fed state. Washout: At least 48 hrs. or 5-half-lives (whichever is longer) will be given between each dose for an individual participant. Note: Participants will be admitted to the unit the day before dosing (Day -1) and will remain in the unit overnight until Day 4 of intervention. **MAD:** The MAD part will be a twice-daily (BID) or three-times daily (TID) 7-day repeat dose design in up to 5 cohorts (Cohorts 4, 5, 6, 7 and 8), each including 8 participants. Dependent on whether a food effect is observed in the SAD phase, the MAD part may also include drug administration after either fed or fasted conditions. Up to a maximum of 5 dose levels will be studied in the MAD part. CCI [redacted] Note: Participants will be admitted to the unit the day before dosing (Day -1) and will remain in the unit overnight until Day 8.
Dosing	**Dose Escalation (SAD):** • For Cohorts 1 and 2, each participant will receive a maximum of 3 ascending oral doses of GSK3494245 and 1 placebo dose under fasted conditions (4 regimens) in a crossover manner.

Overview of Study Design and Key Features	
	• At each dose level, GSK3494245 and placebo will be administered in a 3:1 ratio, within each period, according to the randomization schedule in a blinded manner to 8 participants. • For each cohort and within each intervention period (except Cohort 3), the first 2 participants will act as sentinels. No participant will be a sentinel participant more than once. On Day 1, 1 of the 2 sentinel participants will receive the active dose and the other will receive placebo. Based on the Principal Investigator's review of the 2 sentinel participants after at least the first 24 hrs. post-dose safety data (e.g., vital signs, ECGs, and AEs), the remaining 6 participants can then be randomized to dosing. • For Cohorts 1 and 2, up to a maximum of 8 dose levels will be studied. • In addition, the DEC may decide, based on emergent safety and PK data to include an additional cohort (Cohort 2a) of up to 8 participants following the same design as Cohorts 1 and 2. **<u>Food Effect</u>:** • Cohort 3 will consist of up to 16 healthy participants. • Cohort 3 participants will receive the selected dose of GSK3494245 in both fasted and fed conditions and two doses of placebo, also given under fed and fasted conditions respectively in a 1:1 ratio. • For Cohort 3a, each participant will receive a maximum of 3 ascending oral doses of GSK3494245 and 1 placebo, administered in a 3:1 ratio dose under fed conditions (4 regimens) in a crossover manner. Similar procedures of dosing cohorts 1 -2 will be applied. **<u>MAD:</u>** • Participants in each cohort will be randomised to receive repeat doses of either GSK3494245 or placebo (blinded), administered in a 3:1 ratio according to the randomization schedule. • GSK3494245 or placebo will be administered twice-daily or three-times daily for 7 days using a 12hr dosing interval for BID dosing and a 6-hour interval for TID dosing, with only one dose administered on Day 7. • For each cohort, the first 2 participants will act as sentinels. One sentinel participant will be randomised to active treatment and the other to placebo. Based on the Principal Investigator's review of the 2 sentinel participants after at least the first 48 hr post-dose safety and tolerability data (e.g., vital signs, ECGs, and AEs), the remaining 6 participants can then be randomised to dosing.

Overview of Study Design and Key Features	
Study intervention Assignment	This study is planned to include approximately 80 participants (excluding additional up to 16 subjects from the 2 optional cohorts) **<u>Dose Escalation (SAD)</u>:** Cohort 1, 2 and 3a will each have 6 participants in active versus 2 participants in placebo (i.e., in a 3:1 ratio) at each dose level. **<u>Food Effect</u>:** Cohort 3 will contain up to 16 participants in a 1:1 ratio for (fed and fasted) versus (fasted and fed) for the selected dose of GSK3494245 and placebo. **<u>MAD Part:</u>** • MAD Part consists of up to 40 participants in up to 5 cohorts (excluding possible replacements): • Each of cohort (4,5,6,7 and 8) will have 6 participants in active versus 2 participants will receive placebo (i.e., in 3:1 ratio) at each repeat dose level.
Interim Analysis	No interim analyses are planned for this study.

