Reporting and Analysis Plan

Study ID: 212148

Official Title of Study: Reporting and Analysis Plan for A Double-Blind (Sponsor unblinded) Randomized, Placebo-Controlled, Single and Repeated Oral Dose Escalation Study to Investigate the Safety, Tolerability, Pharmacokinetics (including food effect) of GSK3882347 in Healthy Participants.

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Title	:	Reporting and Analysis Plan for A Double-Blind (Sponsor unblinded) Randomized, Placebo-Controlled, Single and Repeated Oral Dose Escalation Study to Investigate the Safety, Tolerability, Pharmacokinetics (including food effect) of GSK3882347 in Healthy Participants.
Compound Number	:	GSK3882347
Clinical Study Identifier	:	212148
Effective Date	:	[Refer to Document Date]

- **Description**:
- The purpose of this RAP is to describe the planned analyses and output to be included in the Clinical Study Report for Protocol 212148 Amendment 3
- This RAP is intended to describe the safety, tolerability, pharmacokinetics (including food effect) and Biomarker analyses required for the study.
- This RAP will be provided to the study team members to convey the content of the 212148 Statistical Analysis Complete (SAC) deliverable.

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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 212148:

Revision Chronology:		
2019N40073_00	*05 -Nov-2019*	Original
2019N40073_01	*02-Jun-2020*	This amendment includes revisions to the reporting of the primary endpoint, eligibility criteria, including decrease in creatine clearance and screening for COVID-19, COVID-19 related activities, removal of PCI for extemporaneous compounding, procedural changes in-line with clinical site, minor clarifications and consistency corrections, formatting corrections.
2019N40073_02	*10-Jul-2020*	This amendment is in response to questions raised in the MHRA's Grounds for non-acceptance letter which was received on the 02/07/2020 and includes revisions to the overall design (in-house stay for Part 2), boundaries for dose adjustment, justification of maximum dose, exclusion criteria, gastrointestinal events, and individual/study stopping criteria.
2019N400733_03	*21-Oct-2020*	This amendment is to allow for additional blood samples to be taken from selected cohorts in order to evaluate an in vitro CYP3A4 induction flag. Plasma derived from whole blood will be analysed for changes in 4βhydroxycholesterol and cholesterol ratio as a potential in vivo marker of CYP3A4 enzyme activity at baseline and following repeat administration of GSK3882347.

2. SUMMARY OF KEY PROTOCOL INFORMATION

2.1. Changes to the Protocol Defined Statistical Analysis Plan

Changes from the originally planned statistical analysis specified in the protocol are outlined in Table 1.

Table 1 Changes to Protocol Defined Analysis Plan

Protocol	Reporting & Analysis Plan	
Statistical Analysis Plan	**Statistical Analysis Plan**	**Rationale for Changes**
• Dose proportionality analysis of Amount excreted in urine (Ae) was not included in the statistical analysis section of protocol	• Dose proportionality analysis of Ae has been added in Statistical analysis section of RAP	• Since plasma PK may be used as surrogate marker for urine PK an assessment of dose proportionality in both plasma and urine is being explored
• No Biomarker endpoint is evaluated • Biomarker population is not defined in Population for analyses section	• 4β-hydroxycholesterol and cholesterol data included as per amendment 3 is considered under Biomarker endpoint • Biomarker population has been added to the list of analysis populations	• The objective 'To assess potential effect of repeat doses of GSK3882347 on Cytochrome P450 3A4 (CYP3A4) enzyme activity in Part 2', to evaluate the biomarker endpoint plasma 4β-hydroxycholesterol to cholesterol ratio has been added in protocol amendment 3. Since this is a biomarker end point, the population definition has been included

2.2. Study Objectives and Estimands / Endpoints

Objectives	Endpoints
Primary	
• To evaluate the safety and tolerability of GSK3882347 following oral administration of single and repeat doses in healthy adult participants	• Occurrence of adverse events (AEs) and treatment related AEs • Occurrence of clinically significant changes in vital signs, laboratory parameters, and 12-lead electrocardiogram (ECG) findings
• To evaluate the pharmacokinetics of GSK3882347 in plasma and urine following oral administration of single and repeat doses in healthy adult participants	• Single dose (plasma): AUC(0-24), AUC(0-t), AUC(0-∞), Cmax, C24h, tmax, tlag and $t_{1/2}$ of GSK3882347, as data permit • Repeat dose (plasma): AUC(0-tau), Cmax, tmax and Ctau of GSK3882347, as data permit

Objectives	Endpoints
	• Urine concentration at 22-24h collection time-point • Amount excreted in urine (Ae) of unchanged GSK3882347, fraction of the dose excreted in urine (fe) and renal clearance (CLr), as data permit
Secondary	
• To further evaluate the pharmacokinetics of GSK3882347 in plasma • To examine dose proportionality of GSK3882347 following oral administration of single and repeat doses in healthy adult participants • To evaluate the extent of accumulation, time invariance, and achievement of steady-state of GSK3882347 following oral administration of single and repeat doses in healthy adult participants	• Single dose(plasma): AUC(0-12), C12h, CL/F, Vd/F and MRT of GSK3882347, as data permit • Repeat dose (plasma): AUC(0-12) and C12h of GSK3882347, as data permit • AUC(0-inf) and Cmax for single dose and AUC(0-tau) and Cmax for repeat dose, as data permit • Ro (accumulation ratio) using AUC(0-tau) for repeat dose, as data permit • Time invariance using AUC(0-tau) (repeat dose) and AUC(0-inf) (single dose) • Achievement of steady-state (Ctau collected on multiple days)
• To evaluate the effect of food on pharmacokinetics of GSK3882347 following oral administration of single dose in healthy adult participants	• AUC(0-24), AUC(0-t), AUC(0-inf), C24h, Cmax, tmax and tlag, as data permit
Exploratory	
• To assess ECG effects of GSK3882347, including concentration-QTc analysis, following single and repeat doses in healthy adult participants	• Change-from-baseline QTc (ΔQTcF) • Change-from-baseline heart rate, PR and QRS interval (ΔHR, ΔPR and ΔQRS) • Placebo-corrected ΔQTcF, ΔHR, ΔPR and ΔQRS

Objectives	Endpoints
	• Treatment emergent T-wave abnormalities and presence of U-waves • Categorical outlier analysis for HR, QTcF, PR and QRS
• To investigate the plasma and urine metabolic pathways of GSK3882347 in healthy participants	• Characterization of the plasma and urinary metabolites of GSK3882347, estimation of the percentage dose eliminated in urine, where possible
• To characterize the effect of GSK3882347 on intestinal microbiota following single and repeat doses in healthy adult participants	• Change in intestinal microbiome over time
• To assess potential effect of repeat doses of GSK3882347 on Cytochrome P450 3A4 (CYP3A4) enzyme activity in Part 2	• Plasma 4β-hydroxycholesterol to cholesterol ratio at pre-treatment and following repeat dosing of GSK3882347

Note: The exploratory endpoints may be analyzed as GSK3882347 clinical development continues

Safety Estimand

The primary objective is to determine the safety, tolerability and pharmacokinetic profile of GSK3882347 following oral administration of single (Part 1) and repeat doses (Part 2) of GSK3882347 in healthy adult men and women.

The safety estimand is described by the following attributes:

- Population: Healthy adult men and women of non-child bearing potential (WONCBP).
- Treatment condition: In part 1, ascending single oral dose of GSK3882347 or placebo and a food effect. In part 2, four ascending repeat-dose cohorts (Cohorts 3 to 6), who will receive a single oral dose of GSK3882347 or placebo for 7 consecutive days.
- Variable: Occurrence of adverse events (AEs) and treatment related AEs, Occurrence of clinically significant changes in vital signs, laboratory parameters, and 12-lead electrocardiogram (ECG) findings.
- Summary measure: Descriptive statistics (percentage in each category in each arm separately (as no direct comparison between treatment groups will be made) and summary statistics (appropriate for each type of endpoint) in each arm separately.
- Intercurrent events (ICE): Study treatment discontinuation (due to any reason) – the occurrence of the ICE is considered irrelevant in defining the treatment effect of interest. All safety data will be included up to the end of the period or up to the end of the follow-up (FU) (for the last period) in the analysis irrespective of the

occurrence of this ICE and the event/assessment will be assigned to the last treatment before ICE occurred.

Rationale for Estimand:
This attempts to estimate safety effects likely to be attributable to the drug irrespective of whether the participant completed the treatment.

Pharmacokinetic Estimand
The pharmacokinetic estimand is described by the following attributes:

- Population: Healthy adult men and women of non-child bearing potential (WONCBP).
- Treatment condition: In part 1, ascending single oral dose of GSK3882347 or placebo and a food effect. In part 2, four ascending repeat-dose cohorts (Cohorts 3 to 6), who will receive a single oral dose of GSK3882347 or placebo for 7 consecutive days.
- Variable: AUCs, Cmax, C12h, C24h, CL/F, Vd/F, tmax, tlag, t1/2, MRT, C22-24,U, CLr, Ae, fe (See Section 8.1.1)
- Summary measure: Descriptive statistics, treatment ratios, slope of loge(dose), least squares geometric mean, Ro, RCmax, Rctrough, Rss
- Intercurrent events (ICE):
    - Study treatment discontinuation (due to any reason) - while on treatment strategy (treatment effect is only considered before the ICE occurs)
    - Received incorrect dose or meal consume less than 99% of the meal (in fed participants) - hypothetical strategy (the data from a period in which ICE occurs would be considered missing at random and excluded from analyses)

Rationale for Estimands:
The objective of the while on treatment strategy is to estimate the PK parameters when participants have actually taken the dose/treatment condition as per protocol.

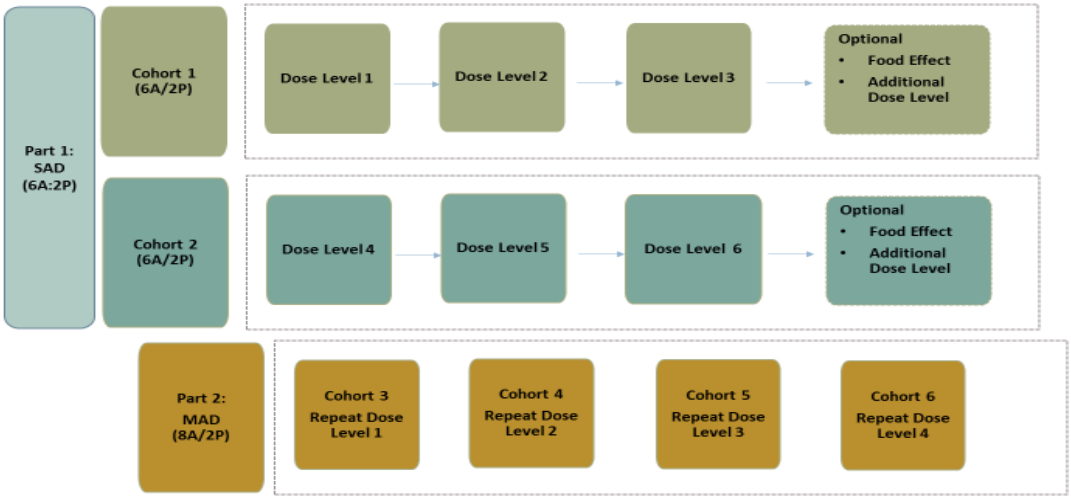
The hypothetical strategy attempts to estimate treatment effects had the intercurrent event not occurred.

2.3. Study Design

Overview of Study Design and Key Features

This is a two-part Phase I, first-time-in-human (FTIH), randomized, double-blind, single-centre, placebo-controlled, dose-escalation study to determine the safety, tolerability and pharmacokinetic profile of GSK3882347 following oral administration of single (Part 1) and repeat doses (Part 2) of GSK3882347 in healthy adult men and women of non-child bearing potential (WONCBP). Part 1 will consist of two cohorts with up to a four-period cross-over. The food effect evaluation will be conducted in last period (Period 4) in only one of the cohorts based on the observed human pharmacokinetics. During Parts 1 and 2, participants who meet the criteria for study entry will be assigned to the current dose level and randomized to receive GSK3882347 or placebo before administration of study intervention on Day1.

Dose escalation will be conducted only if it is supported by safety, tolerability and pharmacokinetic results from the preceding dose level(s). This is the first administration of GSK3882347 in humans; therefore, preliminary safety, tolerability and pharmacokinetic results will be reviewed internally at GSK in conjunction with the study site and study design adjustments may be made based on emerging data from each dose cohort. The repeat dose escalation component (Part 2) of this study will be initiated once safety at an exposure that exceeds the daily exposure predicted at steady state for the Part 2 planned starting dose of 50 mg has been demonstrated in Part 1. This is predicted to occur at the 250 mg single dose. The point at which Part 2 is initiated can be modified based on the emerging safety, tolerability and pharmacokinetic data from Part 1.



