Division	:	Worldwide Development
Information Type	:	Reporting and Analysis Plan (RAP)
Title	:	Reporting and Analysis Plan for the Effects of GSK3640254 on the Single-Dose Pharmacokinetics of Probe Substrates (Caffeine, Metoprolol, Montelukast, Flurbiprofen, Omeprazole, Midazolam, Digoxin, and Pravastatin) in Healthy Subjects
Compound Number	:	GSK3640254
Effective Date	:	19-JUL-2021

Description:

- The purpose of this RAP is to describe the planned analyses and output to be included in the Clinical Study Report for Protocol 213052.
- This RAP is intended to describe the full analyses required for the study.
- This RAP will be provided to the study team members to convey the content of the 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: 213052

2. SUMMARY OF KEY PROTOCOL INFORMATION

This is an open-label, single-sequence, one-way drug interaction study to investigate the effect of GSK3640254 200 mg on the pharmacokinetics (PK) of a metabolic probe cocktail containing the substrate drugs caffeine 200 mg, metoprolol 100 mg, montelukast 10 mg, flurbiprofen 50 mg, omeprazole 40 mg, midazolam 5 mg, digoxin 0.25 mg, and pravastatin 40 mg.

2.1. Changes to the Protocol Defined Statistical Analysis Plan

The Pharmacodynamic Concentration analysis population and Pharmacodynamic Parameter analysis population were added for the purpose of presenting biomarker coproporphyrin-1 (CP-1) data.

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

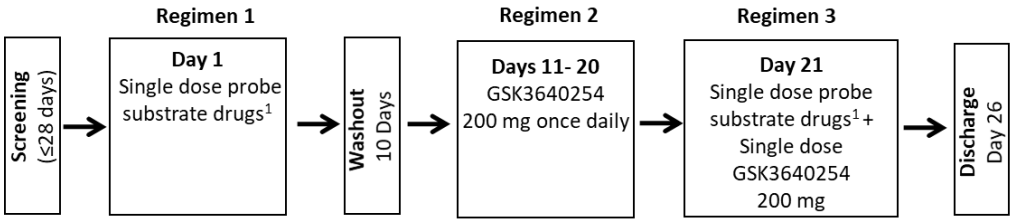
Objectives	Endpoints
Primary Objectives	**Primary Endpoints**
• To assess the effect of GSK3640254 on the PK of caffeine, metoprolol, montelukast, flurbiprofen, omeprazole, midazolam, digoxin, and pravastatin under fed conditions in healthy participants	• AUC(0-t), AUC(0-∞), Cmax, Tmax, and t1/2 for caffeine, metoprolol, montelukast, flurbiprofen, omeprazole, midazolam, digoxin, and pravastatin
Secondary Objectives	**Secondary Endpoints**
• To assess the safety and tolerability of GSK3640254 alone and in combination with caffeine, metoprolol, montelukast, flurbiprofen, omeprazole, midazolam, digoxin, and pravastatin in healthy participants	• Safety and tolerability parameters for adverse events (AEs) /serious adverse events (SAEs), observed and change from baseline clinical laboratory assessments, electrocardiograms (ECG), and vital sign measurements
• To characterize the steady-state PK of GSK3640254 in the presence of caffeine, metoprolol, montelukast, flurbiprofen, omeprazole, midazolam, digoxin, and pravastatin in healthy participants	• AUC(0-t), AUC(0-τ), Cmax, Cτ, Tmax, and t1/2 for GSK3640254
• To characterize the single-dose PK of the metabolites for the probe substrate drugs (α-hydroxymetoprolol, 36-hydroxymontelukast, 5-hydroxyomeprazole, 1-hydroxymidazolam and pravastatin lactone)	• AUC(0-t), AUC(0-∞), Cmax, Tmax, and t1/2 for metabolites, and metabolite to parent ratios for Cmax and AUC(0-∞)

AUC(0-τ) = area under the plasma concentration-time curve from time zero to the end of the dosing interval at steady state; AUC(0-∞) = area under the plasma concentration-time curve from time zero extrapolated to infinity; AUC(0-t) = area under the plasma concentration-time curve from time zero to time t; Cτ = plasma concentration at the end of the dosing interval; Cmax = maximum observed concentration; PK = pharmacokinetics; Tmax = time of maximum observed concentration; t1/2 = apparent terminal phase half-life.

2.3. Study Design

Overview of Study Design and Key Features

Figure 2-1 Study Design Schematic



Probe substrate drugs: Caffeine 200 mg, metoprolol 100 mg, montelukast 10 mg, flurbiprofen 100 mg, omeprazole 40 mg, midazolam 5 mg, digoxin 0.25 mg, and pravastatin 40 mg

Design Features	• A phase 1, open-label, single-sequence, one-way drug-drug interaction study.
	• The study will consist of a screening period and 3 sequential treatment regimens.
	  ○ Screening Period: within 28 days before the first dose of study intervention
	  ○ Treatment A: Caffeine 200 mg, metoprolol 100 mg, montelukast 10 mg, flurbiprofen 50 mg, omeprazole 40 mg, midazolam 5 mg, digoxin 0.25 mg, and pravastatin 40 mg on Day 1 (Regimen 1)
	  ○ Treatment B: GSK3650254 200 mg once daily on Days 11 to 20 (Regimen 2)
	  ○ Treatment C: Caffeine 200 mg, metoprolol 100 mg, montelukast 10 mg, flurbiprofen 50 mg, omeprazole 40 mg, midazolam 5 mg, digoxin 0.25 mg, and pravastatin 40 mg co-administered with GSK3650254 200 mg on Day 21 (Regimen 3)
	• Approximately 20 participants will be enrolled to ensure that 18 evaluable participants complete the study.

Dosing	• Treatment A: Caffeine 200 mg, metoprolol 100 mg, montelukast 10 mg, flurbiprofen 50 mg, omeprazole 40 mg, midazolam 5 mg, digoxin 0.25 mg, and pravastatin 40 mg on Day 1 • Treatment B: GSK3650254 200 mg once daily on Days 11 to 20 • Treatment C: Caffeine 200 mg, metoprolol 100 mg, montelukast 10 mg, flurbiprofen 50 mg, omeprazole 40 mg, midazolam 5 mg, digoxin 0.25 mg, and pravastatin 40 mg co-administered with GSK3650254 200 mg on Day 21
Time & Events	• Refer to Appendix 1: Schedule of Activities
Treatment Assignment	• This is an open-label study. All eligible participants will receive the same treatment.
Interim Analysis	• No interim analysis is planned for this study

2.4. Statistical Hypotheses

There is no formal hypothesis that will be statistically tested in this study.

Administration of GSK3640254 under fed conditions may change the exposure to caffeine, metoprolol, montelukast, flurbiprofen, omeprazole, midazolam, digoxin and pravastatin.

3. PLANNED ANALYSES

3.1. Final Analyses

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

1. All participants have completed the study as defined in the protocol.
2. All required database cleaning activities have been completed and final database release (DBR) and database freeze (DBF) have been declared by Data Management.

4. ANALYSIS POPULATIONS

Population	Definition / Criteria	Analyses Evaluated
Screened	• All participants who signed the informed consent form	• Study Population
Safety	• All participants who received at least 1 dose of study medication. • This population will be used for all demographic, disposition (exclude screen failure), and safety listings, summaries, and figure	• Study Population • Safety
Pharmacokinetic Concentration	• The PK Concentration Population will include all participants who undergo plasma PK sampling and have evaluable PK assay results. This population will be used for the PK concentration listings, summary tables, and plotting of concentration/time data.	• PK Concentration
Pharmacokinetic Parameter	• The PK Parameter Population will include all participants who undergo plasma PK sampling and have evaluable PK parameters estimated. This population will be used for PK parameter listings, summary tables, and statistical analysis tables.	• PK Parameter • PK statistical analysis
Pharmacodynamic Concentration	• The PD Concentration Population will include all participants who undergo plasma PD sampling and have evaluable PD assay results. This population will be used for the PD concentration listings, summary tables, and plotting of concentration/time data.	• PD Concentration
Pharmacodynamic Parameter	• The PD Parameter Population will include all participants who undergo plasma PD sampling and have evaluable PD parameters estimated. This population will be used for PD parameter listings, summary tables, and statistical analysis tables.	• PD Parameter • PD statistical analysis

Refer to Appendix 9: List of Data Displays which details the population used for each display.

4.1. Protocol Deviations

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

Protocol deviations will be tracked by the study team throughout the conduct of the study in accordance with the Study Deviation Tool and Rules. The “significant” protocol deviation in the Study Deviation Tool and Rules is equivalent to “important” protocol deviations.

- Data will be reviewed prior to freezing the database to ensure all significant 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 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 electronic case record form (eCRF).

5. CONSIDERATIONS FOR DATA ANALYSES AND DATA HANDLING CONVENTIONS

5.1. Study Treatment & Sub-group Display Descriptors

Treatment Group Descriptions		
Data Displays for Reporting		
Description	**Code**	**Order in TLF**
Caffeine 200 mg, metoprolol 100 mg, montelukast 10 mg, flurbiprofen 50 mg, omeprazole 40 mg, midazolam 5 mg, digoxin 0.25 mg, and pravastatin 40 mg on Day 1	Treatment A	1
GSK3650254 200 mg once daily on Days 11 to 20	Treatment B	2
Caffeine 200 mg, metoprolol 100 mg, montelukast 10 mg, flurbiprofen 50 mg, omeprazole 40 mg, midazolam 5 mg, digoxin 0.25 mg, and pravastatin 40 mg co-administered with GSK3650254 200 mg on Day 21	Treatment C	3

5.2. Baseline Definitions

For all endpoints (except as noted in baseline definitions), baseline for treatment A is defined as the latest pre-dose assessment with a non-missing value, including those from unscheduled visits, before the dose of Treatment A on Day 1; baseline for treatment B is defined as the latest pre-dose assessment with a non-missing value, including those from unscheduled visits, before the first dose on Day 11; baseline for treatment C is defined as the latest pre-dose assessment with a non-missing value, including those from unscheduled visits, before the dose of Treatment C on Day 21. If time is not collected, Day 1 or Day 11 or Day 21 assessments are assumed to be taken prior to the dose and used as baseline.