2. STATISTICAL HYPOTHESES / SUCCESS CRITERIA

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

3. ANALYSIS SETS

For purposes of analysis, the following analysis sets are defined:

Analysis Set	Definition / Criteria	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 screened) and participants screened but never enrolled into the study (Reserve, Not Used) are excluded from the Enrolled analysis set 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 participant received. *Note: Participants who were not randomized but received at least one dose of study treatment should be listed.*	• Safety • Study Population
Pharmacokinetic (PK)	• All participants in the Safety population who had at least one non-missing PK assessment (Non-quantifiable [NQ] values will be considered as non-missing values).	• PK

3.1. Protocol Deviations

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

Protocol deviations will be tracked by the study team throughout the conduct of the study. These protocol deviations will be reviewed to identify those considered as important as follows:

- Data will be reviewed prior to freezing the database to ensure all important deviations are captured and categorized in the protocol deviations SDTM dataset.
- This dataset will be the basis for the summaries of important protocol deviations.

4. STATISTICAL ANALYSIS

4.1. General consideration

4.1.1. General methodology

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

4.1.2. Baseline definition

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 the 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 or screening (as schedule of assessment in each 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.

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. These are defined as follows:

- 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.

4.2. Overview of Planned Study Population Analyses

The study population analyses will be based on the Safety set, 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.

5. SAFETY ANALYSIS

The primary objective of this study is to evaluate the safety and tolerability of single and repeat doses GSK3494245.

5.1. Adverse Events Analyses

Adverse events analyses including the analysis of adverse events (AEs), Serious (SAEs), drug-related AEs, drug-related SAEs by system organ class, preferred term, and maximum intensity. The summary of common (≥ 5%) AEs by overall frequency will be based on GSK Core Data Standards.

All clinically significant changes in physical examination will be reported as AEs.

5.1.1. COVID-19 Assessment and COVID-19 AEs

COVID-19 assessment for participants with COVID-19 AEs will be summarized.

5.2. 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 and will be represented graphically if needed. Further details of the potential clinical important values will be provided in the Output programming specifications (OPS).

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The Lactic Acid, Bicarbonate, pH parameters will be represented graphically.

5.3. Other Safety Analyses

The analyses of non-laboratory safety test results including vital signs, 12 lead ECG and 24–48-hour telemetry will be based on GSK Core Data Standards, unless otherwise specified. Further details of the potential clinical important values will be provided in the Output programming specifications (OPS).

6. INTERIM ANALYSES

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

7. PHARMACOKINETIC ANALYSES

All PK analyses planned for the study are a part of the secondary objectives and will be based on the PK set.

7.1. Statistical analyses of derived PK parameters

7.1.1. Endpoint/Variables

Pharmacokinetic parameters will be determined from the plasma concentration-time data, as data permits.

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 8.3 (or higher). All calculations of non-compartmental parameters will be based on actual sampling times for the final analysis.

For dose escalation meetings planned sampling times may be used if actual timepoints are not available.

Pharmacokinetic parameters listed in the table below 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.

Table 1 Derivations for PK parameters

Parameter	Parameter Description
Plasma PK parameters	
Cmax	Maximum observed concentration, determined directly from the concentration-time data.
Cmax_D	Maximum observed concentration normalized by dose: Cmax_D=Cmax/D
Tmax	Time to reach Cmax, determined directly from the concentration-time data.
tlag*	Lag time before first observation of drug concentrations
Tlast*	Time of last quantifiable concentration
$t_{1/2}$	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.

Parameter	Parameter Description
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 loge trapezoidal rule for each decremental trapezoid.
AUC(0-t)_D	Area under the concentration-time curve from time zero to the time of the last quantifiable concentration (C(t)) normalized by dose will be calculated as: AUC(0-t)_D=AUC(0-t)/D
Parameter	**Parameter Description**
AUC (0-∞)	Area under the concentration-time curve extrapolated to infinity will be calculated as: $$AUC(0-\infty) = AUC(0-t) + \frac{C(t)}{\lambda_z}$$ (NOTE: λ_z is the terminal phase rate constant and C(t) is the last quantifiable concentration. % 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%).
AUC(0-∞)_D	Area under the concentration-time curve extrapolated to infinity normalized by dose will be calculated as: AUC(0-∞)_D =AUC(0-∞)/D
R_2 adjusted*	The goodness of fit statistic for the terminal elimination phase, adjusted for the number of points used in the estimation of λ_z.
λ_z	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 (R2 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 λ_z in their calculation (i.e., t½, AUC (0-∞) will need to be flagged or excluded from statistical analysis accordingly. The interval used to determine λ_z 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.
λ_z upper limit*	The upper limit on time for values to be included in the calculation of λ_z.
λ_z lower limit*	The lower limit on time for values to be included in the calculation of λ_z.