Notes

- A = active, P = placebo
- SAD = single ascending dose; MAD multiple ascending dose
- Starting SAD dose level = 50mg
- Subsequent dose escalations will be determined based on safety and PK data
- Part 2 (MAD) may start in parallel with Part 1 (SAD)

Figure shows illustration of planned dosing strategy, which may be changed or cancelled

Overview of Study Design and Key Features	
based on preliminary safety, tolerability and PK from preceding doses; and does not represent the randomization strategy.	
Design Features	• This is a two-part Phase I, double-blind (sponsor-unblinded), randomized, placebo-controlled, single and multiple-ascending-dose study in healthy volunteers. • For Part 1, approximately 16 healthy adult participants will be enrolled with a minimum of 8 participants in each cohort, where each cohort may participate in up to 4 periods. • In each cohort of Part 1, each participant will receive three doses (escalations or reductions) of GSK3882347. In the fourth period, one cohort will potentially assess food effect and the other cohort will potentially receive a fourth dose (escalated or reduced) of GSK3882347. • In Part 2, enough healthy adults will be screened to provide approximately 10 participants for randomization within each of the 4 MAD dosing cohorts. • Preliminary safety, tolerability and pharmacokinetic results will be reviewed internally at GSK in conjunction with the study site and study design adjustments may be made based on emerging data from each dose cohort before dose escalation.
Dosing	• Part 1 will consist of 2 separate cohorts of 8 healthy participants each. The planned starting GSK3882347 dose in Part 1 is 50 mg administered as a single oral dose. The dose is planned to increase in subsequent cohorts to 150, 250, 500, 750 and 900 mg. • Part 2 consists of approximately four ascending repeat-dose cohorts (Cohorts 3 to 6), each with 10 participants who will receive a single oral dose of GSK3882347 or placebo for 7 consecutive days. The planned starting dose of GSK3882347 in Part 2 is 50 mg administered as a single dose on Days 1 through 7. The dose is planned to increase in subsequent cohorts to 150, 500 and 900 mg.
Time & Events	Refer to Appendix 2: Schedule of Activities
Treatment Assignment	Approximately 56 randomized participants will be recruited for the entire study, including 16 evaluable participants in the SAD part (Part 1) with 6 active and 2 placebo in each of the two cohorts, and 40 evaluable participants in the MAD part (Part 2) with 8 active and 2 placebo in each of the four cohorts. Additional participants may be recruited as replacement for withdrawn participants.
Interim Analysis	• No formal interim analyses (IA) are planned for this study. • However, preliminary safety, tolerability and PK data will be reviewed prior to each dose escalation in Part 1 (single dose) and Part 2 (repeat dose). • Data for these reviews will be cumulative and can include individual participant data, summaries by study intervention and graphical

Overview of Study Design and Key Features	
	displays. This is a sponsor unblinded trial and select roles within the GSK study team (detailed in Section 9.5.1 of the protocol) will be unblinded for these reviews

2.4. Statistical Analyses

The main purpose of this study is to assess the safety, tolerability, and pharmacokinetic attributes of oral doses of GSK3882347 in healthy participants. Results for the primary analyses will be descriptive in nature. Statistical modelling on select pharmacokinetic parameters will be performed to test for dose proportionality, dose accumulation, time invariance, achievement of steady state and food effects. Point estimates along with 90% confidence intervals will be reported for all secondary endpoints, where appropriate.

3. PLANNED ANALYSES

3.1. Interim Analyses

There will be no formal interim analysis. However, preliminary safety, and PK data will be reviewed in-stream by the GSK study team members prior to each dose escalation in Part 1 (SAD), Part 2 (MAD) and before the food effect in Part 1. Data for these reviews will be cumulative and can include individual participant data, summaries by study intervention and graphical displays. This is a sponsor unblinded trial and select roles within the GSK study team will be unblinded for these reviews. Dose escalation can only occur after the safety, PK profiles are found supportive to proceed with the evaluation of the next higher dose level. The details of internal review process to support dose-escalation are included in the dose escalation plan charter document.

Preliminary results from available safety data may be reported prior to database freeze for the purposes of safety review by GSK, and where required by regulatory bodies. Other selected preliminary data may be unblinded and reported prior to database freeze for internal decision making.

In each case described above, the study will not be officially unblinded and access to the randomization will be restricted to the unblinded site pharmacist. For dose escalation the Sponsor study team physicians, statistician, and clinical pharmacokinetic staff and/or their delegate will have access to unblinded data if required.

After each cohort, the data will be reviewed – the data consists of the PK and safety data. Non-compartmental analysis (NCA) PK analysis will be performed to obtain PK parameters.

3.2. Final Analyses

The final planned primary, secondary and exploratory 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), source data lock (SDL), and database freeze (DBF) has 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.

4. ANALYSIS POPULATIONS

Population	Definition / Criteria	Analyses Evaluated
Screened	• All participants who were screened for eligibility	• Study Population
Enrolled	• All participants who had passed screening and entered the study. 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
Randomized	• All enrolled participants who were randomized into the study irrespective of whether they receive any treatment. Note: This population will be based on the treatment the participant was randomized to.	• Study Population
Safety	• All participants who received at least 1 dose of study intervention. Participants will be analysed according to the treatment they received.	• Study Population • Safety
Pharmacokinetic (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
Biomarker	• All participants in the Safety population who had at least 1 non-missing Biomarker assessment	• Biomarker

4.1. Protocol Deviations

Protocol deviations will be tracked by the study team throughout the conduct of the study in accordance with the Protocol Deviation Management Plan. Data will be reviewed prior to freezing the database to ensure all important deviations are captured and categorised on the protocol deviations dataset. This dataset will be the basis for the summaries and listings of protocol deviations.

A separate listing of all inclusion/exclusion criteria deviations will also be provided. This listing 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**	**Header**	**Order in TLF**
PART 1				
P/PS	Placebo/Placebo Sentinel	Placebo SD	SD PBO	**1**
D1/D1S	GSK3882347 Dose Level 1/ GSK3882347 Dose Level 1 sentinel	GSK3882347 50 mg SD	SD 50mg	**3**
D2/D2S	GSK3882347 Dose Level 2/ GSK3882347 Dose Level 2 sentinel	GSK3882347 150 mg SD	SD 150 mg	**4**
D3/D3S	GSK3882347 Dose Level 3/ GSK3882347 Dose Level 3 sentinel	GSK3882347 250 mg SD	SD 250 mg	**5**
D7/D7S	GSK3882347 Dose Level 7 fed/ GSK3882347 Dose Level 7 fed sentinel	GSK3882347 250 mg SD Fed	SD 250 mg Fed	**6**
D4/D4S	GSK3882347 Dose Level 4/ GSK3882347 Dose Level 4 sentinel	GSK3882347500 mg SD	SD 500 mg	**7**
D5/D5S	GSK3882347 Dose Level 5/ GSK3882347 Dose Level 5 sentinel	GSK3882347 900 mg SD	SD 900 mg	**8**
D6/D6S	GSK3882347 Dose Level 6/ GSK3882347 Dose Level 6 sentinel	GSK3882347 15 mg SD	SD 15 mg	**2**
D8/D8S	GSK3882347 Dose Level 8/ GSK3882347 Dose Level 7 sentinel	This Treatment group not utilized in the study		
PART 2				
RP/RPS	Placebo Repeated/Placebo Repeated Sentinel	Placebo RD	RD PBO	1
R1/R1S	GSK3882347 Repeat Dose Level 1/ GSK3882347 Repeat Dose Level 1 sentinel	GSK3882347 50 mg RD	RD 50mg	2
R2/R2S	GSK3882347 Repeat Dose Level 2/ GSK3882347 Repeat Dose Level 2 sentinel	GSK3882347 150 mg RD	RD 150 mg	3
R3/R3S	GSK3882347 Repeat Dose Level 3/ GSK3882347 Repeat Dose Level 3 sentinel	GSK3882347 500 mg RD	RD 500 mg	4
R4/R4S	GSK3882347 Repeat Dose Level 4/ GSK3882347 Repeat Dose Level 4 sentinel	GSK3882347 900 mg RD	RD 900 mg	5

NOTES:

- Order represents treatments being presented in TFL, as appropriate. Dose levels will be updated after database freeze based on the actual number of dose levels and cohorts.
- Doses will be listed in the increasing order in all summaries.
- Placebo will be pooled by part
- Descriptions and headers will be updated with actual doses after database freeze.

- Doses mentioned in code D1/ D1S, D2/ D2S, D3/D3S and D7/D7S (optional) in Part I shall be for cohort 1. Dose level in code D4/D4S, D5/D5S, D6/D6S and D8/D8S (optional) in Part 1 shall be for cohort 2. Each cohort will have 2 participants on Placebo in each period.
- Each of the four doses in Part 2 will be administered in cohorts 3, 4, 5 and 6.
- Dose Levels 7 and 8 are reserved for testing the food effect. Dose Level 8 was not utilised in the study.

5.2. Baseline Definitions

For all endpoints the baseline value will be the latest pre-dose assessment (at each period for part 1) with a non-missing value, including those from unscheduled visits. If time is not collected, Day 1 assessments are assumed to be taken prior to first dose and used as baseline. The mean will be considered for triplicate measurements taken at the latest pre-dose assessment.

If the latest pre-dose assessment is missing, then the previous assessment time point would be considered as baseline where possible (i.e. if Day 1 (Pre-dose) is missing the Day -1 will be used).

Baseline Definitions – Part 1

Parameter	Screening	Day -1	Day 1 (Pre-Dose)	Baseline Used in Data Display
12-lead Electrocardiogram (ECG) Vital signs (BP, HR, tympanic temperature, respiration rate)	X	X	X	Day 1
Clinical chemistry (including liver chemistries), hematology and urine tests (including urine creatinine)		X		Day -1

Baseline Definitions – Part 2

Parameter	Screening	Day -1	Day 1 (Pre-Dose)	Baseline Used in Data Display
12-lead Electrocardiogram (ECG), Vital signs (BP, HR, Tympanic temperature, respiration rate)	X	X	X	Day 1
Clinical chemistry (including liver chemistries), hematology, and urine tests (including		X		Day -1

Parameter	Screening	Day -1	Day 1 (Pre-Dose)	Baseline Used in Data Display
urine creatinine)				
4β-hydroxycholesterol Sampling			X	Day 1

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
12.3	Appendix 3: Assessment Windows
12.4	Appendix 4: Study Phases and Treatment Emergent Adverse Events
12.5	Appendix 5: Data Display Standards & Handling Conventions
12.6	Appendix 6: Derived and Transformed Data
12.7	Appendix 7: Reporting Standards for Missing Data
12.8	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 participant'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. Details of the planned displays are presented in Appendix 12: List of Data Displays.

7. SAFETY ANALYSES

The safety analyses will be based on the Safety population, unless otherwise specified. Outputs will be presented separately for the two parts (Parts 1 and 2).

All safety data displays will be split by actual treatment received, except where specified below.

Details on the safety estimand are given in Section 2.2.

7.1. Adverse Events Analyses

Adverse Events (AE) will be coded using Medical Dictionary for Regulatory Activities (MedDRA) central coding dictionary. Adverse events analyses will be based on GSK Core Data Standards. The following displays for Adverse events shall be generated: All Adverse Events by System Order Class and Preferred Term, Adverse Events by maximum grade/intensity, Common Serious and Non-Serious Adverse Events, Serious Adverse Events, Drug-related Adverse Events.

COVID-19 events will be listed based on GSK Core Data Standards.

The details of the planned displays are provided in Appendix 12: List of Data Displays.

7.2. Clinical Laboratory Analyses

Laboratory results will be included in the reporting of this study for haematology, clinical chemistry and urinalysis. Based upon laboratory normal ranges, the laboratory test results will be categorized according to the normal range as low (below the lower limit), normal (within the normal range) and high (above the upper limit). Summary statistics for change from baseline will also be tabulated. Laboratory evaluations will be based on GSK Core Data Standards. The details of the planned displays are in Appendix 12: List of Data Displays.

7.3. Other Safety Analyses

The analyses of non-laboratory safety test results including ECGs and vital signs will be based on GSK Core Data Standards, unless otherwise specified. The details of the planned displays are presented in Appendix 12: List of Data Displays.

7.4. Exploratory Safety Analyses

All ECG-related analyses listed in the exploratory objectives/endpoints will be conducted and reported separately.

8. PHARMACOKINETIC ANALYSES

8.1. Pharmacokinetic Parameter Analyses and Summaries

The derived PK parameters (AUC, Cmax) of partially completed participants will be computed if data permits (see Section 8.1.1.2). In the food effect period, derived PK parameters of participants who consume less than 99% of the meal (in fed participants) will be computed.

If feasible, participants who withdraw from study will be replaced until the desired sample size is attained. PK data from withdrawn participants and their replacement will be included in PK analyses. If a participant discontinues from study treatment, they will proceed to follow up and no further PK data will be collected.