Parameter		**Study Assessments Considered as Baseline**					**Baseline Used in Data Display**		
	Check -in (Day -1)	**Day 1 (Pre-Dose)**	**Day 10**	**Day 11 (Pre-Dose)**	**Day 20**	**Day 21 (Pre-Dose)**	**Treatment A**	**Treatment B**	**Treatment C**
Vital Sign	X	X	X	X	X	X	Day 1 (Pre-Dose)[1]	Day 11 (Pre-Dose)[1]	Day 21 (Pre-Dose))[1]
12-Lead ECG	X	X	X	X	X	X	Day 1 (Pre-Dose)[1]	Day 11 (Pre-Dose)[1]	Day 21 (Pre-Dose))[1]
Hematology	X		X		X		Check-in Day -1	Day 10	Day 20
Clinical Chemistry	X		X		X		Check-in Day -1	Day 10	Day 20

Parameter		Study Assessments Considered as Baseline					Baseline Used in Data Display		
	Check-in (Day -1)	Day 1 (Pre-Dose)	Day 10	Day 11 (Pre-Dose)	Day 20	Day 21 (Pre-Dose)	Treatment A	Treatment B	Treatment C
Urinalysis	X		X		X		Check-in Day -1	Day 10	Day 20
Biomarker CP-1 plasma concentration		X				X	Day 1 (Pre-Dose)		Day 21 (Pre-Dose)

[1] The average (for blood pressure and pulse) or the worst case (for interpretation) of the predose triplicate assessments will be used as the baseline.

Unless otherwise stated, if baseline data is missing no derivation will be performed and baseline will be set to missing.

5.3. Other Considerations for Data Analyses and Data Handling Conventions

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

Section	Component
10.1	Appendix 1: Schedule of Activities
10.2	Appendix 2: Study Phases and Treatment Emergent Adverse Events
10.3	Appendix 3: Data Display Standards & Handling Conventions
10.4	Appendix 4: Derived and Transformed Data
10.5	Appendix 5: Reporting Standards for Missing Data
10.6	Appendix 6: Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events
10.7	Appendix 7: 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” or “Screened” population, unless otherwise specified.

Study population analyses including analyses of participant’s disposition, protocol deviations (including inclusion/exclusion criteria deviations), demographic and baseline characteristics, prior and concomitant medications, and exposure will be based on GSK Core Data Standards. Details of the planned displays are presented in Appendix 9: List of Data Displays.

7. PHARMACOKINETIC ANALYSES

7.1. Primary Pharmacokinetic Analyses

7.1.1. Endpoint / Variables

7.1.1.1. Drug Concentration Measures

Refer to Appendix 3: Data Display Standards & Handling Conventions (Section 10.3.3

Reporting Standards for Pharmacokinetics). Plasma concentrations of the probe substrate drugs (caffeine, metoprolol, montelukast, flurbiprofen, omeprazole, midazolam, digoxin, and pravastatin) will be measured and reported.

7.1.1.2. Derived Pharmacokinetic Parameters

Pharmacokinetic parameters will be calculated by standard non-compartmental analysis according to current working practices and using the currently supported version of WinNonlin (8.0 or higher) or SAS (9.4 or higher), as applicable. All calculations of non-compartmental parameters will be based on actual sampling times. Pharmacokinetic parameters listed will be determined from the plasma concentration-time data, as data permit.

Parameter	Parameter Description
Cmax	Maximum observed concentration, determined directly from the concentration-time data.
AUC(0-t)	Area under the plasma concentration-time curve from time zero to time t, to be calculated using the linear trapezoidal rule for each incremental trapezoid and the log trapezoidal rule for each decremental trapezoid.
AUC(0-∞)	Area under the plasma concentration-time curve from time zero extrapolated to infinity, to be calculated using the linear trapezoidal rule for each incremental trapezoid and the log trapezoidal rule for each decremental trapezoid.
Tmax	Time of maximum observed concentration
t1/2	Apparent terminal phase half-life

NOTES:

- Additional parameters may be included as required.

7.1.2. Summary Measure

AUC(0-t), AUC(0-∞), Cmax, Tmax, and t1/2 for caffeine, metoprolol, montelukast, flurbiprofen, omeprazole, midazolam, digoxin, and pravastatin following a single dose of probe drugs (caffeine 200 mg, metoprolol 100 mg, montelukast 10 mg, flurbiprofen 50 mg, omeprazole 40 mg, midazolam 5 mg, digoxin 0.25 mg, and pravastatin 40 mg) on Day 1 in Treatment A (Regimen 1) and a single dose of probe drugs (caffeine 200 mg, metoprolol 100 mg, montelukast 10 mg, flurbiprofen 50 mg, omeprazole 40 mg, midazolam 5 mg, digoxin 0.25 mg, and pravastatin 40 mg) coadministered with GSK3640254 200 mg on Day 21 in Treatment C (Regimen 3) following GSK3640254 200 mg QD administration during days 11 through 20 of Treatment B (Regimen 2) in healthy subjects.

7.1.3. Population of Interest

The primary PK analyses will be based on the PK concentration population for plasma PK concentrations and the PK parameter population for plasma PK parameters and statistical analysis.

7.1.4. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 9: List of Data Displays and will be based on GSK Data Standards and statistical principles.

Unless otherwise specified, endpoints / variables defined in Section 7.1.1 will be summarized using descriptive statistics, graphically presented (where appropriate) and listed.

Primary plasma PK parameters (AUC(0-t), AUC(0-∞), Cmax, Tmax, and t1/2) will be estimated for caffeine, metoprolol, montelukast, flurbiprofen, omeprazole, midazolam, digoxin, and pravastatin (Treatments A and C). Summary statistics (mean (arithmetic and geometric), 95% confidence interval (arithmetic and geometric), median, standard deviation (SD) for observed and ln-transformed data, minimum, maximum, and geometric coefficient of variation) for plasma PK parameter values will be summarized by treatment.

7.1.4.1. Statistical Methodology Specification

The following PK statistical analyses will only be performed if sufficient data are available (i.e., if participants have well defined plasma profiles).

Endpoint / Variables
• Plasma primary PK endpoints include AUC(0-t), AUC(0-∞), and Cmax for caffeine, metoprolol, montelukast, flurbiprofen, omeprazole, midazolam, digoxin, and pravastatin (Treatments A and C), as data permit
Model Specification
• Analyses will be performed on the natural logarithms of AUC(0-t), AUC(0-∞), and Cmax using a linear mixed-effect models with treatment as a fixed effect and measurements within participant as repeated measures. • Effects will be estimated, and 90% confidence intervals (CIs) will be constructed for the following treatment comparison: Treatment C versus Treatment A • Point estimates and 90% CIs for treatment differences on the log scale derived from the model will be exponentiated to obtain estimates for geometric mean ratios and CIs on the original scale.
Model Checking & Diagnostics
• Model assumptions will be applied, but appropriate adjustments may be made based on the data.
Model Results Presentation
• Statistical analysis by analysis of variance (ANOVA) will be presented in tabular format with geometric mean ratios for: Treatment C versus Treatment A

- The geometric mean ratios and associated 90% CIs will also be presented in a forest plot.

7.2. Secondary Pharmacokinetic Analyses

7.2.1. Endpoint / Variables

7.2.1.1. Drug Concentration Measures

Refer to Appendix 3: Data Display Standards & Handling Conventions (Section 10.3.3 Reporting Standards for Pharmacokinetic). Plasma concentrations of GSK3640254 and the metabolites for the probe substrate drugs (α-hydroxymetoprolol, 36-hydroxymontelukast, 5-hydroxyomeprazole, 1-hydroxymidazolam, and pravastatin lactone) will be measured and reported.

7.2.1.2. Derived Pharmacokinetic Parameters

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

Plasma PK parameters listed below will be determined from the total plasma concentration-time data, as data permit.

Parameter	Parameter Description
Cmax	Maximum observed concentration, determined directly from the concentration-time data.
C_τ	Plasma concentration at the end of the dosing interval (GSK3640254 only)
AUC(0-t)	Area under the plasma concentration-time curve from time zero to time t, to be calculated using the linear trapezoidal rule for each incremental trapezoid and the log trapezoidal rule for each decremental trapezoid
AUC(0-∞)	Area under the plasma concentration-time curve from time zero extrapolated to infinity, to be calculated using the linear trapezoidal rule for each incremental trapezoid and the log trapezoidal rule for each decremental trapezoid (probe substrate metabolites only)
AUC(0-τ)	Area under the plasma concentration-time curve from time 0 to the end of the dosing interval at steady state, to be calculated using the linear trapezoidal rule for each incremental trapezoid and the log trapezoidal rule for each decremental trapezoid. (GSK3640254 only)
Tmax	Time of maximum observed concentration
t1/2	Apparent terminal phase half-life
Cmax m/p[1]	Metabolite-to-parent ratio based on Cmax with correction for molecular weight. (probe substrate metabolites only)
AUC m/p[1]	Metabolite-to-parent ratio based on AUC(0-∞) with correction for molecular weight. If data for AUC(0-∞) is insufficient then AUC(0-t) may be used. (probe substrate metabolites only)

NOTES:

- Additional parameters may be included as required.

[1]Molecular weights by analyte: metoprolol: 267.36, α-hydroxymetoprolol: 283.36, montelukast: 586.18, 36-hydroxymontelukast: 602.18, omeprazole: 345.4, 5-hydroxyomeprazole: 361.42, midazolam: 325.78, 1-hydroxymidazolam: 341.77, pravastatin: 424.53, and pravastatin lactone: 406.51.

7.2.2. Summary Measure

AUC(0-t), AUC(0-∞), Cmax, Tmax, t1/2, Cmax m/p, and AUC m/p for the probe substrate metabolites α-hydroxymetoprolol, 36-hydroxymontelukast, 5-hydroxyomeprazole, 1-hydroxymidazolam, and pravastatin lactone following a single dose of probe drugs (caffeine 200 mg, metoprolol 100 mg, montelukast 10 mg, flurbiprofen 50 mg, omeprazole 40 mg, midazolam 5 mg, digoxin 0.25 mg, and pravastatin 40 mg) on Day 1 in Treatment A (Regimen 1) and a single dose of probe drugs (caffeine 200 mg, metoprolol 100 mg, montelukast 10 mg, flurbiprofen 50 mg, omeprazole 40 mg, midazolam 5 mg, digoxin 0.25 mg, and pravastatin 40 mg) coadministered with GSK3640254 200 mg on Day 21 in Treatment C (Regimen 3) following GSK3640254 200 mg QD administration during days 11 through 20 of Treatment B (Regimen 2) in healthy subjects. GSK3640254 AUC(0-t), AUC(0-τ), Cmax, Cτ, Tmax, and t1/2 at steady state following a dose of GSK3640254 200 mg on Day 21 in Treatment C (Regimen 3).

7.2.3. Population of Interest

The secondary PK analyses will be based on the PK concentration population for plasma PK concentrations, and the PK parameter population for plasma and statistical analysis, unless otherwise specified.

7.2.4. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 9: List of Data Displays and statistical principles.

Unless otherwise specified, endpoints/variables defined in Section 7.2.1 will be summarized using descriptive statistics, graphically presented (where appropriate), and listed.