Parameter	Parameter Description
λ_z number of points*	The number of time points used in computing λ_z.
% AUCex*	Percent of AUC_∞ that is extrapolated beyond last quantified concentration
CL/F*	The apparent clearance will be calculated as Dose/AUC (0-∞)
RAUC(0-tau), RCmax, RCtau	Accumulation ratio, calculated from comparison of single dose and multiple dose administration data: *RCmax = Day 7 Cmax/ Day 1 Cmax* *RCtau = Day 7 Ctau/ Day 1 Ctau* Where for RCtau Concentration at the end of the morning dose time interval will be taken

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

7.1.2. Main analytical approach

The following descriptive summaries will be provided for all the 3 cohorts:

- N (number of subjects in the population), n (number of subjects used for the analysis), arithmetic mean, 95% CI (90% CI for Cohort 3 only) for the arithmetic mean, SD, median, minimum, maximum for the untransformed data.
- Geometric mean, 95% CI (90% CI for Cohort 3 only) for the geometric mean, SD of $\log_e$-transformed data and %CVb or %CVw for the untransformed data (except Tmax and T½).

7.1.2.1. Intercurrent Events and handling of missing data

The intercurrent events mentioned in Section 1.1.2. along with the corresponding strategies will be considered during this analysis.

- For treatment discontinuation due to any reason:

  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, Cmax etc. of that partially completed period will be calculated, if data permits.

- For Subject use concomitant/prohibited medication:

  The subject data post consumption of concomitant/prohibited medications (intercurrent event) will be analyzed as collected.

If multiple intercurrent events are observed, then the data will be handled using more than one strategy as described in Section 1.1.2 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 the Output Programming Specification (OPS) document. Data Displays will be based on GSK Data Standards and statistical principles.

7.2. Statistical analysis for comparison of food effect

7.2.1. Endpoints/Variables

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

7.2.2. Main analytical approach

Log_e-transformed data will be statistically analyzed using a mixed model with:

- fed or fasted status, period and their interaction term (if tested as significant) as fixed effects.
- subject as random effect

- Only data of subjects participating in Cohort 3 both periods 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.
- 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:

- The estimated mean differences and 90% CIs of (fed – fasted) will be presented based on the log_e-transformed data.

- The estimated geometric mean ratios and 90% CI of (fed: fasted) after back-transformation will also be presented.

7.2.2.1. Intercurrent events and handling of missing data

The intercurrent events mentioned in Section 1.1.2. along with the corresponding strategies will be considered during this analysis.

- For treatment discontinuation due to any reason:

  Subjects' data available up to the withdrawal will be included in the analysis. If a subject withdraws consent during a period, the missing data post withdrawal will not be imputed.

- For Subject use concomitant/prohibited medication:

  The subject data post consumption of concomitant/prohibited medications (intercurrent event) will be analyzed as collected.

If multiple intercurrent events are observed, then the data will be handled using more than one strategy as described in Section 1.1.2. 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 the Output Programming Specification (OPS) document. Data Displays will be based on GSK Data Standards and statistical principles.

7.3. Statistical analysis for dose proportionality

7.3.1. Endpoints/Variables

Dose proportionality will be assessed following single doses of GSK3494245 separately for the fasted and fed cohorts during the Single Ascending Dose (SAD) via analyses of AUC (0-∞) and Cmax. Only if required, the power model is fitted to dose normalized parameters to assess the dose proportionality for AUC (0-∞) and Cmax (AUC(0-∞)_D and Cmax_D).

7.3.2. Main analytical approach

Power model will also be fitted to assess dose proportionality as follows: $y = \alpha * dose^{\beta}$. In the log transformed manner this power model can be written as following

$\log_e(Y) = \beta \times \log_e(dose) + \log_e(\alpha)$

Where, y denotes the PK parameter being analyzed, dose denotes the dose administered to a subject. α depends upon random intercept subject effect and period effect and β is the coefficient of covariate log(dose).

Log_e transformed data will be analyzed using a mixed effect model:

- Fixed effect: loge (dose), period
- Random effect: Subject

- Data from all available doses will be considered. An unstructured covariance structure will be considered for the G matrix describing the between subject variability. If this model fails to converge, alternative covariance structures may be considered such as Variance Component, Compound Symmetry, etc. Akaike's Information Criteria (AIC) will be used to assist with the selection of covariance structure.
- 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.
- 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.

Model Results:

- The estimates mean slopes and 90% CIs of $\log_e$(dose) will be presented. Note that a slope ≈ 1 implies dose proportionality.

If the power model is failed to converge, analysis will be performed using Analysis of Variance (ANOVA) model to assess dose proportionality. The PK parameters (AUC (0-∞), Cmax) will be dose-normalized first and multiplying by reference dose prior to loge-transformation, will be analyzed separately using mixed effects model.