Details on the pharmacokinetic estimand are given in Section 2.2.

8.1.1. Endpoint / Variables

Part 1 (Single dose):

- Plasma: AUC(0-12), AUC(0-24), AUC(0-t), AUC(0-inf), Cmax, C12h, C24h, CL/F, Vd/F (log-transformed and untransformed), tmax, tlag, t1/2, and MRT (untransformed)
- Urine: $C_{22\text{-}24,U:}$ concentration at 22-24h collection, CLr ($\log_e$-transformed and untransformed), Ae, fe (untransformed), ∑Ae

Part 2 (Repeat dose):

- Plasma: AUC(0-12), AUC(0-tau), Cmax, Ctau, C12h (log-transformed and untransformed), tmax for Days 1 and 7, and Ro (untransformed)

  Urine: $C_{22\text{-}24,U:}$ concentration at 22-24h collection, CLr ($\log_e$-transformed and untransformed), Ae, fe (untransformed), ∑Ae for Days 1 and 7

8.1.1.1. Drug Concentration Measures

Refer to Appendix 5: Data Display Standards & Handling Conventions (Section 12.5.3 Reporting Standards for Pharmacokinetic)

8.1.1.2. Derived Pharmacokinetic Parameters

Plasma pharmacokinetic parameters will be calculated by standard non-compartmental methods according to current CPMS working practices and using the currently supported version of WinNonlin (Currently version 8.0.)

Calculations of pharmacokinetic parameters for the final analysis will be based on actual sampling times. Pharmacokinetic parameters listed below in Table 4 will be determined from the plasma and urine concentration-time data, as data permits. If parameters cannot be determined, a ‘Not done’ or ‘Not calculable’ flag will be present in the data.

Urine pharmacokinetic parameters will be calculated as follows:

- Ae (amount excreted in urine) = urine concentrations x weight of urine sample
- ∑Ae (cumulative amount excreted in urine) = sum of Ae per individual profile
- CLr (renal clearance) = ∑Ae / plasma AUC(0-t)
- fe (fraction of dose eliminated in urine) = ∑Ae / dose administered

Table 2 Derived Pharmacokinetic Parameters

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 log trapezoidal rule for each decremental trapezoid.
AUC(0-inf) or AUC(0-∞)	Area under the concentration-time curve extrapolated to infinity calculated as: $AUC(0\text{-}inf) = AUC(0\text{-}t) + C(t) / \lambda_z$
AUC(0-12)	Area under the concentration-time curve from time zero to 12 hours post-dose
AUC(0-24)	Area under the concentration-time curve from time zero to 24 hours post-dose
AUC(0-τ) or AUC(0-tau)	AUC from time zero during a dosing interval of duration "τ" (tau)
Ro	Observed accumulation ratio (Ro) for AUC will be calculated as follows: Day 7 AUC(0-24)/ Day 1 AUC(0-24)
Ae	Amount of GSK3882347 in urine
$C_{22:24;U}$	Urine concentration between 22-24 hours after dosing
C12h	Plasma concentrations at 12 hours after dosing
C24h	Plasma concentrations at 24 hours after dosing
Cmax	Maximum observed blood concentration, determined directly from the concentration-time data.

Ctau	Plasma concentrations over the dosing interval τ (tau)
Ctrough	Trough concentration
CLr	Renal clearance
CL/F	Apparent total clearance of the drug from plasma after oral administration
fe	Fraction of the dose excreted in the urine
λ_z	The first order rate constant associated with the terminal (log-linear) portion of the concentration-time curve.
MRT	Mean residence time
Rss	Steady state ratio (Rss) will be calculated as follows: Day 7 AUC(0-τ)/ Day 1 AUC(0-inf)
RoCmax	Observed accumulation ratio for Cmax (RoCmax) will be calculated as follows: RoCmax = Day 7 Cmax/ Day 1 Cmax
Tmax	Time to reach Cmax, determined directly from the concentration-time data.
$t_{½}$	Apparent terminal phase half-life will be calculated as: $t_{½} = \ln 2 / \lambda_z$
t_{lag}	Lag time
Vd/F	Apparent volume of distribution after oral administration
∑Ae	Cumulative amount excreted in urine

NOTES: Additional parameters may be included as required.

8.1.2. Summary Measure

Parameters will be summarised according to the method defined in Section 8.1.1. Endpoints/Variables and described below. They will be calculated and tabulated by dose level for study Part 1 and Part 2 separately.

Untransformed Data	N, n, arithmetic mean, 90% confidence interval (CI) for the arithmetic mean, SD, median, minimum, maximum
Log_e-transformed Data	Geometric mean, 90% CI for the geometric mean, SD of log_e-transformed data and $\%CV_b$ (percent coefficient of variation between groups)

8.1.3. Population of Interest

The primary pharmacokinetic analyses will be based on the PK population, unless otherwise specified.

8.1.4. Strategy for Intercurrent (Post-Randomization) Events

There are three kinds of intercurrent events (ICE):

- Study treatment discontinuation (due to any reason) - while on treatment strategy (treatment effect is only considered before the ICE occurs)
- Received incorrect dose or meal or did not consume at least 90% of the meal (in fed participants) - hypothetical strategy (the data from a period in which ICE occurs would be considered missing at random and excluded from analyses)

8.1.5. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 12: List of Data Displays and will be based on GSK Data Standards and statistical principles.

8.1.5.1. Statistical Methodology Specification

Endpoint / Variables
• (Part 1) Single dose plasma: AUC(0-12), AUC(0-24), AUC(0-t), AUC(0-inf), Cmax, C12h, C24h, CL/F, Vd/F (log-transformed and untransformed), tmax, tlag, t1/2 and MRT (untransformed) • (Part 2) Repeat dose plasma: AUC(0-12), AUC(0-tau), Cmax, Ctau, C12h (log-transformed and untransformed), tmax (untransformed) • (Part 1 and Part 2) Single and repeat dose urine $C_{22\text{-}24,U}$, CLr (log-transformed and untransformed) Ae, fe (untransformed)
Results Presentation
• Separate outputs will be produced for Part 1 and Part 2 • Geometric LS means for each treatment and associated 90% CIs for each parameter. • Estimates of within-participant variability (%CVw) for AUC and Cmax (%CVw represents a pooled measure of within-participant variability across treatments). • Comparative plots of individual plasma PK parameters by treatment on linear and semi-logarithmic scales.

8.2. Statistical Analysis of Derived PK Parameters

The following statistical analyses will only be performed if PK concentration levels exceed the lower level of Quantification (LLQ) for the data to be available.

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.

8.2.1. Endpoint / Variables

- Dose proportionality AUC, Cmax, Ctrough, Ae
- Accumulation ratio Ro
- Time invariance using AUC, $C_{22\text{-}24,U}$ (repeat dose)
- Steady state (Ctau)
- Food effect AUC, C24h, Cmax, tmax and tlag

8.2.2. Summary Measure

PK of GSK3882347 after single dose.

- Dose proportionality (Day 1)
- Food effect (equivalent dose comparisons fed vs fasted)

PK of GSK3882347 after repeat dose.

- Dose proportionality (on Day 1 and Day 7)
- Accumulation (Day 7/ Day 1 for each dose)
- Time invariance (Day 7/ Day 1 for each dose)
- Steady state (Day 7/ Day 1 for each dose)

8.2.3. Population of Interest

The secondary pharmacokinetic analyses will be based on the pharmacokinetic population

8.2.4. Strategy for Intercurrent Events

For details of the estimand strategy for intercurrent events see Section 2.2 and Section 8.1.4

8.2.5. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 12: List of Data Displays and will be based on GSK Data Standards and statistical principles.

Unless otherwise specified, endpoints/variables defined in Section 8.1.1 will be summarised using descriptive statistics, graphically presented (where appropriate) and listed.

8.2.5.1. Statistical Methodology Specification

Assessment of dose proportionality will be done on Day 1 in Part 1 (single dose) and Day 1 and 7 in Part 2 (repeat dose). The following PK analyses will only be performed if sufficient data is available (i.e. if participants have well defined plasma profiles).

1. Pharmacokinetic Statistical Analyses (Dose Proportionality - Single and Repeat Dose Study Phases)

Endpoint(s)

- Single Dose: AUC(0-24), AUC(0-t), AUC(0-inf), Cmax, Ae(Urine)
- Repeat Dose: AUC(0-τ), Cmax, Ctrough

Model Specification

- Will be statistically analyzed using the power model

$$y = \exp(\Theta_1 + r_i + \varepsilon) \cdot \text{dose}^{\theta 2}$$

where y denotes the PK parameter being analyzed and r the random subject effect. The θ_s, s=1,2, in the power model will be estimated by linear regression of the $\log_e$-transformed PK parameters on $\log_e$ dose levels.

$$\log(y_{ij}) = \theta_1 + \theta_2 \cdot \log(d_{ij}) + r_i + \varepsilon_{ij} \quad (1)$$

where

- y_{ij} is the observed or predicted PK variable of the j-th dose d_{ij} administered to the i-th participant. In particular, it is an AUC or a Cmax, as applicable.
- θ_1, θ_2 are population intercept and slope, respectively.
- r_i is the random effect associated with participants, it has mean zero and variance s^2
- ϵ_{ij} is a random error term, with mean zero and variance σ^2.
- The covariance structure of the G matrix will be specified as unstructured.

Note, for part 2, participants will not receive more than one dose, therefore the random subject effect (r_i) will not be included in that model.

- If the power model (and attempts at fitting the power model with simplified covariance structures fail to converge) does not indicate dose proportionality, the ANOVA model will be performed:
  - On Day 1 and 7, dose proportionality will also be assessed using the Analysis of Variance (ANOVA) method. Following a $\log_e$ transformation, dose-normalized AUC (0--24), AUC(0-t) and Cmax will be analyzed separately using a mixed effects model. Dose (categorical variable), day and a day by dose interaction will be fitted as a fixed effect, and repeated day/subject=subject type='UN' will be fitted.
    - All doses will be compared to the chosen planned dose which will be decided by the kineticist. To calculate the dose normalized parameters, the derived parameter for each dose will be divided by the relevant dose and multiplied by the chosen planned dose.

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
Model Results Presentation
• Estimates of the slope of $\log_e$(parameter) vs $\log_e$ (dose) will be reported along with corresponding 90% confidence intervals (slope≈1 implies dose proportionality). • If the ANOVA model is used, adjusted geometric means for each dose will be presented along with the standard errors (SE) of the logged data and the 90% CIs. Estimated treatment ratios and corresponding 90% confidence intervals will also be presented.

2. Pharmacokinetic Statistical Analyses - Dose Accumulation for Repeat Dose
Endpoint / Variables
AUC(0-tau), Cmax, Ctrough, and $C_{22\text{-}24}$(Urine)
Model Specification
• $\log_e$-transformed values of endpoints will be statistically analyzed using a Mixed Model with the following effects: o **Fixed effect:** Main: day, dose Interaction: day*dose. o **Random Effect:** Subject Data will be analyzed for all participants in the repeat dosing part. • 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 covariance structure for the G matrix will be used. o If this model fails to converge, alternative covariance structures may be considered such as VC or CS etc. o Akaike's Information Criteria (AIC) will be used to assist with the selection of covariance structure.
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.

Model Results Presentation

Day 7 will be compared to Day 1 in order to estimate the accumulation ratio.
Point estimates and 90% confidence intervals for the differences "Day 7- Day 1" will be constructed using the appropriate error term. The point estimates and associated 90% confidence intervals will then be exponentially back-transformed to provide point and 90% confidence interval estimates for the ratios "Day 7: Day 1" for each active dose. If both the dose and day by dose interaction terms are not significant, a single point estimate and confidence interval pooled across all doses will also be constructed.

3. Pharmacokinetic Statistical Analyses – Time Invariance in Repeat Dose

Endpoint / Variables

Time Invariance Ratio: AUC (0-tau) on Day 7 to AUC (0-inf) on Day 1,

$C_{22\text{-}24,u}$ on Day 7 to $C_{22\text{-}24,u}$ on Day 1

Note: Day 1 AUC(0-t) to be used if Day 1 AUC(0-inf) is not available

Model Specification

- $\log_e$-transformed values of endpoints will be statistically analyzed using Mixed Model ANOVA
  - **Fixed effect:**
    Main: day, dose
    Interaction: day*dose.
  - **Random Effect:** Subject
- Data will be analyzed for all participants in the repeat dosing part of the study.
- AUC(0-inf) on Day 1 will be the reference phase in the analysis, while AUC(0- tau) on Day 7 (both collected at repeat dosing) will be the test phase, using log-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 covariance structure for the G matrix will be used.
  - In the event that this model fails to converge, alternative covariance structures may be considered such as VC or CS.
  - Akaike's Information Criteria (AIC) will be used to assist with the selection of covariance structure.

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.