Secondary plasma PK parameters (AUC(0-t), AUC(0-∞), Cmax, Tmax, t1/2, Cmax m/p, and AUC m/p) will be estimated for the probe substrate metabolites α-hydroxymetoprolol, 36-hydroxymontelukast, 5-hydroxyomeprazole, 1-hydroxymidazolam, and pravastatin lactone (Treatments A and C) and secondary plasma PK parameters (AUC(0-t), AUC(0-τ), Cmax, Cτ, Tmax, and t1/2) will be estimated for GSK3640254 (Treatment C). Summary statistics (mean (arithmetic and geometric), 95% confidence interval (arithmetic and geometric), median, standard deviation (SD) for observed and ln-transformed data, minimum, maximum, and geometric coefficient of variation) for secondary plasma PK parameters of GSK3640254 and probe substrate metabolites will be summarized by treatment.

Predose (trough) PK plasma concentrations for GSK3640254 (Days 17, 18, 19, and 20 [Treatment B]; and Day 21 [Treatment C]) will be summarized using the PK Concentration Population and used to assess achievement of steady state.

7.2.4.1. Statistical Methodology Specification

The following PK statistical analyses will only be performed if sufficient data are available (i.e., if participants have well defined plasma profiles).

Endpoint / Variables
• Plasma primary PK endpoints include AUC(0-t), AUC(0-∞), and Cmax for α-hydroxymetoprolol, 36-hydroxymontelukast, 5-hydroxyomeprazole, 1-hydroxymidazolam, and pravastatin lactone (Treatments A and C), as data permit • For steady state analysis, predose (trough) plasma PK concentrations of GSK3640254.
Model Specification
• Analyses will be performed on the natural logarithms of AUC(0-t), AUC(0-∞), and Cmax using a linear mixed-effect models with treatment as a fixed effect and measurements within participant as repeated measures. • Effects will be estimated, and 90% confidence intervals (CIs) will be constructed for the following treatment comparison: Treatment C versus Treatment A • Point estimates and 90% CIs for treatment differences on the log scale derived from the model will be exponentiated to obtain estimates for geometric mean ratios and CIs on the original scale. • If data permit, log-transformed predose (trough) plasma PK concentrations of GSK3640254 will be analysed to determine whether steady state was achieved using the Helmert transformation approach. A mixed effect model (ANOVA) will be fitted with day as a fixed effect term and participant as a random effect term. The comparison will begin with Day 17 vs. the average of Day 18 through Day 21. If the p-value for Day 17 vs. the average of Day 18 through Day 21 is $\leq$0.05 (i.e. steady state not achieved at Day 17), then the comparison will continue with Day 18 vs. Day 19 through Day 21.
Model Checking & Diagnostics
• Model assumptions will be applied, but appropriate adjustments may be made based on the data.
Model Results Presentation
• Statistical analysis by analysis of variance (ANOVA) will be presented in tabular format with geometric mean ratios for: Treatment C versus Treatment A • For steady state analysis, the ratio of Geometric LS means and its 90% CI will be presented for the comparison(s).

8. PHARMACODYNAMIC/BIOMARKER ANALYSES

8.1. Exploratory Pharmacodynamic/Biomarker Analyses

8.1.1. Endpoint / Variables

8.1.1.1. Drug Concentration Measures

Plasma concentrations of the biomarker CP-1 will be measured, and observed and baseline-adjusted CP-1 concentrations will be reported. For Treatment A, the Day 1 predose assessment will serve as baseline. For Treatment C, the day 21 predose assessment will serve as baseline.

8.1.1.2. Derived Pharmacodynamic Parameters

Pharmacodynamic parameters will be calculated by standard non-compartmental analysis according to current working practices and using the currently supported version of WinNonlin (8.0 or higher) or SAS (9.4 or higher), as applicable. All calculations of non-compartmental parameters will be based on actual sampling times. Pharmacodynamic parameters listed will be determined from the baseline-adjusted plasma concentration-time data, as data permit.

Parameter	Parameter Description
Emax	Maximum PD effect, determined directly from the PD concentration-time data.
AUEC(0-24)	Area under the plasma effect-time curve from time zero to time 24 hours postdose, to be calculated using the linear trapezoidal rule for each incremental trapezoid and the log trapezoidal rule for each decremental trapezoid.
AUC(0-120)	Area under the plasma effect-time curve from time zero extrapolated to 120 hours postdose, to be calculated using the linear trapezoidal rule for each incremental trapezoid and the log trapezoidal rule for each decremental trapezoid.
TEmax	Time of maximum PD effect

NOTES:

- Additional parameters may be included as required.

8.1.2. Summary Measure

AUEC(0-24), AUEC(0-120), Emax, and TEmax for CP-1 following a single dose of probe drugs (caffeine 200 mg, metoprolol 100 mg, montelukast 10 mg, flurbiprofen 50 mg, omeprazole 40 mg, midazolam 5 mg, digoxin 0.25 mg, and pravastatin 40 mg) on Day 1 in Treatment A (Regimen 1) and a single dose of probe drugs (caffeine 200 mg, metoprolol 100 mg, montelukast 10 mg, flurbiprofen 50 mg, omeprazole 40 mg, midazolam 5 mg, digoxin 0.25 mg, and pravastatin 40 mg) coadministered with GSK3640254 200 mg on Day 21 in Treatment C (Regimen 3) following GSK3640254 200 mg QD administration during days 11 through 20 of Treatment B (Regimen 2) in healthy subjects.

8.1.3. Population of Interest

The exploratory PD analyses will be based on the PD concentration population for plasma PD concentrations and the PD parameter population for plasma PD parameters and statistical analysis.

8.1.4. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 9: 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 summarized using descriptive statistics, graphically presented (where appropriate) and listed.

Exploratory plasma PD parameters (AUEC(0-24), AUEC(0-120), Emax, and TEmax) will be estimated for CP-1 (Treatments A and C). Summary statistics (mean (arithmetic and geometric), 95% confidence interval (arithmetic and geometric), median, standard deviation (SD) for observed and ln-transformed data, minimum, maximum, and geometric coefficient of variation) for plasma PD parameter values will be summarized by treatment.

8.1.4.1. Statistical Methodology Specification

The following PD statistical analyses will only be performed if sufficient data are available (i.e., if participants have well defined plasma profiles).

Endpoint / Variables
• Plasma exploratory PD endpoints include AUEC(0-24), AUEC(0-120), and Emax for CP-1 (Treatments A and C), as data permit
Model Specification
• Analyses will be performed on the natural logarithms of AUEC(0-24), AUEC(0-120), and Emax using a linear mixed-effect models with treatment as a fixed effect and measurements within participant as repeated measures. • Effects will be estimated, and 90% confidence intervals (CIs) will be constructed for the following treatment comparison: Treatment C versus Treatment A • Point estimates and 90% CIs for treatment differences on the log scale derived from the model will be exponentiated to obtain estimates for geometric mean ratios and CIs on the original scale.
Model Checking & Diagnostics
• Model assumptions will be applied, but appropriate adjustments may be made based on the data.
Model Results Presentation
• Statistical analysis by analysis of variance (ANOVA) will be presented in tabular format with geometric mean ratios for: Treatment C versus Treatment A

9. SAFETY ANALYSES

The safety analyses will be based on the Safety population unless otherwise specified.

9.1. Adverse Events Analyses

Adverse events analyses including the analysis of AEs, SAEs, AEs of special interest, and other significant AEs will be based on GSK Core Data Standards. The details of the planned displays are provided in Appendix 9: List of Data Displays.

For studies with greater than one treatment period (e.g., crossover study), if AE onset is during one period and worsens during a later period, it would be counted in both periods. For the later period the onset date of AE with elevated grade would be the first dose date of the later treatment period.

9.2. Clinical Laboratory Analyses

Laboratory evaluations including the analyses of chemistry laboratory tests, hematology laboratory tests, urinalysis, liver function tests, and pregnancy test will be based on GSK Core Data Standards and will be graded using the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events (Version 2.1, July 2017). The details of the planned displays are in Appendix 9: List of Data Displays.

9.3. Adverse Events of Special Interest

At the end of the study, QT prolongation, gastrointestinal intolerability/toxicity, psychiatric events, and nervous system disorders will be summarized by treatment. A listing will also be provided accordingly.

QT prolongation AE of special interest will be defined as cardiac disorders system organ class (SOC) plus preferred terms (PTs) using the Medical Dictionary for Regulatory Activities (MedDRA) Standardized MedDRA Query (SMQ) “Torsade de pointes/QT Prolongation” (narrow and broad terms) plus seizure.

Gastrointestinal intolerability/toxicity AEs of special interest will be defined within three narrow sub-SMQs [Gastrointestinal nonspecific symptoms and therapeutic procedures SMQ; Gastrointestinal nonspecific dysfunction SMQ; Gastrointestinal nonspecific inflammation (SMQ)] plus a selection of relevant broad PTs from the Gastrointestinal non-specific symptoms and therapeutic procedures SMQ.

Psychiatric AEs of special interest will be defined within the following:

- Sub-SMQ “Suicide/self-injury” (SMQ) from parent SMQ of “Depression and Suicide/Self Injury”. Only narrow terms from the sub-SMQ selected.
- Sub-SMQ “Depression (excluding suicide and self-injury)” (SMQ) from parent SMQ of “Depression and Suicide/Self Injury”. Only narrow terms from the sub-SMQ selected.
- All preferred terms from high level group term (HLGT) “Manic and Bipolar mood disorders and disturbances” under SOC “Psychiatric disorders”.

- Narrow terms from SMQ “Psychosis and psychotic disorders” selected.
- All preferred terms from HLGT “Anxiety disorders and symptoms”, under SOC 'Psychiatric disorders'.
- All preferred terms from HLGT “Sleep Disorders and Disturbances” and HLGT “Sleep disturbances (incl subtypes)”.

Nervous system disorders AEs of special interest will be defined within the following:

- Four HLGTs under Nervous System Disorders SOC: “Headaches”; “Mental impairment disorders (excluding dementia)”; “Disturbance in consciousness” and “Seizures and seizure disorder”

Skin and subcutaneous tissue disorder AEs of special interest will be defined with the following preferred terms:

Dermatitis, Dermatitis allergic, Dermatitis atopic, Eczema, Eczema eyelids, Eczema nummular, Eyelid irritation, Skin irritation, Urticarial dermatitis, Eyelid pruritis, Pruritus, Pruritus allergic, Rash pruritic, Rash, Rash macular, Rash maculopapular, Rash morbilliform, Rash papular, Rash pruritic, Urticaria, Drug eruption and Rash pustular.

9.4. Other Safety Analyses

The analyses of non-laboratory safety test results including ECGs, vital signs, liver events, and Columbia Suicide Severity Rating Scale (C-SSRS) will be based on GSK Core Data Standards, unless otherwise specified. A figure of mean change from baseline in QTcF interval along with the 2-sided 95% CI using Student’s t distribution will be presented by treatment and visit. The details of the planned displays are presented in Appendix 9: List of Data Displays.