- Fixed effect: loge (dose), period
- Random effect: Subject

The reference dose will be chosen based on the lowest clinically relevant dose over which PK can be adequately described.

- Data from all available doses will be considered. An unstructured covariance structure will be considered for the G matrix describing the between subject variability. If this model fails to converge, alternative covariance structures may be considered such as Variance Component, Compound Symmetry, etc. Akaike's Information Criteria (AIC) will be used to assist with the selection of covariance structure.
- 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.

- 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.

Model Results:

Adjusted geometric means for each dose will be presented along with the standard errors (SE) and 90% CIs. Estimated treatment ratios to reference dose (First or lowest dose of each part) and corresponding 90% CI will also be presented.

7.3.2.1. Intercurrent events and handling of missing data

The intercurrent events mentioned in Section 1.1.2. along with the corresponding strategies will be considered during this analysis.

- For treatment discontinuation due to any reason:

  Subjects' data available up to the withdrawal will be included in the analysis where treatment discontinuation had not occurred. If a subject withdraws consent during a period, the missing data post withdrawal will not be imputed.

- For Subject use concomitant/prohibited medication:

  The subject data post consumption of concomitant/prohibited medications (intercurrent event) will be analyzed as collected.

If multiple intercurrent events are observed, then the data will be handled using more than one strategy as described in Section 1.1.2. 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 the Output Programming Specification (OPS) document. Data Displays will be based on GSK Data Standards and statistical principles.

7.4. Statistical analysis for Accumulation

7.4.1. Endpoints/Variables

- The extent of accumulation of GSK3494245 will be based on AUC($RAUC_{(0\text{-}tau)}$), Cmax ($RCmax_{)}$ and Ctau (RCtau).

7.4.2. Main analytical approach

Statistical analysis will be to estimate the accumulation ratio, Ro, on the pharmacokinetics of GSK3494245. Following $\log_e$-transformation, AUC(0-tau) on Day 1 and AUC(0-tau) on the day of last dose will be analyzed by a mixed effect model.

- Fixed effect: dose, day, and dose*day
- Random effect: Subject

- Data from all available doses will be considered. An unstructured covariance structure will be considered for the G matrix describing the between subject variability.
- 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.
- 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.
- 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) (3) First order autoregressive.

Model Results:

- For each dose, point estimates and 90% confidence intervals for the differences "Day 7 - Day 1" (for BID) or "Day 6 evening dose - Day 1 morning dose" (for TID) will be constructed using the appropriate error term.
- The geometric mean ratio and 90% CI for the ratios "Day 7: Day 1" (for BID) or "Day 6- Day 1" (for TID) after back transformation for each active dose.
- If both the dose and day by dose interaction terms are not significant, a single point estimate and confidence interval pooled across all doses will also be constructed.

Note: RCmax and RCtau will be estimated in a similar approach

7.4.2.1. Intercurrent events and handling of missing data

The intercurrent events mentioned in Section 1.1.2. along with the corresponding strategies will be considered during this analysis.

- For treatment discontinuation due to any reason:

  Subjects' data available up to the withdrawal will be included in the analysis where treatment discontinuation had not occurred. If a subject withdraws consent during a period, the missing data post withdrawal will not be imputed.

- For Subject use concomitant/prohibited medication:

  The subject data post consumption of concomitant/prohibited medications (intercurrent event) will be analyzed as collected.

If multiple intercurrent events are observed, then the data will be handled using more than one strategy as described in Section 1.1.2. 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 the Output Programming Specification (OPS) document. Data Displays will be based on GSK Data Standards and statistical principles.

7.5. Statistical analysis for Time Invariance (MAD part)

7.5.1. Endpoints/Variables

- The statistical analysis will be based on the ratio of AUC(0-tau) (i.e., AUC (0-12) for dosing is BID**)** on day 7 to AUC (0-∞) on day 1**.** If TID regimen is conducted, statistical analysis will be based on the ratio of AUC(0-tau) on Day 6 evening dose to AUC (0-∞) on Day 1.

Main analytical approach

A statistical analysis will be performed using mixed effect model on $\log_e$ transformed endpoint.

  - Fixed effect: Day
  - Random effect: Subject

- Data from all available doses will be considered. An unstructured covariance structure will be considered for the G matrix describing the between subject variability.
- 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.
- 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.

- 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) (3) First order autoregressive.