Model Results Presentation
The time invariance ratio of GSK3882347 will be estimated by calculating the ratio of the generalized least square means of AUC (0- τ) on Day 7 to AUC (0-inf) on Day 1, along with the corresponding 90% CI at each dose level. Point estimates and 90% CIs will be presented by exponentiating the difference in least squares means of AUC (0-τ) Day 7 and AUC (0-inf) Day 1 along with the associated CI limits.

4. Pharmacokinetic Statistical Analyses – Steady state for Repeat Dose
Endpoint / Variables
Trough plasma concentration at end of dosing (Ctau) **Note : Include Day 3 to Day6 Pre dose concentration**
Model Specification
The $\log_e$-transformed endpoint will be statistically analyzed using a mixed model (MM) using log-transformed dose data. • Fixed effects: day(continuous variable) • Random effect: Subject Note: day as continuous variable The analysis is done separately for each treatment • 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 covariance structure for the G matrix will be used. o If this model fails to converge, alternative covariance structures may be considered such as VC or CS. Akaike's Information Criteria (AIC) will be used to assist with the selection of covariance structure.
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
Model Results Presentation
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. If the day-by-dose interaction were not significant, then the point estimates and 90% CIs for the individual dose levels will also be pooled across all doses for a single D7/D1 ratio.

Steady-state will be assessed visually by plotting trough concentration levels, Cτ, collected pre-morning dose versus collection day by dose.

5. Pharmacokinetic Statistical Analyses - Food Effect for Single Dose
Endpoint(s)
AUC(0-24), AUC(0-t), AUC(0-inf), C24h, Cmax
Model Specification

• Will be statistically analyzed using a mixed model (MM) using $\log_e$ transformed data
• Terms fitted in the mixed effect ANOVA model will include:
  o Fixed effect: fed/fasted
  o Random Effect: Subject
• Only data from the same dose level as the fed dose group will be included in this analysis, all other dose level data will be excluded.
• 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 covariance structure for the G matrix will be used.
  o If this model fails to converge, alternative covariance structures may be considered such as VC or CS.
  o Akaike's Information Criteria (AIC) will be used to assist with the selection of covariance structure.

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.
Model Results Presentation
Point estimates and corresponding 90% confidence intervals will be constructed for the comparisons of interest of GSK3882347 fed – GSK3882347 fasted, using the residual variance. These will then be back-transformed to provide point estimates and corresponding 90% confidence intervals for the geometric mean ratios fed: fasted.
Non-parametric Analysis
Endpoint(s)
t_{max} and t_{lag} Note: These endpoints will not be log transformed for analysis
Model Specification
Wilcoxon matched pair test Only data from the same dose level as the fed dose group will be included in this analysis, all other dose level data will be excluded.

Model Results Presentation
Point estimate and corresponding 90% CI for the median difference (fed-fasted) will be presented

8.3. Exploratory Pharmacokinetic Analyses

The analyses for characterization of the plasma and urinary metabolites of GSK3882347, estimation of the percentage dose eliminated in urine (where possible) will be reported separately by DMPK.

8.4. Microbiome analysis

Change in intestinal microbiome over time will be analysed by Diversigen and reported separately.

9. POPULATION PHARMACOKINETIC (POPPK) ANALYSES

Population pharmacokinetic analyses will be performed under a separate CPMS RAP and reported separately.

10. BIOMARKER ANALYSES

10.1. Exploratory Biomarker Analyses

10.1.1. Endpoint / Variables

Part 2 (Repeat dose): Plasma 4β-hydroxycholesterol to cholesterol ratio

Plasma 4β-hydroxycholesterol and cholesterol will be provided in the Biomarker data set (provided by Covance) and the below described ratios will be derived for this endpoint

- Ratio of Plasma 4β-hydroxycholesterol to Cholesterol at each visit
- Ratio to baseline (ratio post/ratio pre-dose) of Plasma 4B-hydroxycholesterol to Cholesterol ratios.
- Ratio of Plasma 4β-hydroxycholesterol at Post-baseline to Baseline visit

10.1.2. Summary Measure

Derived Ratios of Plasma 4B-hydroxycholesterol to Cholesterol is summarized.

10.1.3. Population of Interest

The biomarker analyses will be based on the Biomarker population, unless otherwise specified.

10.1.4. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 12: List of Data Displays and will be based on GSK Data Standards and statistical principles.

Endpoints / variables defined in Section 10.1.1 will be summarised using descriptive statistics, graphically presented and listed.

11. REFERENCES

Darpo B., Garnett C., Benson C.T., Keirns J., Leishman D., et. al. Cardiac safety research consortium: Can the thorough QT/QTc study be replaced by early QT assessment in routine clinical pharmacology studies? Scientific update and a research proposal for a path forward. Am Heart J 2014; 168:262-72.

US Department of Health and Human Services (DHHS), Food and Drug Administration, Center for Drug Evaluation and Research (CDER). Guidance for Industry. Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers. July 2005.. Available from: http://www.fda.gov/downloads/Drugs/.../Guidances/UCM078932.pdf

European Medicines Agency. Guideline on Strategies to Identify and Mitigate Risks for First-In-Human and Early Clinical Trials With Investigational Medicinal Products (EMEA/CHMP/SWP/28367/07 Rev. 1). Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002988.pdf

Fihn SD. Clinical practice. Acute uncomplicated urinary tract infection in women. N Engl J Med. 2003;349(3):259-66.

Flamm RK, Sader HS, Farell DJ, Jones RN. Ceftazidime-avibactam and comparator agents tested against urinary tract isolates from a global surveillance program (2011). Diagn Microbiol Infect Dis. 2014;80(3):233-8.

Foxman B, Barlow R, D'Arcy H, Gillespie B, Sobel JD. Urinary tract infection: self-reported incidence and associated costs. Ann Epidemiol. 2000;10(8):509-15.

Foxman B. Epidemiology of urinary tract infections: incidence, morbidity, and economic costs. Am J Med. 2002;113(Suppl 1A):5S-13S.

Foxman B. The epidemiology of urinary tract infection. Nat Rev Urol. 2010;7(12):653-60.

GlaxoSmithKline Document Number 2019N403317_01. Investigator's Brochure for GSK3882347, June 2020.

Gupta K, Hooton TM, Miller L; Uncomplicated UTI IDSA Guideline Committee. Managing uncomplicated urinary tract infection — making sense out of resistance data. Clin Infect Dis. 2011a;53(10):1041-2.

Gupta K, Hooton TM, Naber KG, Wullt B, Colgan R, Miller LG, et al. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: a 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. Clin Infect Dis. 2011b;52(5):e103-20.

Hooton TM. Clinical practice. Uncomplicated urinary tract infection. N Engl J Med. 2012;366(11):1028-37.

James LP, Letzig L, Simpson PM, Capparelli E, Roberts DW, Hinson JA, Davern TJ, Lee WM. Pharmacokinetics of Acetaminophen-Adduct in Adults with Acetaminophen Overdose and Acute Liver Failure. Drug Metab Dispos 2009; 37:1779-1784.

O'Neill, J., et. al. (2016) The review on antimicrobial resistance. Tackling drug-resistant infections globally. Report sponsored by the Wellcome Trust and U.K. Government, available at https://amr-review.org/

Sanchez GV, Babiker A, Master RN, Luu T, Mathur A, Bordon J. Antibiotic resistance among urinary isolates from female outpatients in the United States in 2003 and 2012. Antimicrob Agents Chemother. 2016;60(5):2680-3.

Stamm WE, Hooton TM. Management of urinary tract infections in adults. N Engl J Med. 1993;329(18):1328-34.

Talan DA, Stamm WE, Hooton TM, Moran GJ, Burke T, Iravani A, et al. Comparison of ciprofloxacin (7 days) and trimethoprim-sulfamethoxazole (14 days) for acute uncomplicated pyelonephritis in women: a randomized trial. JAMA. 2000;283(12):1583-90.

The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E8. General Considerations for Clinical Trials (CPMP/ICH/291/95).

US Department of Health and Human Services, DHHS, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Clinical Pharmacology. Draft Guidance for Industry. Assessing the Effects of Food on Drugs in INDs and NDAs — Clinical Pharmacology Considerations. February 2019. Available from: https://www.fda.gov/media/121313/download.

12. APPENDICES

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

- Protocol deviations will be tracked by the study team throughout the conduct of the study in accordance with the Protocol Deviation Management Plan.
    - 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 on the protocol deviations dataset.
    - This dataset will be the basis for the summaries and listings of protocol deviations.
- 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.

12.2. Appendix 2: Schedule of Activities

12.2.1. Protocol Defined Schedule of Events

Table 3 Time and Events Table: Screening and Follow-up Visits; Single and Repeat Dose Escalation (Parts 1 and 2)

Procedure	Screening Period (up to 30 days before Day 1)	Follow-up Visit (14 days ± 3 days after the last study intervention)	Notes
Informed consent	X		
Inclusion and exclusion criteria	X		Recheck clinical status before randomization and/or first dose of study intervention
Demography	X		
Medical history (includes substance usage and family history of premature cardiovascular disease) and medication history	X		Substances: drugs, alcohol, tobacco and caffeine
Full physical examination including height and weight	X		
Brief 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)
AE Review		X	
SAE Review	X	X	Serious AEs will be collected from the signing of informed consent
Concomitant medication review	X	X	
Vital signs (BP, HR, tympanic temperature, respiration rate)	X	X	Single measurements will be obtained
Holter monitoring	X		Approximately 24 hour screening
12-lead safety electrocardiogram	X	X	Single measurements will be obtained
Clinical chemistry (including liver chemistries), hematology, and urine tests (including urine creatinine)	X	X	
Human Immunodeficiency Virus (HIV), Hepatitis B surface antigen and hepatitis C screen	X		
COVID-19 screening	X		Frequency in accordance with site procedures

Procedure	Screening Period (up to 30 days before Day 1)	Follow-up Visit (14 days ± 3 days after the last study intervention)	Notes
Urine Drug, Smoke Breathalyzer and Alcohol Breath Tests	X		
b-hCG pregnancy/Estradiol/FSH Tests	X		Pregnancy test as appropriate. Urine Pregnancy Kits (HCP Pregnancy Test Strip). Estradiol and FSH at screening as appropriate. Only women of non-childbearing potential may participate
Stool microbiome collection/stool type assessment		X	Participants will be given instructions and collection items for specimen collection for the follow up visit. Total of 3 collection time points: Day -1, prior to discharge and follow-up. The other sample collections can be found in SoA Table 4 for Part 1 and Table 5 and Table 6 for Part 2.
Out Patient Visit	X	X*	*At least 7 days and no greater than 14 days after the last study intervention Additional follow-up visits may be scheduled if there are clinical findings at the follow-up visit
AE = adverse event, β-hCG = beta human chorionic gonadotropin, BP = blood pressure, FSH = follicle-stimulating hormone, HR = heart rate, SAE = serious adverse event.			

- The timing and number of planned study assessments, including: safety and pharmacokinetic assessments may be altered during the study based on newly available data (e.g., to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.
- Any changes in the timing or addition of time points for any planned study assessments as the result of emerging pharmacokinetic/pharmacodynamic data from this study must be documented and approved by the relevant study team member and then archived in the sponsor and site study files but will not constitute a protocol amendment. The Competent Authority (CA) and ethics committee (EC) will be informed of any safety issues that constitute a substantial amendment and require alteration of the safety monitoring scheme or amendment of the informed consent form (ICF). The changes will be approved by the CA and the EC before implementation.

Table 4 Part 1 - Single Dose Escalation and Food Effect

	Study Days																		
Procedure	**-1**	**1**												**2**		**3**	**4**	**5**	**Notes**
		Predose	**0**	**0.25**	**0.5**	**1**	**1.5**	**2**	**4**	**6**	**8**	**12**	**16**	**24**	**32**	**48**	**72**	**96**	**Hours relative to study intervention**
Inclusion and exclusion criteria	X																		
Brief physical examination	X													X		X		X	
Urine Drug, Smoke Breathalyzer/Alcohol Breath Tests	X																		Additional testing may be performed at other timepoints
β-hCG pregnancy test	X																		Pregnancy test as appropriate
Admission to clinical unit	X																		Participants to be admitted to the unit the day before dosing (Day -1) and remain in house until discharge
Randomization		X																	Randomization will occur before first dose in Period 1
Administration of study intervention			X																No minimum time interval is required between the sentinels at each dose level. Approximately 15 minutes will be observed between the dosing of the remaining participants
AE Review			X	←----------Continuous review----------→															
SAE Review	←----------Continuous review----------→																		Serious AEs will be collected from the signing of informed consent.