9.5. COVID 19 Related Analyses

Based on GSK’s “Impact of Covid-19 on Assessment of Safety in Clinical Trials Points to Consider”, it is GSK’s recommendation that study teams should capture COVID-19 cases based on the WHO criteria using the categories of: suspected, probable, and confirmed cases. COVID-19 eCRF pages are used in the study for data collection and analysis purposes. After a discussion with the study team, the following analyses will be included:

- Number of subjects with suspected, probable or confirmed for COVID-19 infection
- Number of subjects who had a COVID-19 diagnosis test performed and the number of subjects with positive, negative, or indeterminate results
- Incidence of COVID-19 as reported as an AE and SAE
- Incidence of treatment discontinuation due to AE of COVID-19 infection
- Severity, duration, and outcome of COVID-19 AEs

If percentage of COVID-19 cases is >10% (> 5 subjects with an AE of COVID-19), a summary of COVID-19 symptoms for subjects with COVID-19 AE will be added.

Further display details are provided in Appendix 9: List of Data Displays.

10. REFERENCES

ViiV Healthcare group of companies Document Number 2019N422949_00 (25Feb2020) Effects of GSK3640254 on the Single-Dose Pharmacokinetics of Probe Substrates (Caffeine, Metoprolol, Montelukast, Flurbiprofen, Omeprazole, Midazolam, Digoxin, and Pravastatin) in Healthy Subjects

11. APPENDICES

11.1. Appendix 1: Schedule of Activities

11.1.1. Protocol Defined Schedule of Events

Screening Visit

Procedure	Screening (up to 28 days before Day 1)
Outpatient visit	X
Informed consent	X
Inclusion and exclusion criteria	X
Demography	X
Full physical examination including height and weight[1]	X
Laboratory assessments (hematology, chemistry, urinalysis)	X
12-lead electrocardiogram	X
Vital sign measurements	X
Medication/drug/alcohol history	X
Past and current medical conditions	X
Columbia-Suicide Severity Rating Scale	X
Serum pregnancy test	X
Follicle-stimulating hormone (as needed, to confirm postmenopausal status)	X
Drug, alcohol, and cotinine screen	X
HIV, Hepatitis B and C screening	X

HIV = human immunodeficiency virus.

1 A full physical examination will include, at a minimum, assessments of the skin, cardiovascular, respiratory, gastrointestinal, and neurological systems.

Time and Events Table

Procedure		Regimen 1 Treatment A (Day 1) Washout (Days 2-10)					Regimen 2 Treatment B		Regimen 3 Treatment C						Notes
	Check-in Day –1	Day 1	Day 2-5	Day 6	Days 7-9	Day 10	Days 11-19	Day 20	Day 21	Day 22	Day 23	Day 24	Day 25	Day 26	
Admit to clinic	X														
Discharge from clinic														X	
Brief physical examination	X							X					X		Includes, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).
Vital sign measurements	X	X	D2			X	D11, D14, and D17	X	X	X	X	X	X	X	Blood pressure and pulse measured in triplicate at pre-dose on Days 1, 11, and 21. Respiratory rate measured pre-dose and post-dose every 15 minutes for the first 2 hours and every 30 minutes for the subsequent 2 hours on Days 1 and 21 (may be monitored longer if indicated by clinical condition).
Pulse oximetry		X							X						Continuous pulse oximetry measured pre-dose and through 4 hours after dosing on Days 1 and 21 (may be monitored longer if indicated by clinical condition).
Twelve-lead ECG	X	X	D2, D3, and D5			X	D11	X	X	X	X		X		ECGs on Days 1, 11, and 21, will be taken pre-dose, and at 2 and 4 hours post-dose. Pre-dose ECGs on Days 1, 11, and 21 will be taken in triplicate.
Drug, alcohol, and cotinine screen	X														See Appendix 2 for tests.

Procedure		Regimen 1 Treatment A (Day 1) Washout (Days 2-10)					Regimen 2 Treatment B		Regimen 3 Treatment C						Notes
	Check-in Day –1	Day 1	Day 2-5	Day 6	Days 7-9	Day 10	Days 11-19	Day 20	Day 21	Day 22	Day 23	Day 24	Day 25	Day 26	
Laboratory assessments (hematology, chemistry, urinalysis)	X		D2 and D5			X	D15	X		X			X		See Appendix 2 for tests.
Pregnancy test	X												X		
Columbia-Suicide Severity Rating Scale						X		X		X			X		
Study intervention: probe substrate drugs		X							X						See Protocol Section 6.1 for study intervention details.
Study intervention: GSK3640254 200 mg							X	X	X						See Protocol Section 6.1 for study intervention details.
Probe substrate drug PK sampling		Pre-dose and 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 48, 72, 96, and 120 hours post-dose.							Pre-dose and 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 48, 72, 96, and 120 hours post-dose						
GSK3640254 PK sampling							Pre-dose on Days 17, 18, 19, 20 and 21. Post Day 21 dose at 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 12, 24, 48, 72, 96, and 120 hours.								
AE review		←========== →													
SAE review	←========== →														
Concomitant medication review	←========== →														

Abbreviations: AE = adverse event; D = day; ECG = electrocardiogram; PK = pharmacokinetic; SAE = serious adverse event.

11.2. Appendix 2: Study Phases and Treatment Emergent Adverse Events

11.2.1. Study Phases

Assessments and events will be classified according to the time of occurrence relative to study treatment start date(/time) and stop date(/time).

11.2.1.1. Study Phases for Lab, Electrocardiograms, and Vital Signs

Assessments and events will be classified according to the time of occurrence relative to study treatment start date(/time) and stop date(/time).

Study Phase	Definition
Pre-Treatment	Date and Time ≤ Study Treatment Start Date and Time
On-Treatment	Study Treatment Start Date and Time <Date and Time ≤ Study Treatment Stop Date and Time + 5 days
Post-Treatment	Date and Time >Study Treatment Stop Date and Time + 5 days

11.2.1.2. Study Phases for Concomitant Medication

Study Phase	Definition
Prior	If medication end date is not missing and is before Day 1
Concomitant	Any medication that is not a prior

NOTES:

- Please refer to Appendix 5: 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.

11.2.2. Treatment Emergent Flag for Adverse Events

Flag	Definition
Treatment Emergent	• If AE onset date and time is on or after treatment start date and time & on or before treatment stop date and time + 5 days. • Study Treatment Start Date and Time ≤ AE Start Date and Time ≤ Study Treatment Stop Date and Time + 5 days. • If the AE onset date is completely missing, the AE is considered as treatment emergent.

NOTES:

- If the study treatment stop date is missing, then the AE will be considered to be On-Treatment.
- Please refer to Appendix 5: Reporting Standards for Missing Data for handling of missing and partial dates for AEs. Use the rules in this table if the adverse event onset date is completely missing.

11.3. Appendix 3: Data Display Standards & Handling Conventions

11.3.1. Reporting Process

Software	
• The currently supported versions of SAS software (9.4) will be used.	
Reporting Area	
HARP Server	\\us1salx00259.corpnet2.com
HARP Compound	\gsk3640254\mid213052\final_01
Analysis Datasets	
• Analysis datasets will be created according to CDISC standards (SDTM IG Version 3.2 & ADaM IG Version 1.1). • For creation of ADaM datasets (ADC1/ADCM/ADAE), the same version of dictionary datasets will be implemented for conversion from SI to SDTM.	
Generation of RTF Files	
• RTF files will be generated for all reporting efforts described in the RAP.	

11.3.2. 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 participant level listings in the main body of the GSK Clinical Study Report. All participant level listings should be located in the modular appendices as ICH or non-ICH listings.

Formats
• All data will be reported according to the actual treatment the participant received unless otherwise stated. • GSK IDSL Statistical Principles (5.03 & 6.06.3) for decimal places (DP's) will be rounded to integer, unless otherwise specified. • 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.

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.
  • Visits outside the protocol defined time-windows (i.e. recorded as protocol deviations) will be included in listings but omitted from figures (mean figures only for PK concentrations), summaries, and statistical analyses (excluding statistical analyses of PK parameters).

Unscheduled Visits
• Unscheduled visits will not be included in summary tables except for determining the worst-case values. • Unscheduled visits will not be included in figures. • All unscheduled visits will be included in listings.
Descriptive Summary Statistics
Continuous Data: Refer to IDSL Statistical Principle 6.06.1
Categorical Data: N, n, frequency, %
Graphical Displays
• Refer to IDSL Statistical Principals 7.01 to 7.13.
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 participant level listings in the main body of the GSK Clinical Study Report. All participant level listings should be located in the modular appendices as ICH or non-ICH listings.

Formats
• All data will be reported according to the actual treatment the participant received unless otherwise stated. • GSK IDSL Statistical Principles (5.03 & 6.06.3) for decimal places (DP's) will be rounded to integer, unless otherwise specified.

• 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.	
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.
  • Visits outside the protocol defined time-windows (i.e. recorded as protocol deviations) will be included in listings but omitted from figures (mean figures only for PK concentrations), summaries, and statistical analyses (excluding statistical analyses of PK parameters).	

Unscheduled Visits	
• Unscheduled visits will not be included in summary tables except for determining the worst-case values. • Unscheduled visits will not be included in figures. • All unscheduled visits will be included in listings.	
Descriptive Summary Statistics	
Continuous Data	Refer to IDSL Statistical Principle 6.06.1
Categorical Data	N, n, frequency, %
Graphical Displays	
• Refer to IDSL Statistical Principals 7.01 to 7.13.	

11.3.3. Reporting Standards for Pharmacokinetics

Pharmacokinetic Concentration Data	

Descriptive Summary Statistics, Graphical Displays and Listings	Refer to IDSL PK Display Standards.
	Refer to IDSL Statistical Principle 6.06.1.
	For continuous data:
	• Not quantifiables (NQs) at the beginning of a participant profile (i.e. before the first incidence of a measurable concentration) are deemed to be zero as it is assumed that in this circumstance no drug is yet measurable in the blood.
	• For NQs at the end of the participant profile (i.e. after the last incidence of a measurable concentration);
	  • for individual plots and PK analyses these are dropped (set to missing) as they do not provide any useful information (and can erroneously indicate that absolutely no drug is present)
	  • for summary statistics, these are set to 0 (to avoid skewing of the summary statistics)
	• Individual NQs which fall between two measurable concentrations are set to missing (individual values of this nature are assumed to be an anomaly)
	If two or more NQ values occur in succession between measurable concentrations, the profile will be deemed to have terminated at the last measurable concentration prior to these NQs. For the purpose of individual participant plots, these NQs will be set to 0, and the subsequent measurable concentrations will be retained. For the derivation of pharmacokinetic parameters, these NQs and any subsequent measurable concentrations will be omitted (set to missing).
	Note: Concentration values will be imputed as per GUI_51487 for descriptive summary statistics/analysis and summarized graphical displays only.