Model Results:

- The summary measure will be the point estimate and 90% CIs of mean difference of 'AUC(0-tau) at Day 7– 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 7: AUC(0-∞) at Day 1' and 90 % CI of ratio will also be presented for each active dose.

7.5.1.1. Intercurrent events and handling of missing data

The intercurrent events mentioned in Section 1.1.2. along with the corresponding strategies will be considered during this analysis.

- For treatment discontinuation due to any reason:

  Subjects' data available up to the withdrawal will be included in the analysis where treatment discontinuation had not occurred. If a subject withdraws consent during a period, the missing data post withdrawal will not be imputed.

- For Subject use concomitant/prohibited medication:

  The subject data post consumption of concomitant/prohibited medications (intercurrent event) will be analyzed as collected.

If multiple intercurrent events are observed, then the data will be handled using more than one strategy as described in Section 1.1.2. 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 the Output Programming Specification (OPS) document. Data Displays will be based on GSK Data Standards and statistical principles.

7.6. Statistical analysis for Steady state (MAD part)

7.6.1. Endpoints/Variables

- Steady state will be assessed following repeat dose of GSK3494245 (MAD part) via analyses of trough plasma concentration (Ctau).

7.6.2. Main analytical approach

A statistical analysis will be performed using mixed effect model on $\log_e$ transformed endpoint.

- Fixed effect: log(dose)
- Random effect: Subject

- Data from all available doses will be considered. An unstructured covariance structure will be considered for the G matrix describing the between subject variability.
- 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.
- 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.
- 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) (3) First order autoregressive.

Model Results:

- The coefficients of the slopes for the day effect on log scale for each dose, along with corresponding 90% confidence intervals, will be used to determine whether steady state was achieved.

7.6.2.1. Intercurrent events and handling of missing data

The intercurrent events mentioned in Section 1.1.2. along with the corresponding strategies will be considered during this analysis.

- For treatment discontinuation due to any reason:

  Subjects' data available up to the withdrawal will be included in the analysis where treatment discontinuation had not occurred. If a subject withdraws consent during a period, the missing data post withdrawal will not be imputed.

- For Subject use concomitant/prohibited medication:

  The subject data post consumption of concomitant/prohibited medications (intercurrent event) will be analyzed as collected.

If multiple intercurrent events are observed, then the data will be handled using more than one strategy as described in Section 1.1.2. 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 the Output Programming Specification (OPS) document. Data Displays will be based on GSK Data Standards and statistical principles.

7.7. Other Analysis

Dose proportionality will be assessed following multiple doses of GSK3494245 for the Multiple Ascending Dose (MAD) via analyses of AUC (0-∞) and Cmax for Day 7 (BID) or Day 6 (TID) and Day 1. Please refer Section 7.3.2 Main analytical approach for the statistical analysis procedure.

8. SAMPLE SIZE DETERMINATION

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

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

Sample size in Cohort 3 was calculated based on the precision estimate for fed versus fasted status. The objective of Cohort 3 (SAD part) is to determine if food effects the PK of GSK3494245 and to inform the dosing regimen for the MAD part. A precision estimate was therefore used to determine the sample size, based on assumed within subject coefficient of variation (CV_w) for AUC of 20% and C_{max} of 30% respectively. A maximum of 16 participants will be recruited with the aim of getting evaluable data from 12 participants. If the estimates for the CV_w decrease following review of the data from Cohorts 1 and 2, then fewer participants may be recruited, with the aim of obtaining as few as 10 evaluable participants. The number of planned evaluable participants will not be less than 10, nor will the number of recruited participants be greater than 14.

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

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

8.1. Sample Size Sensitivity

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

Table 2 Sample Size Sensitivity for Cohorts 1, 2, 3a and 4-8 Precision Estimates

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

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

Sample size sensitivity for fixed within subject coefficient of variation.

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

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

9. SUPPORTING DOCUMENTATION

9.1. Appendix 1: Abbreviations & Trademarks

9.1.1. 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

Abbreviation	Description
EMA	European Medical 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
IP	Investigational Product
LDH	Lactate Dehydrogenase
MAD	Multiple Ascending Dose
MCH	Mean Corpuscular Hemoglobin
MCV	Mean Corpuscular Volume
CCI	[redacted]
NOAEL	No Observable Adverse Effect Limit
PCI	Potential Clinical Importance
PD	Pharmacodynamic
PDMP	Protocol Deviation Management Plan
PK	Pharmacokinetic

Abbreviation	Description
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

Abbreviation	Description
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
WONCBP	Women of Non-Childbearing Potential

9.1.2. Trademarks

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SAS
WinNonlin

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