Ad hoc COVID-19 testing based on clinical presentations and site procedures	←----------Continuous review----------→																	X	Sample collected upon discharge
Concomitant medication review			X	←----------Continuous review----------→															
Vital signs (BP, HR, tympanic temperature, respiration rate)	X	X*				X		X	X	X	X	X		X		X	X	X	*Triplicate measurements of blood pressure and pulse rate will be obtained pre-dose and averaged. Single measurements will be obtained at all other timepoints. Timings will be reviewed as cohorts progress and may be adjusted to ensure appropriate measurements relative to peak drug concentrations for subsequent cohorts.
12-lead safety electrocardiogram	X	X*				X		X	X	X	X	X		X					Triplicate 12-lead safety ECGs will be obtained no more than 15 minutes apart within 1-hour pre-dose and single measurements will be obtained at all other timepoints.

Continuous cardiac monitoring**		X*	←----------Continuous review----------→																**Participants will be semi-supine resting for at least 10 minutes prior to and 5 minutes after each time point for ECG extractions. *3 time points (-45, -30 and -15 minutes) prior to dosing. When ECG extractions coincide with safety ECGs, vital signs assessment and blood draws, procedures should occur in that order. Will not be collected in food effect.
Clinical chemistry (including liver chemistries), hematology, and urine tests (including urine creatinine)	X													X		X	X	X	
PK Blood Sample		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Details of PK sample collection and storage will be provided in the Study Reference Manual.
Metabolite Blood Sample		X		X	X	X	X	X	X	X	X	X	X	X					No metabolite blood samples will be collected in the food effect groups

PK/Metabolite Urine Sample		X	See urine collection sampling times*	*Urine collection times (hours) 0-2, 2-4, 4-6, 6-8, 8-10, 10-12, 12-22, 22-24, 24-26, 26-32, 32-38, 38-48, 48- 60, 60-72, 72-84, 84-96 post dosing. If participant is unable to void at a specified timepoint, this should be recorded in the CRF. Participants will void bladder prior to dosing. Voids from urine will be combined into 0-24 hr pool for metabolite analysis, after aliquots for PK are removed.
Genetic sample (optional)		X		Collect the genetic sample only if the participant has a signed consent specific for this purpose. Informed consent for optional sub-studies (e.g., genetics research) must be obtained before collecting a sample.
Stool microbiome collection/stool type assessment	X	Continuous stool type assessment of all bowel movements		Participants will be given instructions and collection items for specimen collection. A last sample will be collected on the day closest to the day of discharge (Day 5). The follow-up sample is indicated in SoA Table 3.

Meal (post dose)	X	See Notes for meal times																	Prior to dosing, participants will fast for 8 hrs overnight. No food is allowed for at least 4 hrs post-dose; after which meals will be permitted as per site schedule. Participants will receive standardized meals scheduled at the same time in each period. Water is permitted with dosing and at all times except 1-hour pre-dose through 2-hours post-dose.
Test Meal		X																	Food Effect (Period 4) Part 1 only, participants will eat a high fat meal prior to dosing as specified in the Study Reference Manual.
Daily fluids (intake/output)		X*	See assessment times											X		X	X	X	*Assessed approximately over 24 hours
Discharge																		X	
AE = adverse event, BP = blood pressure, HR = heart rate, PK = Pharmacokinetic, SAE = serious adverse event.																			

- The timing and number of planned study assessments, including: safety and pharmacokinetic assessments may be altered during the study based on newly available data (e.g., to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.
- Any changes in the timing or addition of time points for any planned study assessments as the result of emerging pharmacokinetic/pharmacodynamic data from this study must be documented and approved by the relevant study team member and then archived in the sponsor and site study files but will not constitute a protocol amendment. The Competent Authority (CA) and ethics committee (EC) will be informed of any safety issues that constitute a substantial amendment and require alteration of the safety monitoring scheme or amendment of the informed consent form (ICF). The changes will be approved by the CA and the EC before implementation.

Table 5 Part 2 – 7-Day Repeat Dose Escalation (Days 1 and 7)

	Study Days													
Procedure	1 and 7													**Notes**
	-1	**Predose**	**0**	**0.25**	**0.5**	**1**	**1.5**	**2**	**4**	**6**	**8**	**12**	**16**	**Hours relative to study intervention**
Inclusion and exclusion criteria	X													Recheck clinical status before randomization and/or 1st dose of study treatment
Brief physical examination	X													
Urine Drug, Smoke Breathalyzer/Alcohol Breath Tests	X													Additional testing may be performed at other timepoints
β-hCG pregnancy test	X													Pregnancy test as appropriate
Admission to clinical unit	X													
Randomization		X												Randomization will occur before first dose on Day 1 only.
Administration of study intervention			X											
AE Review			X	←----------Continuous review----------→										
SAE Review	←----------Continuous review----------→													Serious AEs will be collected from the signing of informed consent.
Ad hoc COVID-19 testing based on clinical presentation and site procedures	←----------Continuous review----------→													
Concomitant medication review			X	←----------Continuous review----------→										

	Study Days													
Procedure	1 and 7													**Notes**
	-1	**Predose**	**0**	**0.25**	**0.5**	**1**	**1.5**	**2**	**4**	**6**	**8**	**12**	**16**	**Hours relative to study intervention**
Vital signs (BP, HR, tympanic temperature, respiration rate)	X	X*				X		X	X	X	X	X		Vital signs will be obtained within 1 hour of pre-dose and at 1, 2, 4, 6, 8, 12 and 24 hours after study administration on Days 1 and 7. *Triplicate readings of blood pressure and pulse rate will be taken pre-dose and averaged on Days 1 and 7. Single measurements will be obtained at all other timepoints. Timings will be reviewed as cohorts progress and may be adjusted to ensure appropriate measurements relative to peak concentrations for subsequent cohorts.

	Study Days													
Procedure	1 and 7													**Notes**
	-1	**Predose**	**0**	**0.25**	**0.5**	**1**	**1.5**	**2**	**4**	**6**	**8**	**12**	**16**	**Hours relative to study intervention**
12-lead safety electrocardiogram	X	X*				X		X	X	X	X	X		*Triplicate 12-lead safety ECGs will be obtained no more than 15 minutes apart within 1-hour pre-dose on Days 1 and 7. Single 12-lead safety ECGs will be obtained at 1, 2, 4, 6, 8, 12 and 24 hours after study administration on Days 1 and 7.
Continuous cardiac monitoring**		X*	←----------Continuous review----------→											**Participants will be semi-supine resting for at least 10 minutes prior to and 5 minutes after each time point for ECG extractions. *3 time points (-45, -30 and -15 minutes) prior to dosing on Day 1. When ECG extractions coincide with safety ECGs, vital signs assessment and blood draws, procedures should occur in that order.
Clinical chemistry (including liver chemistries), hematology, and urine tests (including urine creatinine)	X													

	Study Days													
Procedure	**1 and 7**													**Notes**
	-1	**Predose**	**0**	**0.25**	**0.5**	**1**	**1.5**	**2**	**4**	**6**	**8**	**12**	**16**	**Hours relative to study intervention**
PK Blood Sample		X		X	X	X	X	X	X	X	X	X	X	Details of PK sample collection and storage will be provided in the Study Reference Manual.
4β-hydroxycholesterol sampling		X												Sample to be taken pre-dose on Day 1 in a fasted state.
Metabolite Blood Sample		X		X	X	X	X	X	X	X	X	X	X	
PK/Metabolite Urine Sample		X	See urine collection times*											*Urine collection times (hours) 0-2, 2-4, 4-6, 6-8, 8-10, 10-12, 12-22, 22-24 post dosing. Participants will void bladder prior to dosing. 0-24-hr urine samples will be collected. Voids from urine will be combined into 0-24 hr pool for metabolite analysis, after aliquots for PK are removed.
Genetic sample (optional)		X												Collect the genetic sample only if the participant has a signed consent specific for this purpose. Informed consent for optional sub-studies (e.g., genetics research) must be obtained before collecting a sample.

	Study Days													
Procedure	**1 and 7**													**Notes**
	-1	**Predose**	**0**	**0.25**	**0.5**	**1**	**1.5**	**2**	**4**	**6**	**8**	**12**	**16**	**Hours relative to study intervention**
Stool microbiome collection/stool type assessment	X	*Continuous stool type assessment of all bowel movements while in the clinical unit.												Participants will be given instructions and collection items for specimen collection. The stool sample can be collected up to 72 hours (3 days) prior to the visit the stool sample is required (Day -1).
Meal (post-dose)	X	See Notes for meal times												Prior to dosing on Days 1 and 7, participants will fast for 8 hrs overnight. No food is allowed for at least 4 hrs post-dose; after which meals will be permitted as per site schedule. Water is permitted with dosing and at all times except 1-hour pre-dose through 2-hours post-dose. Participants will receive standardized meals scheduled at the same time in each period.
Daily fluids (intake/output)		X*	See assessment times.											*Assessed approximately over 24 hours

AE = adverse event, BP = blood pressure, HR = heart rate, PK = Pharmacokinetic, SAE = serious adverse event.

24-hour procedures are presented in Table 4.

The 4β-hydroxycholesterol sample may not be available from all Cohorts in Part 2, due to the timing of the amendment when this was added.

- The timing and number of planned study assessments, including: safety and pharmacokinetic assessments may be altered during the study based on newly available data (e.g., to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.
- Any changes in the timing or addition of time points for any planned study assessments as the result of emerging pharmacokinetic/pharmacodynamic data from this study must be documented and approved by the relevant study team member and then archived in the sponsor and site study files but will not constitute a protocol amendment. The Competent Authority (CA) and ethics committee (EC) will be informed of any safety issues that constitute a substantial amendment and require alteration of the safety monitoring scheme or amendment of the informed consent form (ICF). The changes will be approved by the CA and the EC before implementation.

Table 6 Part 2 – 7-Day Repeat Dose Escalation (Days 2 through 6 and Day 8 to 12)

	Study Days									
Procedure	**2**		**3**	**4**	**5**	**6**	**8**		**9-12**	**Notes**
	(24hrs post-Day 1 dose)	**0**	**0**	**0**	**0**	**0**	**(24 hrs post-Day 7 dose)**	**0**	**0**	
Brief physical examination		X	X	X	X	X		X	X*	*Upon discharge
Administration of study intervention		X	X	X	X	X				No minimum time interval is required between the sentinels at each dose level. Approximately 15 minutes will be observed between the dosing of the remaining participants
AE Review	←----------Continuous review----------→									
SAE Review	←----------Continuous review----------→									
Ad hoc COVID-19 testing based on clinical presentation and site procedures	←----------Continuous review----------→								X*	*Sample collected just prior to discharge for COVID-19 testing
Concomitant medication review	←----------Continuous review----------→									

Vital signs (BP, HR, tympanic temperature, respiration rate)	X		X	X	X	X	X		X	Single measurements will be obtained within 1-hour pre-dose and daily in the morning on days 9-12 until discharge. Timings will be reviewed as cohorts progress and may be adjusted to ensure appropriate measurements relative to peak concentrations for subsequent cohorts.
12-lead safety electrocardiogram	X		X	X	X	X	X		X	Single 12-lead safety ECGs will be obtained within 1 hour before pre-dose and daily in the morning on days 9-12 until discharge.
Continuous cardiac monitoring**	X						X			**Participants will be semi-supine resting for at least 10 minutes prior to and 5 minutes after each time point for ECG extractions. When ECG extractions coincide with safety ECGs, vital signs assessment and blood draws, procedures should occur in that order.

Clinical chemistry (including liver and kidney chemistries), hematology, and urine tests (including urine creatinine)		X	X	X	X	X		X	X*	*Just prior to discharge.
PK Blood Sample	X		X*	X*	X*	X*	X			*Trough PK samples
4β-hydroxycholesterol sampling							X			Sample to be taken at 24hr post AM dose on Day 7. Sample should be in a fasted state.
PK Metabolite Sample	X						X			
PK Urine Sample	X		X*	X*	X*	X*	X			*Trough PK samples
Stool microbiome collection/ stool type assessment	*Continuous stool type assessment of all bowel movements while in the clinical unit.								X**	A last sample will be collected on the day closest to the day of discharge. The stool sample can be collected up to 72 hours (3 days) prior to the visit the stool sample is required (Days 9-12). **This includes the last sample collected on the day closest to the day of discharge (Days 9-12) for microbiome. The Day -1 sample is indicated in SoA Table 4 and follow-up sample is indicated in SoA Table 3..

Meal		X	X	X	X	X		X	X	Participants will receive standardized meals scheduled at the same time in each period.
Daily fluids (intake/output)	X						X			
Discharge								X	X	Participants will be discharged from the clinical unit after the assessments are completed.

AE = adverse event, BP = blood pressure, HR = heart rate, PK = Pharmacokinetic, SAE = serious adverse event.
The 4β-hydroxycholesterol sample may not be available from all Cohorts in Part 2, due to the timing of the amendment when this was added.