Pharmacokinetic Parameter Data	
Descriptive Summary Statistics, Graphical Displays and Listings	N, n, arithmetic mean, 95% CI of arithmetic mean, geometric mean, 95% CI of geometric mean, SD, SD of logged data CV (%), and between-subject geometric coefficient of variation (CVb (%)) will be reported. CV_b (%) = $\sqrt{}$ (exp(SD^2) - 1) * 100 (SD = SD of Ln-Transformed data)
Parameters Not Being Ln-Transformed	Tmax, Cmax m/p, AUC m/p, λz, λz lower, λz upper, and λz no. of points.
Parameters Not Being Summarized	λz, λz lower, λz upper, and λz no. of points.
Listings	Include the first point, last point and number of points used in the determination of λz and Rsq_adjusted for listings.

11.4. Appendix 4: Derived and Transformed Data

11.4.1. General

Multiple Measurements at One Analysis Time Point
• Mean of the measurements will be calculated and used in any derivation of summary statistics but if listed, all data will be presented. • The worst finding/interpretation associated with multiple measurements as the finding/interpretation for that time point. • 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

• Calculated as the number of days from Dose Date on Day 1:
  • Assessment Date = Missing
  → Study Day = Missing
  • Assessment Date <Dose Date on Day 1
  → Study Day = Assessment Date –Dose Date on Day 1
  • Assessment Date >= Dose Date on Day 1
  → Study Day = Assessment Date – Dose Date on Day 1 + 1

Period Day

• Calculated as the number of days from First Dose Date for the respective period:
  • Assessment Date = Missing
  → Period Day = Missing
  • Assessment Date <Dose Date on Day 1
  → Period Day = Assessment Date – Dose Date on Day 1
  • First Dose Date on Day 1 <= Assessment Date <First Dose Date on Day 11
  → Period Day = Assessment Date – Dose Date on Day 1 + 1
  • First Dose Date on Day 11 <=Assessment Date <= First Dose Date on Day 21
  → Period Day = Assessment Date – First Dose Date on Day 11 + 1
  • Assessment Date >= First Dose Date on Day 21
  → Period Day = Assessment Date – First Dose Date on Day 21 + 1

11.4.2. Study Population

Age

• GSK standard IDSL algorithms will be used for calculating age where birth date will be imputed as follows:
  ○ Any participant with a missing day will have this imputed as day '15'.
  ○ Any participant with a missing day and month will have this imputed as '30th June'.
• Birth date will be presented in listings as 'YYYY'.

Body Mass Index (BMI)
• Calculated as Weight (kg) / [Height $(m)^2$]

11.4.3. Safety

Adverse Events
AEs of Special Interest
• QT prolongation • Gastrointestinal intolerability/toxicity • Psychiatric events • Nervous system disorders • Skin and subcutaneous tissue disorders

12-Lead Electrocardiograms
QTcB Interval
• QTcB interval in msec will be calculated using QT interval (msec) and RR interval (msec) as $QTcB = \frac{QT}{\sqrt{\frac{RR}{1000}}}$ where RR interval in msec is calculated using QT interval (msec) and QTcF interval (msec) as $RR = (\frac{QT}{QTcF})^3 \times 1000$

11.5. Appendix 5: Reporting Standards for Missing Data

11.5.1. Premature Withdrawals

Element	Reporting Detail
General	• Participant study completion (i.e., as specified in the protocol) was defined as the participant had completed all phases of the study including the final date on which data were or are expected to be collected. • Withdrawn participants will not 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.

11.5.2. 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: o These data will be indicated by the use of a “blank” in participant listing displays. Unless all data for a specific visit are missing in which case the data is excluded from the table. o Answers such as “Not applicable” and “Not evaluable” are not considered to be missing data and should be displayed as such.
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.

11.5.2.1. Handling of Missing and Partial Dates

Element	Reporting Detail
General	• Partial dates will be displayed as captured in participant listing displays.
Adverse Events	• The eCRF 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: o 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 2: Study Phases and Treatment Emergent Adverse Events. o 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	o Partial dates for any concomitant medications recorded in the eCRF will be imputed using the following convention: o If the partial date is a start date, a ”01” will be used for the day and “Jan” will be used for the month o 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. o The recorded partial date will be displayed in listings.

11.6. Appendix 6: Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events

11.6.1. Laboratory Values

Laboratory abnormalities will be graded according to the DAIDS grading table Version 2.1, July 2017. Laboratory results are converted to use SI units; only the numeric part of the criteria will be used. If for a laboratory parameter there are multiple grades sharing the same criteria, the maximum grade will be used.

Hematology				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Absolute Lymphocyte Count, Low (cell/mm^3; cells/L) >5 years of age (not HIV infected)	600 to <650 0.600 × 10^9 to <0.650 × 10^9	500 to <600 0.500 × 10^9 to <0.600 × 10^9	350 to <500 0.350 × 10^9 to <0.500 × 10^9	<350 <0.350 × 10^9
Absolute Neutrophil Count, Low (cells/mm^3; cells/L) >7 days of age	800 to 1,000 0.800 × 10^9 to 1.000 × 10^9	600 to 799 0.600 × 10^9 to 0.799 × 10^9	400 to 599 0.400 × 10^9 to 0.599 × 10^9	<400 <0.400 × 10^9
Hemoglobin, Low (g/dL; mmol/L) ≥13 years of age (male only)	10.0 to 10.9 6.19 to 6.76	9.0 to <10.0 5.57 to <6.19	7.0 to <9.0 4.34 to <5.57	<7.0 <4.34
Hemoglobin, Low (g/dL; mmol/L) ≥13 years of age (female only)	9.5 to 10.4 5.88 to 6.48	8.5 to <9.5 5.25 to <5.88	6.5 to <8.5 4.03 to <5.25	<6.5 <4.03
Platelets, Decreased (cells/mm^3; cells/L)	100,000 to <125,000 100.000 × 10^9 to <125.000 × 10^9	50,000 to <100,000 50.000 × 10^9 to <100.000 × 10^9	25,000 to <50,000 25.000 × 10^9 to <50.000 × 10^9	<25,000 <25.000 × 10^9
White Blood Cell, Decreased (cells/mm^3; cells/L) >7 days of age	2,000 to 2,499 2.000 × 10^9 to 2.499 × 10^9	1,500 to 1,999 1.500 × 10^9 to 1.999 × 10^9	1,000 to 1,499 1.000 × 10^9 to 1.499 × 10^9	<1,000 <1.000 × 10^9

Clinical Chemistry				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Albumin, Low (g/dL; g/L)	3.0 to <LLN 30 to <LLN	≥2.0 to <3.0 ≥20 to <30	<2.0 <20	NA
Alkaline Phosphatase, High	1.25 to <2.5 × ULN	2.5 to <5.0 × ULN	5.0 to <10.0 × ULN	≥10.0 × ULN
Alanine Aminotransferase, High	1.25 to <2.5 × ULN	2.5 to <5.0 × ULN	5.0 to <10.0 × ULN	≥10.0 ULN
Amylase (Total), High	1.1 to <1.5 × ULN	1.5 to <3.0 × ULN	3.0 to <5.0 × ULN	≥5.0 × ULN
Aspartate Aminotransferase, High	1.25 to <2.5 × ULN	2.5 to <5.0 × ULN	5.0 to <10.0 × ULN	≥10.0 × ULN
Bicarbonate, Low (mEq/L; mmol/L)	16.0 to <LLN 16.0 to <LLN	11.0 to <16.0 11.0 to <16.0	8.0 to <11.0 8.0 to <110.	<8.0 <8.0
Direct Bilirubin, High >28 days of age	NA	NA	>ULN with other signs and symptoms of hepatotoxicity	>ULN with life-threatening consequences (e.g., signs and symptoms of liver failure)
Total Bilirubin, High >28 days of age	1.1 to <1.6 × ULN	1.6 to <2.6 × ULN	2.6 to <5.0 × ULN	≥5.0 × ULN
Calcium, High (mg/dL; mmol/L) ≥7 days of age	10.6 to <11.5 2.65 to <2.88	11.5 to <12.5 2.88 to <3.13	12.5 to <13.5 3.13 to <3.38	≥13.5 ≥3.38
Calcium, Low (mg/dL; mmol/L) ≥7 days of age	7.8 to <8.4 1.95 to <2.10	7.0 to <7.8 1.75 to <1.95	6.1 to <7.0 1.53 to <1.75	<6.1 <1.53
Creatine Kinase, High	3 to <6 × ULN	6 to <10 × ULN	10 to <20 × ULN	≥20 × ULN
Creatinine, High *Choose the method that selects for the higher grade*	1.1 to 1.3 × ULN	>1.3 to 1.8 × ULN OR Increase to 1.3 to <1.5 × participant's baseline	>1.8 to <3.5 ULN OR Increase to 1.5 to <2.0 × participant's baseline	≥3.5 × ULN OR Increase of ≥2.0 × participant's baseline
Glucose Fasting, High (mg/dL; mmol/L)	110 to 125 6.11 to <6.95	>125 to 250 6.95 to <13.89	>250 to 500 13.89 to <27.75	≥500 ≥27.75
Glucose, Low (mg/dL; mmol/L) ≥1 month of age	55 to 64 3.05 to <3.55	40 to <55 2.22 to <3.05	30 to <40 1.67 to <2.22	<30 <1.67
Lipase, High	1.1 to <1.5 × ULN	1.5 to <3.0 × ULN	3.0 to <5.0 × ULN	≥5.0 × ULN

Cholesterol, Fasting, High (mg/dL; mmol/L) ≥18 years of age	200 to <240 5.18 to <6.19	240 to <300 6.19 to <7.77	≥300 ≥7.77	NA
Triglycerides, Fasting, High (mg/dL; mmol/L)	150 to 300 1.71 to 3.42	>300 to 500 >3.42 to 5.7	>500 to <1.000 >5.7 to 11.4	>1,000 >11.4
Phosphate, Low (mg/dL; mmol/L) >14 years of age	2.0 to <LLN 0.65 to <LLN	1.4 to <2.0 0.45 to <0.65	1.0 to <1.4 0.32 to <0.45	<1.0 <0.32
Potassium, High (mEq/L; mmol/L)	5.6 to <6.0 5.6 to <6.0	6.0 to <6.5 6.0 to <6.5	6.5 to <7.0 6.5 to <7.0	≥7.0 ≥7.0
Potassium, Low (mEq/L; mmol/L)	3.0 to <3.4 3.0 to <3.4	2.5 to <3.0 2.5 to <3.0	2.0 to <2.5 2.0 to <2.5	<2.0 <2.0
Sodium, High (mEq/L; mmol/L)	146 to <150 146 to <150	150 to <154 150 to <154	154 to <160 154 to <160	≥160 ≥160
Sodium, Low (mEq/L; mmol/L)	130 to <135 130 to <135	125 to <130 125 to <130	121 to <125 121 to <125	≤ 120 ≤ 120
Uric Acid, High (mEq/L; mmol/L)	7.5 to <10.0 0.45 to <0.59	10.0 to <12.0 0.59 to <0.71	12.0 to <15.0 0.71 to <0.89	≥15.0 ≥0.89

NA=not applicable; LLN = lower limit of normal; ULN=upper limit of normal.

Urinalysis				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Glucose/Glycosuria (random collection tested by dipstick)	Trace to 1+ or ≤ 250 mg	2+ or >250 to ≤ 500 mg	>2+ or >500 mg	NA
Protein/Proteinuria (random collection tested by dipstick)	1+	2+	3+ or higher	NA
Red Blood Cells (RBCs)/Hematuria (not to be reported based on dipstick findings or on blood believed to be of menstrual origin)	6 to <10 RBCs per high power field	≥10 RBCs per high power field	Gross, with or without clots OR with RBC casts OR intervention indicated	Life-threatening consequences

NA=not applicable

11.7. Appendix 7: Values of Potential Clinical Importance

11.7.1. ECG

ECG Parameter	Units	Potential Clinically Important Range	
		Lower	Upper
Absolute			
Absolute QTc Interval	msec		>450
Absolute PR Interval	msec	<110	>200
Absolute QRS Interval	msec	<75	>110
Change from Baseline			
Increase from Baseline QTc	msec		>60

11.7.2. Vital Signs

Vital Sign Parameter (Absolute)	Units	Potential Clinically Important Range	
		Lower	Upper
Systolic Blood Pressure	mmHg	<85	>140
Diastolic Blood Pressure	mmHg	<45	>90
Heart Rate	bpm	<40	>100

11.8. Appendix 8: Abbreviations & Trade Marks

11.8.1. Abbreviations

Abbreviation	Description
ADaM	analysis data model
AE	adverse event
ALT	alanine aminotransferase
AUC	area under the plasma concentration-time curve
AUC(0-τ)	auc from time 0 to the end of the dosing interval at steady state
CDISC	Clinical Data Interchange Standards Consortium
CI	confidence interval
Cmax	maximum observed concentration
C-SSRS	columbia suicide severity rating scale
Cτ	plasma concentration at the end of the dosing interval
CV_b	coefficient of variation (between)
DBF	database freeze
DBR	database release
DP	decimal places
ECG	electrocardiogram
eCRF	electronic case record form
GSK	GlaxoSmithKline
HIV	human immunodeficiency virus
ICH	international conference on harmonization
IDSL	integrated data standards library
LLN	lower limit of normal
NQ	not quantifiable
PK	pharmacokinetic
QD	once daily
RAP	reporting & analysis plan
SAC	statistical analysis complete
SAE	serious adverse event
SD	standard deviation
SDTM	study data tabulation model
Tmax	time of maximum observed concentration
ULN	upper limit of normal

11.8.2. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
NONE

Trademarks not owned by the GlaxoSmithKline Group of Companies
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11.9. Appendix 9: List of Data Displays

11.9.1. Data Display Numbering

The following numbering will be applied for RAP generated displays:

Section	Tables	Figures
Study Population	1.1 to 1.9	
Safety	2.1 to 2.29	2.1 to 2.1
Pharmacokinetic	3.1 to 3.37	3.1 to 3.39
Pharmacodynamic	4.1 to 4.4	4.1 to 4.4
Section	**Listings**	
ICH Listings	1 to 34	
Non-ICH Listings	35 to 54	

11.9.2. Mock Example Shell Referencing

Non-IDSL specifications will be referenced as indicated and if required example mock-up displays provided in the Table/Listing/Figure Shells.

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

NOTES:

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

11.9.3. Deliverables

Delivery	Description
SAC	Final Statistical Analysis Complete

11.9.4. Study Population Tables

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition					
1.1.	Enrolled	NS1	Summary of Number of Subjects Enrolled by Country and Site ID		SAC
1.2.	Screened	SP1	Summary of Study Population		SAC
1.3.	Safety	ES1	Summary of Subject Disposition for the Subject Conclusion Record		SAC
1.4.	Screened	ES6	Summary of Screening Status and Reasons for Screen Failures		SAC
Protocol Deviation					
1.5.	Safety	DV1	Summary of Important Protocol Deviations		SAC
Demographic and Baseline Characteristics					
1.6.	Safety	DM1	Summary of Demographic Characteristics		SAC
1.7.	Safety	DM5	Summary of Race and Racial Combinations		SAC
1.8.	Safety	EX1	Summary of Exposure to Study Treatment		SAC

11.9.5. Safety Tables

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Adverse Events (AEs)					
2.1.	Safety	AE1CP	Summary of Adverse Events by System Organ Class and Preferred Term		SAC
2.2.	Safety	AE1CP	Summary of Drug-Related Adverse Events by System Organ Class and Preferred Term		SAC
2.3.	Safety	AE3	Summary of Common (>=5%) Adverse Events by Overall Frequency		SAC
2.4.	Safety	AE15	Summary of Common (>=5%) Non-serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences)		SAC
2.5.	Safety	AE16	Summary of Serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences)		SAC
2.6.	Safety	AE5A	Summary of Adverse Events by System Organ Class and Preferred Term and Maximum Intensity		SAC
2.7.	Safety	AE1CP	Summary of Adverse Events of Special Interest		SAC
Laboratory: Chemistry					
2.8.	Safety	LB1	Summary of Clinical Chemistry Changes from Baseline		SAC
2.9.	Safety	LB1	Summary of Clinical Chemistry Values		SAC
2.10.	Safety	LB16	Summary of Clinical Chemistry Results by Maximum Grade Increase Post-Baseline Relative to Baseline		SAC
Laboratory: Hematology					
2.11.	Safety	LB1	Summary of Hematology Changes from Baseline		SAC
2.12.	Safety	LB1	Summary of Hematology Values		SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.13.	Safety	LB16	Summary of Hematology Results by Maximum Grade Increase Post-Baseline Relative to Baseline		SAC
Laboratory: Urinalysis					
2.14.	Safety	UR3	Summary of Urinalysis Dipstick Results		SAC
2.15.	Safety	LB1	Summary of Urine Concentration Changes from Baseline		SAC
2.16.	Safety	LB1	Summary of Urine Concentration Values		SAC
2.17.	Safety	LB16	Summary of Urinalysis by Maximum Grade Increase Post-Baseline Relative to Baseline		SAC
ECG					
2.18.	Safety	SAFE_T1	Summary of ECG Findings		SAC
2.19.	Safety	EG2	Summary of ECG Changes from Baseline		SAC
2.20.	Safety	EG2	Summary of ECG Values		SAC
2.21.	Safety	EG10	Summary of Maximum QTc Values Post-Baseline Relative to Baseline by Category		SAC
2.22.	Safety	EG11	Summary of Maximum Increase in QTc Values Post-Baseline Relative to Baseline by Category		SAC
Vital Signs					
2.23.	Safety	VS1	Summary of Vital Sign Changes from Baseline		SAC
2.24.	Safety	VS1	Summary of Vital Sign Values		SAC
C-SSRS					
2.25.	Safety	CSSRS4	Listing of C-SSRS Suicidal Ideation and Behavior Data	Only include participants who have suicidal ideation or behavior	SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Liver Event					
2.26.	Safety	LIVER1	Summary of Liver Monitoring/Stopping Event Reporting		SAC
2.27.	Safety	LIVER10	Summary of Hepatobiliary Laboratory Abnormalities		SAC
COVID-19 Related AE					
2.28.	Safety	PAN1	Summary of COVID-19 Assessment		SAC
2.29	Safety	SAFE_T2	Summary of COVID-19 Adverse Event Summary		SAC
2.30	Safety	PAN11	Summary of COVID-19 Symptoms for Subjects with Adverse Events	Conditional Display	SAC

11.9.6. Safety Figures

Safety: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
ECG					
2.1.	Safety	EG9	Mean (95% CI) Change from Baseline in QTcF Interval by Timepoint and Treatment		SAC

11.9.7. Pharmacokinetic Tables

Pharmacokinetic: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
PK Concentration Data					
3.1.	PK Concentration	PKCT1	Summary of Caffeine Plasma Pharmacokinetic Concentration-Time Data (units) by Treatment		SAC
3.2.	PK Concentration	PKCT1	Summary of Metoprolol and Alpha-hydroxymetoprolol Plasma Pharmacokinetic Concentration-Time Data (units) by Treatment		SAC
3.3.	PK Concentration	PKCT1	Summary of Montelukast and 36-Hydroxymontelukast Plasma Pharmacokinetic Concentration-Time Data (units) by Treatment		SAC
3.4.	PK Concentration	PKCT1	Summary of Flurbiprofen Plasma Pharmacokinetic Concentration-Time Data (units) by Treatment		SAC
3.5.	PK Concentration	PKCT1	Summary of Omeprazole and 5-Hydroxyomeprazole Plasma Pharmacokinetic Concentration-Time Data (units) by Treatment		SAC
3.6.	PK Concentration	PKCT1	Summary of Midazolam and 1-Hydroxymidazolam Plasma Pharmacokinetic Concentration-Time Data (units) by Treatment		SAC
3.7.	PK Concentration	PKCT1	Summary of Digoxin Plasma Pharmacokinetic Concentration-Time Data (units) by Treatment		SAC
3.8.	PK Concentration	PKCT1	Summary of Pravastatin Acid and Pravastatin Lactone Plasma Pharmacokinetic Concentration-Time Data (units) by Treatment		SAC
3.9.	PK Concentration	PKCT1	Summary of GSK3640254 Plasma Pharmacokinetic Concentration-Time Data (units)		SAC
3.10.	PK Concentration	PKCT1	Summary of Predose (Trough) GSK3640254 Plasma Concentration Data (ng/mL) by Treatment		SAC
PK Derived Parameters					
3.11.	PK Parameter	PKPT4	Summary Statistics of Derived Caffeine Plasma Pharmacokinetic Parameters (Non-Transformed) Based on Actual Time by Treatment	Parameters with units	SAC