-
- The start of Part 2 can be modified from emerging data from Part 1.
- The timing and number of planned study assessments, including safety and pharmacokinetic assessments may be altered during the study based on newly available data (e.g., to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.
- Any changes in the timing or addition of time points for any planned study assessments as the result of emerging pharmacokinetic/pharmacodynamic data from this study must be documented and approved by the relevant study team member and then archived in the sponsor and site study files but will not constitute a protocol amendment. The Competent Authority (CA) and ethics committee (EC) will be informed of any safety issues that constitute a substantial amendment and require alteration of the safety monitoring scheme or amendment of the informed consent form (ICF). The changes will be approved by the CA and the EC before implementation.

12.3. Appendix 3: Assessment Windows

- Actual times will be used in the derivation of PK parameters and in the individual concentration-time plots. Planned times will be used in the descriptive summaries and in mean and median plots
- PK concentration listings shall have both the planned and actual times
- Planned time will be used for all other analysis Appendix 4: Study Phases and Treatment Emergent Adverse Events

12.4. Appendix 4: Study Phases

In Part 1 the study phase and study period for adverse events and concomitant medication as follows:

Study Phase	Definition
Pre-Treatment	Date and time of event < Date and time of First dose in Period 1
Treatment	Date and time of event ≥ Date and time of first dose in Period 1

Study Period	Definition
Period 1	Date and time of First dose in Period 1 ≤ Date and time of event < Date and time of first dose in Period 2 or last visit of study if participant did not take a dose in Period 2
Period 2	Date and time of first dose in Period 2 ≤ Date and time of event < Date and time of first dose in Period 3 or last visit of study if participant did not take a dose in Period 3
Period 3	Date and time of first dose in Period 3 ≤ Date and time of event < Date and time of first dose in Period 4 or last visit of study if participant did not take a dose in Period 4
Period 4	Date and time of event ≥ Date and time of first dose in Period 4

For Part 2 Cohorts 3, 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 ≤ Date of Unit discharge, in each cohort
Post-Treatment	Date > Date of unit discharge, in each cohort

12.4.1. Study Phases for Concomitant Medication

Study Phase	Definition
Prior	If medication end date is not missing and is before 28 days prior to 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.

12.5. Appendix 5: Data Display Standards & Handling Conventions

12.5.1. Reporting Process

Software	
• The currently supported versions of SAS software will be used.	
Reporting Area	
HARP Server	: uk1salx00175
HARP Compound	: GSK3882347
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.	

12.5.2. 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 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 participant's listings.
Unscheduled Visits
• Unscheduled visits will not be included in summary tables and figures (except for situations where worse case post-baseline is summarised) 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.

12.5.3. 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	• Ae (amount excreted in urine) = urine concentrations x weight (volume) of urine sample • Σ(Ae) (cumulative amount excreted in urine) = sum of Ae per individual profile • CLr (renal clearance) = Σ (Ae) / plasma AUC(0-t) • fe (fraction of dose eliminated in urine) = Σ (Ae) / dose administered Note: Urine sample volume needs to be merged with PK concentration data set to derive urine PK parameters
Pharmacokinetic Parameter Data	
Is NQ impacted PK Parameters Rule Being Followed	Yes, refer to [Standards for Handling NQ Impacted PK Parameters].
Descriptive Summary Statistics, Graphical Displays and Listings	Refer to IDSL PK Display Standards. log_e-transformed data: N, n, geometric mean, 90% CI of geometric mean, standard deviation (SD) of loge transformed data and the coefficient of variation CV_b in % will be reported. Here CV_b (%) = $\sqrt{e^{SD^2} - 1} \times 100$, where SD^2 = variance of log_e transformed data. Parameters Not Being log_e-transformed: tmax, $t_{1/2}$, t_{lag}, Ae, fe, and MRT.

12.6. Appendix 6: Derived and Transformed Data

12.6.1. General

Multiple Measurements at One Analysis Time Point
• Mean of the measurements will be calculated and used in any derivation of summary statistics but when 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
• In Part 1 for each period: Period Study day is calculated as the number of days from First Dose Date in the period for each participant as follows: o Ref Date = Missing → Period Study Day = Missing o Ref Date < First Dose Date in the period → Period Study Day = Ref Date – Period First Dose Date o Ref Data ≥ First Dose Date in the period → Period Study Day = Ref Date – (Period First Dose Date) + 1 • In Part 1 and 2: Study day is calculated as the number of days from First Dose Date in each cohort for each participant as follows: o Ref Date = Missing → Study Day = Missing o Ref Date < First Dose Date → Study Day = Ref Date – First Dose Date o Ref Data ≥ First Dose Date → Study Day = Ref Date – (First Dose Date) + 1

12.6.2. Safety

LAB Parameter
Reticulocyte Index
Reticulocyte Index (RI) = Reticulocyte count (%) X [Measured haematocrit / Normal haematocrit] * 0.5
ECG Parameters
RR Interval
• IF RR interval (msec) is not provided directly, then RR can be derived as: [1] If QTcB is machine read & QTcF is not provided, then: $$RR = \left[\left(\frac{QT}{QTcB}\right)^2\right] * 1000$$ [2] If QTcF is machine read and QTcB is not provided, then: $$RR = \left[\left(\frac{QT}{QTcF}\right)^3\right] * 1000$$ • If ECGs are manually read, the RR value preceding the measurement QT interval should be a collected value THEN do not derive.
Corrected QT Intervals
• When not entered directly in the eCRF (ClinBase), corrected QT intervals using the Bazett's (QTcB) and Fredericia's (QTcF) formulas will be calculated, in msec, depending on the availability of other measurements. • IF RR interval (msec) is provided then missing QTcB and/or QTcF will be derived as: $$QTcB = \frac{QT}{\sqrt{\frac{RR}{1000}}} \qquad QTcF = \frac{QT}{\sqrt[3]{\frac{RR}{1000}}}$$

12.6.3. Pharmacokinetic

PK parameters
• The PK Population will include all participants who undergo PK sampling and have evaluable PK assay results. • See Section 8.1.1.2 for derived Pharmacokinetic parameters

12.7. Appendix 7: Reporting Standards for Missing Data

12.7.1. Premature Withdrawals

Element	Reporting Detail
General	• Participant study completion - . A participant is considered to have completed the study if he/she has completed all phases of the study including the last visit • Withdrawn participants 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

12.7.2. 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:
	  • 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.
	  • Answers such as “Not applicable” and “Not evaluable” are not considered to be missing data and should be displayed as such.
	  • Missing safety data (labs, ECG, Vitals) will not be imputed
	  •

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.

12.7.2.1. Handling of Missing and Partial Dates

Element	Reporting Detail
General	• Partial dates will be displayed as captured in subject listing displays.

Adverse Events	• The Database allows for the possibility of partial dates (i.e., only month and year) to be recorded for AE start and end dates; that is, the day of the month may be missing. In such a case, the following conventions will be applied for calculating the time to onset and the duration of the event:
	  ○ Missing Start Day: First of the month will be used unless this is before the start date of study treatment; in this case the study treatment start date will be used and hence the event is considered On-treatment as per Appendix 4: Study Phases
	  ○ Missing Stop Day: Last day of the month will be used, unless this is after the stop date of study treatment; in this case the study treatment stop date will be used.
	• Completely missing start or end dates will remain missing, with no imputation applied. Consequently, time to onset and duration of such events will be missing.

Concomitant Medications/Medical History	• Partial dates for any concomitant medications recorded in the eCRF 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

Element	Reporting Detail
	○ 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: If only the start date is completely missing, we assume that the medication has been taken from the beginning of the study for the patient If only the stop date is missing, assume that the medication has been taken till the end of the compete study for the patient • If both start and end date is missing, we assume that the medication has been taken for the duration of the study for the patient.

12.8. Appendix 8: Values of Potential Clinical Importance

12.8.1. Laboratory Values

Haematology				
Laboratory Parameter	**Units**	**Category**	**Clinical Concern Range**	
			Low Flag (< x)	**High Flag (>x)**
Haematocrit	Ratio of 1	Male	0.39	0.54
		Female	0.36	0.54
		Δ from BL	↓0.075	
Haemoglobin	g/L	Male	124	180
		Female	10.7	180
		Δ from BL	↓25	
Lymphocytes	$x10^9$/ L		0.8	
Neutrophil Count	$x10^9$/ L		1.5	
Platelet Count	$x10^9$/ L		100	550
While Blood Cell Count (WBC)	$x10^9$/ L		3	20

Clinical Chemistry				
Laboratory Parameter	**Units**	**Category**	**Clinical Concern Range**	
			Low Flag (< x)	**High Flag (>x)**
Albumin	mmol/L		30	
Calcium	mmol/L		2	2.75
Creatinine	µmol/L	Δ from BL		↑44.2
Glucose	mmol/L		3	9
Potassium	mmol/L		3	5.5
Sodium	mmol/L		130	150

Liver Function			
Test Analyte	**Units**	**Category**	**Clinical Concern Range**
ALT/SGPT	U/L	High	≥ 2x ULN
AST/SGOT	U/L	High	≥ 2x ULN
AlkPhos	U/L	High	≥ 2x ULN
T Bilirubin	µmol/L	High	≥ 1.5x ULN
T. Bilirubin + ALT	µmol/L IU/L	High	Bilirubin≥1.5xULN AND ALT≥2xULN

12.8.2. ECG

ECG Parameter	Units	Clinical Concern Range	
		Lower	Upper
Absolute			
Absolute QTc Interval	msec		>450
Absolute PR Interval	msec	<110	>220
Absolute QRS Interval	msec	<75	>110
Change from Baseline			
Increase from Baseline QTc	msec		>60

12.8.3. 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

12.9. Appendix 9: Population Pharmacokinetic (PopPK) Analyses

Population pharmacokinetic analyses will be performed under a separate CPMS RAP and will be reported separately.

12.10. Appendix 10: Pharmacokinetic / Pharmacodynamic Analyses

A detailed population PK/PD data analysis plan will be prepared in a separate RAP.

12.11. Appendix 11: Abbreviations & Trade Marks

12.11.1. Abbreviations

Abbreviation	Description
ADaM	Analysis Data Model
AE	Adverse Event
Ae	Amount excreted in urine
AIC	Akaike's Information Criteria
ALT	alanine aminotransferase
AST	aspartate aminotransferase
A&R	Analysis and Reporting
AUC	Area under the concentration-time curve
AUC(0-τ)/ AUC(0-inf)	AUC extrapolated from time zero to infinity
AUC(0-τ)	AUC over the dosing interval tau
AUC(0-12)	AUC from time zero to 12 hours after
AUC(0-24)	AUC from time zero to 24 hours after dosing
AUC(0-t)	AUC from time zero to the last quantifiable concentration after dosing
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
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)
Cmax	Maximum observed concentration
Ctau	Trough concentration
Clast	last observable concentration
CL/F	Apparent Clearance
$C_{22:24,u}$	Urine concentration between 22-24 hours post dose
C24h	Concentration at 24 hours
DBF	Database Freeze
DBR	Database Release
DOB	Date of Birth
DP	Decimal Places
eCRF	Electronic Case Record Form
EMA	European Medicines Agency
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Clinical Results Disclosure Requirements
GSK	GlaxoSmithKline
IA	Interim Analysis
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
MAD	Multiple ascending dose
MRT	Mean residence time
PCI	Potential Clinical Importance
PDMP	Protocol Deviation Management Plan
PK	Pharmacokinetic
PP	Per Protocol
PopPK	Population PK
QC	Quality Control
QTcF	Frederica's QT Interval Corrected for Heart Rate
QTcB	Bazett's QT Interval Corrected for Heart Rate
RAP	Reporting & Analysis Plan
SAC	Statistical Analysis Complete
SAD	Single ascending dose
SDSP	Study Data Standardization Plan
SDTM	Study Data Tabulation Model
SOP	Standard Operation Procedure
TA	Therapeutic Area
TFL	Tables, Figures & Listings
Tmax	Time Taken to Maximum Observed Plasma Drug Concentration
Tlag	Lag time before observation of drug concentrations
t1/2	Terminal phase half-life
tau	Dosing interval
tlast	time of last quantifiable concentration
V_d/F	Apparent volume of distribution

12.11.2. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
None

Trademarks not owned by the GlaxoSmithKline Group of Companies
Phoenix (Pharsight Corporation)
WinNonlin

12.12. Appendix 12: List of Data Displays

12.12.1. Data Display Numbering

The following numbering will be applied for RAP generated displays:

Section	Tables	Figures
Study Population	1.1 to 1.14	
Safety	2.1 to 2.36	2.1 to 2.8
Pharmacokinetic	3.1 to 3.29	3.1 to 3.17
Biomarker	4.1	4.1 to 4.2
Section	**Listings**	
ICH Listings	1 to 56	
Non ICH Listings	57 to 73	
Covid-19 Listings	74 to 75	
Conditional Listings	76 to78	

12.12.2. Mock Example Shell Referencing

Non IDSL specifications will be referenced as indicated and if required example mock-up displays provided in Appendix 13: 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
Biomarker	BIO_Fn	BIO_Tn	BIO_Ln

NOTES:

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

12.12.3. Deliverables

Delivery [Priority] [1]	Description
SAC	Final Statistical Analysis Complete

NOTES:

1. Indicates priority (i.e. order) in which displays will be generated for the reporting effort

12.12.4. Study Population Tables

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition					
1.1.	Safety	ES1xo	Summary of Subject Status and Subject Disposition for the Study Conclusion Record – Part 1	ICH E3, FDAAA, EudraCT	SAC
1.2.	Safety	ES1	Summary of Subject Status and Subject Disposition for the Study Conclusion Record – Part 2	ICH E3, FDAAA, EudraCT	SAC
1.3.	Safety	SD1	Summary of Treatment Status and Reasons for Discontinuation of Study Treatment – Part 2		SAC
1.4.	Safety	ES4	Summary of Subject Disposition at Each Study Epoch – Part 1		SAC
1.5.	Screened	ES6	Summary of Screening Status and Reasons for Screen Failure		SAC
Protocol Deviation					
1.6.	Safety	DV1	Summary of Important Protocol Deviations – Part 1	ICH E3, Add 'Total' column as it is cross over design	SAC
1.7.	Safety	DV1	Summary of Important Protocol Deviations – Part 2	ICH E3	SAC
Population Analysed					
1.8.	Enrolled	SP1	Summary of Study Populations – Part 1		SAC
1.9.	Enrolled	SP1	Summary of Study Populations – Part 2		SAC
Demographic and Baseline Characteristics					
1.10.	Safety	DM1xo	Summary of Demographic Characteristics – Part 1	ICH E3, FDAAA, EudraCT	SAC
1.11.	Safety	DM1	Summary of Demographic Characteristics – Part 2	ICH E3, FDAAA, EudraCT	SAC
1.12.	Safety	DM6xo	Summary of Race and Racial Combinations Details – Part 1		SAC
1.13.	Safety	DM6	Summary of Race and Racial Combinations Details – Part 2		SAC

12.12.5. Safety Tables

No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable [Priority]
Adverse Events (AEs)					
2.1.	Safety	AE1xo	Summary of All Adverse Events by System Organ Class and Preferred Term – Part 1	ICH E3	SAC
2.2.	Safety	AE1	Summary of All Adverse Events by System Organ Class and Preferred Term – Part 2	ICH E3	SAC
2.3.	Safety	AE5A	Summary of All Adverse Events by Maximum Grade / Intensity by System Organ Class and Preferred Term – Part 1		SAC
2.4.	Safety	AE5A	Summary of All Adverse Events by Maximum Grade / Intensity by System Organ Class and Preferred Term – Part 2		SAC
2.5.	Safety	AE1xo	Summary All Drug-Related Adverse Events by System Organ Class and Preferred Term – Part 1		SAC
2.6.	Safety	AE1	Summary All Drug-Related Adverse Events by System Organ Class and Preferred Term – Part 2		SAC
2.7.	Safety	AE15	Summary of Common (>=10%) Non-serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences) – Part 1	FDAAA, EudraCT	SAC
2.8.	Safety	AE15	Summary of Common (>=10%) Non-serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences) – Part 2	FDAAA, EudraCT	SAC
2.9.	Safety	AE16	Summary of Serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences) – Part 1	FDAAA, EudraCT	SAC
2.10.	Safety	AE16	Summary of Serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences) – Part 2	FDAAA, EudraCT	SAC

No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable [Priority]
Laboratory: Chemistry					
2.11.	Safety	LB1	Summary of Chemistry Changes from Baseline – Part 1	ICH E3	SAC
2.12.	Safety	LB1	Summary of Chemistry Changes from Baseline – Part 2	ICH E3	SAC
2.13.	Safety	LB17A	Summary of Worst-Case Chemistry Results by PCI Criteria Post-Baseline Relative to Baseline – Part 1	ICH E3	SAC
2.14.	Safety	LB17	Summary of Worst-Case Chemistry Results by PCI Criteria Post-Baseline Relative to Baseline – Part 2	ICH E3	SAC
Laboratory: Hematology					
2.15.	Safety	LB1	Summary of Hematology Changes from Baseline – Part 1	ICH E3	SAC
2.16.	Safety	LB1	Summary of Hematology Changes from Baseline – Part 2	ICH E3	SAC
2.17.	Safety	LB17A	Summary of Worst-Case Hematology Results by PCI Criteria Post-Baseline Relative to Baseline – Part 1	ICH E3	SAC
2.18.	Safety	LB17	Summary of Worst-Case Hematology Results by PCI Criteria Post-Baseline Relative to Baseline – Part 2	ICH E3	SAC
Laboratory: Urinalysis					
2.19.	Safety	LB1	Summary of Urine Concentration Changes from Baseline – Part 1	ICH E3	SAC
2.20.	Safety	LB1	Summary of Urine Concentration Changes from Baseline – Part 2	ICH E3	SAC
2.21.	Safety	UR1	Summary of Worst-Case Urinalysis Results (Discrete or Character Values) Post-Baseline Relative to Baseline – Part 1		SAC
2.22.	Safety	UR1	Summary of Worst-Case Urinalysis Results (Discrete or Character Values) Post-Baseline Relative to Baseline – Part 2		SAC
ECG					
2.23.	Safety	EG1	Summary of ECG Findings – Part 1	IDSL	SAC
2.24.	Safety	EG1	Summary of ECG Findings – Part 2	IDSL	SAC

No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable [Priority]
2.25.	Safety	EG2	Summary of Change from Baseline in ECG Values – Part 1	IDSL	SAC
2.26.	Safety	EG2	Summary of Change from Baseline in ECG Values – Part 2		SAC
2.27.	Safety	EG10	Summary of Maximum QTc Values Post-Baseline Relative to Baseline by Category – Part 1	IDSL	
2.28.	Safety	EG10	Summary of Maximum QTc Values Post-Baseline Relative to Baseline by Category – Part 2	IDSL	SAC
Vital Signs					
2.29.	Safety	VS1	Summary of Change from Baseline in Vital Signs – Part 1	ICH E3	SAC
2.30.	Safety	VS1	Summary of Change from Baseline in Vital Signs – Part 2		SAC
2.31.	Safety	VS7A	Summary of Worst-Case Vital Signs Results by PCI Criteria Post-Baseline Relative to Baseline – Part 1		SAC
2.32.	Safety	VS7	Summary of Worst-Case Vital Signs Results by PCI Criteria Post-Baseline Relative to Baseline – Part 2		SAC

12.12.6. Safety Figures

Safety: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Laboratory					
2.1.	Safety	LIVER14	Scatter Plot of Maximum vs. Baseline for ALT- Part 1	IDSL	SAC
2.2.	Safety	LIVER14	Scatter Plot of Maximum vs. Baseline for ALT- Part 2	IDSL	SAC
2.3.	Safety	LIVER9	Scatter Plot of Maximum ALT vs. Maximum Total Bilirubin – Part 1	IDSL	SAC
2.4.	Safety	LIVER9	Scatter Plot of Maximum ALT vs. Maximum Total Bilirubin – Part 2	IDSL	SAC

12.12.7. Pharmacokinetic Tables

No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
PK concentration					
3.1.	PK	PK01	Summary of Plasma GSK3882347 Pharmacokinetic Concentration -Time Data by treatment – Part 1		SAC
3.2.	PK	PK01	Summary of Plasma GSK3882347 Pharmacokinetic Concentration -Time Data by treatment – Part 2		SAC

No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable [Priority]
Plasma PK Parameter					
3.3.	PK	PK03	Summary of Derived Plasma GSK3882347 Pharmacokinetic Parameters by treatment – Part 1	AUC(0-12), AUC(0-24), AUC(0-t), AUC(0-inf), Cmax, C12h, C24h, CL/F, Vd/F, tmax, tlag, t1/2, MRT	SAC
3.4.	PK	PK03	Summary of Derived Plasma GSK3882347 Pharmacokinetic Parameters by treatment – Part 2	AUC(0-12), AUC(0-tau), Cmax, C12h, Ctau, tmax	SAC
3.5.	PK	PK05	Summary of Derived Plasma GSK3882347 Pharmacokinetic Parameters (log-transformed data) by treatment – Part 1	AUC(0-12), AUC(0-24), AUC(0-t), AUC(0-inf), Cmax, C12h, C24h, CL/F, Vd/F	SAC
3.6.	PK	PK05	Summary of Derived Plasma GSK3882347 Pharmacokinetic Parameters (log-transformed data) by treatment – Part 2	AUC(0-12), AUC(0-tau), Cmax, C12h, Ctau	SAC
3.7.	PK	PK_T1	Statistical Analysis of Log transformed Plasma GSK3882347 Pharmacokinetic Parameters Assessing Dose Proportionality (Power Model) – Part 1	AUC(0-t), AUC(0-inf), Cmax Day 1	SAC
3.8.	PK	PK_T1	Statistical Analysis of Log-transformed Plasma GSK3882347 Pharmacokinetic Parameters Assessing Dose Proportionality (Power Model) – Part 2	AUC(0-τ), Cmax, Ctrough Day 1 and Day 7	SAC
3.9.	PK	PK_T2	Statistical Analysis of Log-transformed Plasma GSK3882347 Pharmacokinetic Parameters Assessing Accumulation Ratio	Ro (AUC(0-tau)), RCmax, RCtrough	SAC
3.10.	PK	PK_T3	Statistical Analysis of Log-transformed Plasma GSK3882347 Pharmacokinetic Parameters Assessing Time Invariance	AUC (0-tau) on Day 7 to AUC (0-inf) on Day 1	SAC

No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable [Priority]
3.11.	PK	PK_T4	Statistical Analysis of Log-transformed Plasma GSK3882347 Parameters Assessing Steady-State	C_{tau}	SAC
3.12.	PK	PK_T5	Statistical Analysis of Log-transformed Plasma GSK3882347 Pharmacokinetic Parameters Assessing Food Effect – Part 1	AUC(0-24), AUC(0-t), AUC(0-inf), C24h, Cmax	SAC
3.13.	PK	PK_T6	Non-Parametric Analysis of Pharmacokinetic Parameter Assessing Food Effect – Part 1	t_{max} and t_{lag}	SAC
Urine PK					
3.14.	PK	PK02	Summary of Urine GSK3882347 Pharmacokinetic Concentration -Time Data by treatment – Part 1		SAC
3.15.	PK	PK02	Summary of Urine GSK3882347 Pharmacokinetic Concentration -Time Data by treatment – Part 2		SAC
3.16.	PK	PK02	Summary of Pharmacokinetic Urine Excretion Rate-Time Data – Part 1		SAC
3.17.	PK	PK02	Summary of Pharmacokinetic Urine Excretion Rate-Time Data – Part 2		SAC
Urine PK Parameters					
3.18.	PK	PK03	Summary of Derived Urine GSK3882347 Pharmacokinetic Parameters by treatment – Part 1	$C_{22\text{-}24,u,}$ CLr, Ae, fe	SAC
3.19.	PK	PK03	Summary of Derived Urine GSK3882347 Pharmacokinetic Parameters by treatment – Part 2	$C_{22\text{-}24,u,}$ CLr, Ae, fe	SAC
3.20.	PK	PK05	Summary of Derived Urine GSK3882347 Pharmacokinetic Parameters (log-transformed data) by treatment – Part 1	$C_{22\text{-}24,u,}$ CLr	SAC
3.21.	PK	PK05	Summary of Derived Urine GSK3882347 Pharmacokinetic Parameters (log-transformed data) by treatment – Part 2	$C_{22\text{-}24,u,}$ CLr	SAC

No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable [Priority]
3.22.	PK	PK_T1	Statistical Analysis of Log-transformed Urine GSK3882347 Pharmacokinetic Parameters Assessing Dose Proportionality (Power Model) – Part 1	Ae Day 1	SAC
3.23.	PK	PK_T1	Statistical Analysis of Log-transformed Urine GSK3882347 Pharmacokinetic Parameters Assessing Dose Proportionality (Power Model) – Part 2	Ae Day 1 and Day 7	SAC
3.24.	PK	PK_T2	Statistical Analysis of Log-transformed Urine GSK3882347 Pharmacokinetic Parameters Assessing Accumulation Ratio – Part 2	Ro ($C_{22\text{-}24,u}$)	SAC
3.25.	PK	PK_T3	Statistical Analysis of Log-transformed Urine GSK3882347 Pharmacokinetic Parameters Assessing Time Invariance – Part 2	$C_{22\text{-}24,u}$ on Day 7 to $C_{22\text{-}24,u}$ on Day 1	SAC
Conditional Tables (If Dose proportionality power model does not converge)					
3.26.	PK	PK_T7	Statistical Analysis of Log transformed Plasma GSK3882347 Pharmacokinetic Parameters Assessing Dose Proportionality (ANOVA) – Part 1	AUC(0-t), AUC(0-inf), Cmax Day 1	SAC
3.27.	PK	PK_T7	Statistical Analysis of Log transformed Plasma GSK3882347 Pharmacokinetic Parameters Assessing Dose Proportionality (ANOVA) – Part 2	AUC(0-τ), Cmax, Ctrough Day 1 and Day 7 Analysis by Day	SAC
3.28.	PK	PK_T7	Statistical Analysis of Log transformed Urine GSK3882347 Pharmacokinetic Parameters Assessing Dose Proportionality (ANOVA) – Part 1	Ae Day 1	SAC
3.29.	PK	PK_T7	Statistical Analysis of Log transformed Urine GSK3882347 Pharmacokinetic Parameters Assessing Dose Proportionality (ANOVA) – Part 2	Ae Day 1 and Day 7	SAC