Pharmacokinetic: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.12.	PK Parameter	PKPT4	Summary Statistics of Derived Metoprolol and Alpha-hydroxymetoprolol Plasma Pharmacokinetic Parameters (Non-Transformed) Based on Actual Time by Treatment	Parameters with units	SAC
3.13.	PK Parameter	PKPT4	Summary Statistics of Derived Montelukast and 36-Hydroxymontelukast Plasma Pharmacokinetic Parameters (Non-Transformed) Based on Actual Time by Treatment	Parameters with units	SAC
3.14.	PK Parameter	PKPT4	Summary Statistics of Derived Flurbiprofen Plasma Pharmacokinetic Parameters (Non-Transformed) Based on Actual Time by Treatment	Parameters with units	SAC
3.15.	PK Parameter	PKPT4	Summary Statistics of Derived Omeprazole and 5-Hydroxyomeprazole Plasma Pharmacokinetic Parameters (Non-Transformed) Based on Actual Time by Treatment	Parameters with units	SAC
3.16.	PK Parameter	PKPT4	Summary Statistics of Derived Midazolam and 1-Hydroxymidazolam Plasma Pharmacokinetic Parameters (Non-Transformed) Based on Actual Time by Treatment	Parameters with units	SAC
3.17.	PK Parameter	PKPT4	Summary Statistics of Derived Digoxin Plasma Pharmacokinetic Parameters (Non-Transformed) Based on Actual Time by Treatment	Parameters with units	SAC
3.18.	PK Parameter	PKPT4	Summary Statistics of Derived Pravastatin Acid and Pravastatin Lactone Plasma Pharmacokinetic Parameters (Non-Transformed) Based on Actual Time by Treatment	Parameters with units	SAC
3.19.	PK Parameter	PKPT4	Summary Statistics of Derived GSK3640254 Plasma Pharmacokinetic Parameters (Non-Transformed) Based on Actual Time	Parameters with units	SAC
3.20.	PK Parameter	PKPT4	Summary Statistics of Derived Caffeine Plasma Pharmacokinetic Parameters (Ln-Transformed) Based on Actual Time by Treatment	Parameters with units	SAC
3.21.	PK Parameter	PKPT4	Summary Statistics of Derived Metoprolol and Alpha-hydroxymetoprolol Plasma Pharmacokinetic Parameters (Ln-Transformed) Based on Actual Time by Treatment	Parameters with units	SAC

Pharmacokinetic: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.22.	PK Parameter	PKPT4	Summary Statistics of Derived Montelukast and 36-Hydroxymontelukast Plasma Pharmacokinetic Parameters (Ln-Transformed) Based on Actual Time by Treatment	Parameters with units	SAC
3.23.	PK Parameter	PKPT4	Summary Statistics of Derived Flurbiprofen Plasma Pharmacokinetic Parameters (Ln-Transformed) Based on Actual Time by Treatment	Parameters with units	SAC
3.24.	PK Parameter	PKPT4	Summary Statistics of Derived Omeprazole and 5-Hydroxyomeprazole Plasma Pharmacokinetic Parameters (Ln-Transformed) Based on Actual Time by Treatment	Parameters with units	SAC
3.25.	PK Parameter	PKPT4	Summary Statistics of Derived Midazolam and 1-Hydroxymidazolam Plasma Pharmacokinetic Parameters (Ln-Transformed) Based on Actual Time by Treatment	Parameters with units	SAC
3.26.	PK Parameter	PKPT4	Summary Statistics of Derived Digoxin Plasma Pharmacokinetic Parameters (Ln-Transformed) Based on Actual Time by Treatment	Parameters with units	SAC
3.27.	PK Parameter	PKPT4	Summary Statistics of Derived Pravastatin Acid and Pravastatin Lactone Plasma Pharmacokinetic Parameters (Ln-Transformed) Based on Actual Time by Treatment	Parameters with units	SAC
3.28.	PK Parameter	PKPT4	Summary Statistics of Derived GSK3640254 Plasma Pharmacokinetic Parameters (Ln-Transformed) Based on Actual Time	Parameters with units	SAC
PK Analysis					
3.29.	PK Parameter	PKPT3	Statistical Analysis of Caffeine Plasma Pharmacokinetic Parameters		SAC
3.30.	PK Parameter	PKPT3	Statistical Analysis of Metoprolol and Alpha-hydroxymetoprolol Plasma Pharmacokinetic Parameters		SAC
3.31.	PK Parameter	PKPT3	Statistical Analysis of Montelukast and 36-Hydroxymontelukast Plasma Pharmacokinetic Parameters		SAC
3.32.	PK Parameter	PKPT3	Statistical Analysis of Flurbiprofen Plasma Pharmacokinetic Parameters		SAC

Pharmacokinetic: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.33.	PK Parameter	PKPT3	Statistical Analysis of Omeprazole and 5-Hydroxyomeprazole Plasma Pharmacokinetic Parameters		SAC
3.34.	PK Parameter	PKPT3	Statistical Analysis of Midazolam and 1-Hydroxymidazolam Plasma Pharmacokinetic Parameters		SAC
3.35.	PK Parameter	PKPT3	Statistical Analysis of Digoxin Plasma Pharmacokinetic Parameters		SAC
3.36.	PK Parameter	PKPT3	Statistical Analysis of Pravastatin Acid and Pravastatin Lactone Plasma Pharmacokinetic Parameters		SAC
3.37.	PK Parameter	PKPT3	Statistical Analysis of Predose (Trough) GSK3640254 Plasma Concentration Data (unit)		SAC

11.9.8. Pharmacodynamic Tables

Pharmacodynamic: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
PD Concentration Data					
4.1	PD Concentration	PKCT1	Summary of CP-1 Baseline-adjusted Plasma Pharmacodynamic Concentration-Time Data (units) by Treatment		SAC
PD Derived Parameters					
4.2	PD Parameter	PKPT4	Summary Statistics of Derived CP-1 Plasma Pharmacodynamic Parameters (Non-Transformed) Based on Actual Time by Treatment	Parameters with units	SAC
4.3	PD Parameter	PKPT4	Summary Statistics of Derived CP-1 Plasma Pharmacodynamic Parameters (Ln-Transformed) Based on Actual Time by Treatment	Parameters with units	SAC
PD Analysis					
4.4	PD Parameter	PKPT3	Statistical Analysis of CP-1 Plasma Pharmacodynamic Parameters		SAC

11.9.9. Pharmacokinetic Figures

Pharmacokinetic: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Individual Concentration Plots					
3.1.	PK Concentration	PKCF1P	Individual Caffeine Plasma Concentration-Time Plots by Participant (Linear and Semi-Logarithmic)	Paginate by Participant Dashed line represents the LLQ Treatments Overlaid	SAC
3.2.	PK Concentration	PKCF2	Individual Metoprolol and Alpha-hydroxymetoprolol Plasma Concentration-Time Plots by Participant (Linear and Semi-Logarithmic)	Paginate by Participant Dashed line represents the LLQ Treatments Overlaid	SAC
3.3.	PK Concentration	PKCF2	Individual Montelukast and 36-Hydroxymontelukast Plasma Concentration-Time Plots by Participant (Linear and Semi-Logarithmic)	Paginate by Participant Dashed line represents the LLQ Individual Overlaid	SAC
3.4.	PK Concentration	PKCF2	Individual Flurbiprofen Plasma Concentration-Time Plots by Participant (Linear and Semi-Logarithmic)	Paginate by Participant Dashed line represents the LLQ Individual Overlaid	SAC
3.5.	PK Concentration	PKCF2	Individual Omeprazole and 5-Hydroxyomeprazole Plasma Concentration-Time Plots by Participant (Linear and Semi-Logarithmic)	Paginate by Participant Dashed line represents the LLQ Individual Overlaid	SAC
3.6.	PK Concentration	PKCF2	Individual Midazolam and 1-Hydroxymidazolam Plasma Concentration-Time Plots by Participant (Linear and Semi-Logarithmic)	Paginate by Participant Dashed line represents the LLQ Individual Overlaid	SAC
3.7.	PK Concentration	PKCF2	Individual Digoxin Plasma Concentration-Time Plots by Participant (Linear and Semi-Logarithmic)	Paginate by Participant Dashed line represents the LLQ Individual Overlaid	SAC

Pharmacokinetic: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.8.	PK Concentration	PKCF2	Individual Pravastatin Acid and Pravastatin Lactone Plasma Concentration-Time Plots by Participant (Linear and Semi-Logarithmic)	Paginate by Participant Dashed line represents the LLQ Individual Overlaid	SAC
3.9.	PK Concentration	PKCF2	Individual GSK3640254 Plasma Concentration-Time Plots by Participant (Linear and Semi-Logarithmic)	Paginate by Participant Dashed line represents the LLQ Individual Overlaid	SAC
3.10.	PK Concentration	PKCF2	Individual Caffeine Plasma Concentration-Time Plots by Treatment (Linear and Semi-Logarithmic)	Paginate by Treatment Dashed line represents the LLQ Individual Overlaid	SAC
3.11.	PK Concentration	PKCF1P	Individual Metoprolol and Alpha-hydroxymetoprolol Plasma Concentration-Time Plots by Treatment (Linear and Semi-Logarithmic)	Paginate by Treatment Dashed line represents the LLQ Individual Overlaid	SAC
3.12.	PK Concentration	PKCF1P	Individual Montelukast and 36-Hydroxymontelukast Plasma Concentration-Time Plots by Treatment (Linear and Semi-Logarithmic)	Paginate by Treatment Dashed line represents the LLQ Individual Overlaid	SAC
3.13.	PK Concentration	PKCF1P	Individual Flurbiprofen Plasma Concentration-Time Plots by Treatment (Linear and Semi-Logarithmic)	Paginate by Treatment Dashed line represents the LLQ Individual Overlaid	SAC
3.14.	PK Concentration	PKCF1P	Individual Omeprazole and 5-Hydroxyomeprazole Plasma Concentration-Time Plots by Treatment (Linear and Semi-Logarithmic)	Paginate by Treatment Dashed line represents the LLQ Individual Overlaid	SAC
3.15.	PK Concentration	PKCF1P	Individual Midazolam and 1-Hydroxymidazolam Plasma Concentration-Time Plots by Treatment (Linear and Semi-Logarithmic)	Paginate by Treatment Dashed line represents the LLQ Individual Overlaid	SAC