12.12.8. Pharmacokinetic Figures

Pharmacokinetic: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Plasma PK Plots					
3.1.	PK	PK16b	Individual Subject Plasma GSK3882347 Concentration-time Plot (Linear and Semi-log) by Subject-Part 1		SAC
3.2.	PK	PK16a	Individual Subject Plasma GSK3882347 Concentration-time Plot (Linear and Semi-log) by Subject-Part 2	Day 1 and Day 7 superimposed	SAC
3.3.	PK	PK24	Individual Subject Plasma GSK3882347 Concentration-time Plot (Linear and Semi-log) by Treatment – Part 1		SAC
3.4.	PK	PK24	Individual Subject Plasma GSK3882347 Concentration-time Plot (Linear and Semi-log) by Treatment – Part 2		SAC
3.5.	PK	PK17	Mean Plasma GSK3882347 Concentration-Time Plots (Linear and Semi-log) – Part 1		SAC
3.6.	PK	PK17	Mean Plasma GSK3882347 Concentration-Time Plots (Linear and Semi-log) – Part 2		SAC
3.7.	PK	PK18	Median Plasma GSK3882347 Concentration-Time Plots (Linear and Semi-log) – Part 1		SAC
3.8.	PK	PK18	Median Plasma GSK3882347 Concentration-Time Plots (Linear and Semi-log) – Part 2		SAC
3.9.	PK	PK26	Individual Plasma GSK3882347 Pre-dose Concentration versus Day (Linear and Semi-log) – Part2		SAC

Urine PK plots					
3.10.	PK	PK21	Individual Subject Urine GSK3882347 Concentration-time Plot (Linear and Semi-log) by Subject-Part 1		SAC
3.11.	PK	PK21	Individual Subject Urine GSK3882347 Concentration-time Plot (Linear and Semi-log) by Subject-Part 2	Day 1 and Day 7 superimposed	SAC
3.12.	PK	PK21	Individual Urine Excretion Rate-Time Plots (Linear and Semi-log) – Part 1		SAC
3.13.	PK	PK21	Individual Urine Excretion Rate-Time Plots (Linear and Semi-log) – Part 2		SAC
3.14.	PK	PK22	Mean Urine Excretion Rate-Time Plots (Linear and Semi-log) – Part 1		SAC
3.15.	PK	PK22	Mean Urine Excretion Rate-Time Plots (Linear and Semi-log) – Part 2		SAC
3.16.	PK	PK23	Median Urine Excretion Rate-Time Plots (Linear and Semi-log) – Part 1		SAC
3.17.	PK	PK23	Median Urine Excretion Rate-Time Plots (Linear and Semi-log) – Part 2		SAC

12.12.9. Biomarker Tables

Pharmacodynamic (and or Biomarker): Tables					
No.	**Population**	**GSK Standard/ Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Biomarker					
4.1.	Biomarker	BIO_T1	Summary of Ratio to Baseline in Plasma 4β-hydroxycholesterol and 4β-hydroxycholesterol to cholesterol ratio – Part 2		SAC

12.12.10. Biomarker Figures

Pharmacodynamic (and or Biomarker): Figures					
No.	**Population**	**GSK Standard/ Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
[Insert Endpoint Category]					
4.1.	Biomarker	BIO_F1	Individual Plot of Plasma 4β-Hydroxycholesterol to Cholesterol Ratio Over Time by Dose – Part 2	Please note that the mock shell given is an example shell, not study specific. Change the parameter accordingly	SAC

12.12.11. ICH Listings

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition					
1.	Screened	ES7	Listing of Reasons for Screen Failure – Part 1 and Part 2	Journal Guidelines **Note: Include Part as 3rd column**	SAC
2.	Safety	ES2	Listing of Reasons for Study Withdrawal – Part 1	ICH E3	SAC
3.	Safety	ES2	Listing of Reasons for Study Withdrawal – Part 2	ICH E3	SAC
4.	Safety	SD2	Listing of Reasons for Study Treatment Discontinuation – Part 2	ICH E3	SAC
5.	Safety	BL1xo	Listing of Subjects for whom the Treatment Blind was Broken – Part 1	ICH E3	SAC
6.	Safety	BL1	Listing of Subjects for whom the Treatment Blind was Broken – Part 2	ICH E3	SAC
7.	Safety	TA1xo	Listing of Planned and Actual Treatments -Part 1		SAC
8.	Safety	TA1	Listing of Planned and Actual Treatments - Part 2		SAC
9.	Screened	ES9	Listing of Subjects Who Were Rescreened		SAC
Protocol Deviations					
10.	Safety	DV2xo	Listing of Important Protocol Deviations – Part 1		SAC
11.	Safety	DV2	Listing of Important Protocol Deviations – Part 2		SAC

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
12.	Randomized	IE3xo	Listing of Participants with Inclusion/Exclusion Criteria Deviations – Part 1	ICH E3	SAC
13.	Randomized	IE3	Listing of Participants with Inclusion/Exclusion Criteria Deviations – Part 2	ICH E3	SAC
Populations Analysed					
14.	Safety	SP3xo	Listing of Participants Excluded from Any Population – Part 1		SAC
15.	Safety	SP3	Listing of Participants Excluded from Any Population – Part 2		SAC
Demographic and Baseline Characteristics					
16.	Safety	DM2xo	Listing of Demographic Characteristics – Part 1		SAC
17.	Safety	DM2	Listing of Demographic Characteristics – Part 2		SAC
18.	Safety	DM9xo	Listing of Race – Part 1		SAC
19.	Safety	DM9	Listing of Race – Part 2		SAC
Prior and Concomitant Medications					
20.	Safety	MH2xo	Listing of Current (and/or Past) Medical Conditions – Part 1	Include Past/current as page by variable	SAC
21.	Safety	MH2xo	Listing of Current (and/or Past) Medical Conditions – Part 1	Include Past/current as page by variable	SAC
22.	Safety	CM10xo	Listing of Concomitant Medications – Part 1		SAC
23.	Safety	CM10	Listing of Concomitant Medications – Part 2		SAC

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Exposure and Treatment Compliance					
24.	Safety	EX3xo	Listing of Exposure Data – Part 1		SAC
25.	Safety	EX3	Listing of Exposure Data – Part 2		SAC
Adverse Events					
26.	Safety	AE8CPxo	Listing of All Adverse Events – Part 1		SAC
27.	Safety	AE8CP	Listing of All Adverse Events – Part 2		SAC
28.	Safety	AE7	Listing of Subject Numbers for Individual Adverse Events Part 1	ICH E3	SAC
29.	Safety	AE7	Listing of Subject Numbers for Individual Adverse Events Part 2	ICH E3	SAC
Serious and Other Significant Adverse Events					
30.	Safety	AE8CPxo	Listing of Serious Adverse Events – Part 1		SAC
31.	Safety	AE8CP	Listing of Serious Adverse Events – Part 2		SAC
32.	Safety	AE14	Listing of Reasons for Considering as a Serious Adverse Event – Part 1	ICH E3	SAC
33.	Safety	AE14	Listing of Reasons for Considering as a Serious Adverse Event – Part 2	ICH E3	SAC
34.	Safety	AE8CPxo	Listing of Adverse Events Leading to Withdrawal from Study / Permanent Discontinuation of Study Treatment – Part 1		SAC

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
35.	Safety	AE8CP	Listing of Adverse Events Leading to Withdrawal from Study / Permanent Discontinuation of Study Treatment – Part 2		SAC
All Laboratory					
36.	Safety	LB5xo	Listing of All Clinical Chemistry Values for Subjects with Any Value Outside of Potential Clinical Importance – Part 1		SAC
37.	Safety	LB5	Listing of All Clinical Chemistry Values for Subjects with Any Value Outside of Potential Clinical Importance – Part 2		SAC
38.	Safety	LB5xo	Listing of All Haematology Values for Subjects with Any Value Outside of Potential Clinical Importance – Part 1		SAC
39.	Safety	LB5	Listing of All Haematology Values for Subjects with Any Value Outside of Potential Clinical Importance – Part 2		SAC
40.	Safety	UR2xo	Listing of Urinalysis Data for Subjects with Any Value of Potential Clinical Importance – Part 1		SAC
41.	Safety	UR2	Listing of Urinalysis Data for Subjects with Any Value of Potential Clinical Importance – Part 2		SAC
ECG					
42.	Safety	EG5xo	Listing of All ECG Findings for Subjects with an Abnormal Finding - Part 1		SAC
43.	Safety	EG5	Listing of All ECG Findings for Subjects with an Abnormal Finding - Part 2		SAC

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
44.	Safety	EG3xo	Listing of All ECG Values for Subjects with Any Value of Potential Clinical Importance – Part 1		SAC
45.	Safety	EG3	Listing of All ECG Values for Subjects with Any Value of Potential Clinical Importance – Part 2		SAC
Vital Signs					
46.	Safety	VS4xo	Listing of All Vital Signs for Subjects with Any Value of Potential Clinical Importance - Part 1		SAC
47.	Safety	VS4	Listing of All Vital Signs for Subjects with Any Value of Potential Clinical Importance - Part 2		SAC
Pharmacogenetics					
Meal					
48.	Safety	SAFE_L1	Listing of Meal Consumption – Part 1	May need to add columns according to the results in dataset	SAC

12.12.12. Non-ICH Listings

Non-ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
49.	Safety	SAFE_L3	Listing for Bristol Stool Form Scale – Part 1		SAC
50.	Safety	SAFE_L3	Listing for Bristol Stool Form Scale – Part 2		SAC
51.	Safety	SAFE_L2	Listing of fluid intake and output – Part 1		SAC
52.	Safety	SAFE_L2	Listing of Fluid intake and output – Part 2		SAC
Pharmacokinetic					
53.	PK	PK07xo	Listing of Plasma GSK3882347 Pharmacokinetic Concentration-Time Data – Part 1		SAC
54.	PK	PK07	Listing of Plasma GSK3882347 Pharmacokinetic Concentration-Time Data – Part 2		SAC
55.	PK	PK13xo	Listing of Derived Plasma GSK3882347 Pharmacokinetic Parameters – Part 1		SAC
56.	PK	PK13	Listing of Derived Plasma GSK3882347 Pharmacokinetic Parameters – Part 2		SAC
57.	PK	PK09xo	Listing of Urine Sample Collections – Part 1		SAC
58.	PK	PK09	Listing of Urine Sample Collections – Part 2		SAC
59.	PK	PK13xo	Listing of Derived Urine GSK3882347 Pharmacokinetic Parameters – Part 1		SAC

Non-ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
49.	Safety	SAFE_L3	Listing for Bristol Stool Form Scale – Part 1		SAC
50.	Safety	SAFE_L3	Listing for Bristol Stool Form Scale – Part 2		SAC
51.	Safety	SAFE_L2	Listing of fluid intake and output – Part 1		SAC
52.	Safety	SAFE_L2	Listing of Fluid intake and output – Part 2		SAC
60.	PK	PK13	Listing of Derived Urine GSK3882347 Pharmacokinetic Parameters – Part 2		SAC
Biomarker					
61.	Biomarker	BIO_L1	Listing of Plasma 4β-hydroxycholesterol and Cholesterol concentrations and Plasma 4β-hydroxycholesterol to Cholesterol Ratio – Part 2		SAC

12.12.13. Covid-19 Listings

No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable [Priority]
62.	Safety	PAN7	Listing of All Subjects with Visits and Assessments Impacted by the Pandemic for Subjects with COVID-19 Adverse Events Part 1 and Part 2	Add Period also in the Visit column	SAC

12.12.14. Conditional Listings

No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable [Priority]
Liver Events					
63.	Safety	LIVER5	Listing of Liver Monitoring/Stopping Event Reporting – Part 1 and 2	Add 'Part' as a column	SAC
64.	Safety	LIVER15	Liver Stopping Event Profile – Part 1 and 2	Add 'Part' as a column	SAC
65.	Safety	LIVER13	Listing of Subjects Meeting Hepatobiliary Laboratory Criteria Post-Baseline – Part 1 and 2	Add 'Part' as a column	SAC

12.13. Appendix 13: Example Mock Shells for Data Displays

Data Display Specification will be made available on request.