Pharmacokinetic: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.16.	PK Concentration	PKCF1P	Individual Digoxin Plasma Concentration-Time Plots by Treatment (Linear and Semi-Logarithmic)	Paginate by Treatment Dashed line represents the LLQ Individual Overlaid	SAC
3.17.	PK Concentration	PKCF1P	Individual Pravastatin Acid and Pravastatin Lactone Plasma Concentration-Time Plots by Treatment (Linear and Semi-Logarithmic)	Paginate by Treatment Dashed line represents the LLQ Individual Overlaid	SAC
3.18.	PK Concentration	PKCF1P	Individual GSK3640254 Plasma Concentration-Time Plots	Paginate by Treatment Dashed line represents the LLQ Individual Overlaid	SAC
Mean / Median Concentration Plots					
3.19.	PK Concentration	PKCF1P	Mean (± Standard Deviation) Caffeine Plasma Concentration-Time Plots by Treatment (Linear and Semi-Logarithmic)	Treatments Overlaid	SAC
3.20.	PK Concentration	PKCF1P	Mean (± Standard Deviation) Metoprolol and Alpha-hydroxymetoprolol Plasma Concentration-Time Plots by Treatment (Linear and Semi-Logarithmic)	Treatments Overlaid	SAC
3.21.	PK Concentration	PKCF1P	Mean (± Standard Deviation) Montelukast and 36-Hydroxymontelukast Plasma Concentration-Time Plots by Treatment (Linear and Semi-Logarithmic)	Treatments Overlaid	SAC
3.22.	PK Concentration	PKCF1P	Mean (± Standard Deviation) Flurbiprofen Plasma Concentration-Time Plots by Treatment (Linear and Semi-Logarithmic)	Treatments Overlaid	SAC
3.23.	PK Concentration	PKCF1P	Mean (± Standard Deviation) Omeprazole and 5-Hydroxyomeprazole Plasma Concentration-Time Plots by Treatment (Linear and Semi-Logarithmic)	Treatments Overlaid	SAC
3.24.	PK Concentration	PKCF1P	Mean (± Standard Deviation) Midazolam and 1-Hydroxymidazolam Plasma Concentration-Time Plots by Treatment (Linear and Semi-Logarithmic)	Treatments Overlaid	SAC
3.25.	PK Concentration	PKCF1P	Mean (± Standard Deviation) Digoxin Plasma Concentration-Time Plots by Treatment (Linear and Semi-Logarithmic)	Treatments Overlaid	SAC

Pharmacokinetic: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.26.	PK Concentration	PKCF1P	Mean (± Standard Deviation) Pravastatin Acid and Pravastatin Lactone Plasma Concentration-Time Plots by Treatment (Linear and Semi-Logarithmic)	Treatments Overlaid	SAC
3.27.	PK Concentration	PKCF1P	Mean (± Standard Deviation) GSK3640254 Plasma Concentration-Time Plots by Treatment (Linear and Semi-Logarithmic)	Treatments Overlaid	SAC
3.28.	PK Concentration	PKCF1P	Mean (± Standard Deviation) Predose (Trough) GSK3640254 Plasma Concentration-Time Plots (Linear and Semi-Logarithmic)	Treatments Overlaid	SAC
3.29.	PK Concentration	PKCF3	Median (Range) Caffeine Plasma Concentration-Time Plots by Treatment (Linear and Semi-Logarithmic)	Treatments Overlaid	SAC
3.30.	PK Concentration	PKCF3	Median (Range) Metoprolol and Alpha-hydroxymetoprolol Plasma Concentration-Time Plots by Treatment (Linear and Semi-Logarithmic)	Treatments Overlaid	SAC
3.31.	PK Concentration	PKCF3	Median (Range) Montelukast and 36-Hydroxymontelukast Plasma Concentration-Time Plots by Treatment (Linear and Semi-Logarithmic)	Treatments Overlaid	SAC
3.32.	PK Concentration	PKCF3	Median (Range) Flurbiprofen Plasma Concentration-Time Plots by Treatment (Linear and Semi-Logarithmic)	Treatments Overlaid	SAC
3.33.	PK Concentration	PKCF3	Median (Range) Omeprazole and 5-Hydroxyomeprazole Plasma Concentration-Time Plots by Treatment (Linear and Semi-Logarithmic)	Treatments Overlaid	SAC
3.34.	PK Concentration	PKCF3	Median (Range) Midazolam and 1-Hydroxymidazolam Plasma Concentration-Time Plots by Treatment (Linear and Semi-Logarithmic)	Treatments Overlaid	SAC
3.35.	PK Concentration	PKCF3	Median (Range) Digoxin Plasma Concentration-Time Plots by Treatment (Linear and Semi-Logarithmic)	Treatments Overlaid	SAC
3.36.	PK Concentration	PKCF3	Median (Range) Pravastatin Acid and Pravastatin Lactone Plasma Concentration-Time Plots by Treatment (Linear and Semi-Logarithmic)	Treatments Overlaid	SAC

Pharmacokinetic: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.37.	PK Concentration	PKCF3	Median (Range) GSK3640254 Plasma Concentration-Time Plots (Linear and Semi-Logarithmic)	Treatments Overlaid	SAC
3.38.	PK Concentration	PKCF1P	Median (Range) Predose (Trough) GSK3640254 Plasma Concentration-Time Plots by Treatment (Linear and Semi-Logarithmic)	Treatments Overlaid	SAC
Statistical Figures					
3.39.	PK Parameter	Not available	Geometric Mean Treatment Ratio (C/A) and 90% Confidence Interval of Pharmacokinetic Parameters for Probe Substrate Drugs	GMR and 90% CI	SAC

11.9.10. Pharmacodynamic Figures

Pharmacodynamic: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Individual Concentration Plots					
4.1	PD Concentration	PKCF1P	Individual CP-1 Plasma Concentration-Time Plots by Participant (Linear and Semi-Logarithmic)	Paginate by Participant Dashed line represents the LLQ Treatments Overlaid	SAC
4.2	PD Concentration	PKCF2	Individual CP-1 Plasma Concentration-Time Plots by Treatment (Linear and Semi-Logarithmic)	Paginate by Treatment Dashed line represents the LLQ Individual Overlaid	SAC
Mean / Median Concentration Plots					
4.3	PD Concentration	PKCF1P	Mean (± Standard Deviation) CP-1 Plasma Concentration-Time Plots by Treatment (Linear and Semi-Logarithmic)	Treatments Overlaid	SAC
4.4	PD Concentration	PKCF3	Median (Range) CP-1 Plasma Concentration-Time Plots by Treatment (Linear and Semi-Logarithmic)	Treatments Overlaid	SAC

11.9.11. ICH Listings

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition					
1.	Safety	ES3	Listing of Reasons for Study Withdrawal		SAC
2.	Safety	SD2	Listing of Reasons for Study Treatment Discontinuation		SAC
3.	Screened	ES7	Listing of Reasons for Screen Failure		SAC
Protocol Deviations					
4.	Safety	DV2	Listing of Important Protocol Deviations		SAC
5.	Safety	IE3	Listing of Subjects with Inclusion/Exclusion Criteria Deviations		SAC
Populations Analyzed					
6.	Safety	SP3A	Listing of Subjects Excluded from Any Population		SAC
Demographic and Baseline Characteristics					
7.	Safety	DM2	Listing of Demographic Characteristics		SAC
8.	Safety	DM9	Listing of Race		SAC
Prior and Concomitant Medications					
9.	Safety	CM5	Listing of Concomitant Medications	Based on GSK Drug Dictionary	SAC
Exposure and Treatment Compliance					
10.	Safety	EX4	Listing of Exposure Data		SAC
11.	Safety	POP_L1	Listing of Meal Data		SAC
Adverse Events					
12.	Safety	AE2	Listing of Relationship Between System Organ Class and Verbatim Text		SAC
13.	Safety	AE7	Listing of Subject Numbers for Individual Adverse Events		SAC
14.	Safety	AE9CP	Listing of All Adverse Events		SAC

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
15.	Safety	AE9CP	Listing of Adverse Events of Special Interest		SAC
Serious and Other Significant Adverse Events					
16.	Safety	AE9CP	Listing of Study Drug Related Adverse Events		SAC
17.	Safety	AE9CP	Listing of Serious Adverse Events (Fatal & Non-Fatal)		SAC
18.	Safety	AE14	Listing of Reasons for Considering as a Serious Adverse Event		SAC
19.	Safety	AE9CP	Listing of Adverse Events Leading to Withdrawal from Study		SAC
Hepatobiliary (Liver)					
20.	Safety	MH2	Listing of Medical Conditions for Subjects with Liver Stopping Events		SAC
21.	Safety	SU2	Listing of Substance Use for Subjects with Liver Stopping Events		SAC
All Laboratory					
22.	Safety	LB5A	Listing of Clinical Chemistry with any Toxicities		SAC
23.	Safety	LB5A	Listing of All Clinical Chemistry Data for Subjects with any Toxicities		SAC
24.	Safety	LB5A	Listing of Hematology with any Toxicities		SAC
25.	Safety	LB5A	Listing of All Hematology Data for Subjects with any Toxicities		SAC
26.	Safety	LB5A	Listing of Urinalysis with any Toxicities		SAC
27.	Safety	LB5A	Listing of All Urinalysis Data for Subjects with any Toxicities		SAC
ECG					
28.	Safety	EG6	Listing of All ECG Findings		SAC
29.	Safety	EG6	Listing of All Abnormal ECG Findings		SAC
30.	Safety	EG4	Listing of All ECG Values		SAC
Vital Signs					
31.	Safety	VS5	Listing of All Vital Signs of Potential Clinical Importance		SAC
32.	Safety	VS5	Listing of All Vital Signs for Subjects with any Value of Potential Clinical Importance		SAC

11.9.12. Non-ICH Listings

Non-ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Pharmacokinetics					
33.	PK Concentration	PKCL1P	Listing of Caffeine Plasma Concentration-Time Data by Treatment		SAC
34.	PK Concentration	PKCL1P	Listing of Metoprolol and Alpha-hydroxymetoprolol Plasma Concentration-Time Data by Treatment		SAC
35.	PK Concentration	PKCL1P	Listing of Montelukast and 36-Hydroxymontelukast Plasma Concentration-Time Data by Treatment		SAC
36.	PK Concentration	PKCL1P	Listing of Flurbiprofen Plasma Concentration-Time Data by Treatment		SAC
37.	PK Parameter	PKPL1P	Listing of Omeprazole and 5-Hydroxyomeprazole Plasma Concentration-Time Data by Treatment		SAC
38.	PK Parameter	PKPL1P	Listing of Midazolam and 1-Hydroxymidazolam Plasma Concentration-Time Data by Treatment		SAC
39.	PK Parameter	PKPL1P	Listing of Digoxin Plasma Concentration-Time Data by Treatment		SAC
40.	PK Parameter	PKPL1P	Listing of Pravastatin Acid and Pravastatin Lactone Plasma Concentration-Time Data by Treatment		SAC
41.	PK Parameter	PKPL1P	Listing of GSK3640254 Plasma Concentration-Time Data by Treatment		SAC
42.	PK Parameter	PKPL1P	Listing of Caffeine Plasma Pharmacokinetic Parameters Based on Actual Time by Treatment		SAC
43.	PK Parameter	PKPL1P	Listing of Metoprolol and Alpha-hydroxymetoprolol Plasma Pharmacokinetic Parameters Based on Actual Time by Treatment		SAC
44.	PK Parameter	PKPL1P	Listing of Montelukast and 36-Hydroxymontelukast Plasma Pharmacokinetic Parameters Based on Actual Time by Treatment		SAC

Non-ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
45.	PK Parameter	PKPL1P	Listing of Flurbiprofen Plasma Pharmacokinetic Parameters Based on Actual Time by Treatment		SAC
46.	PK Parameter	PKPL1P	Listing of Omeprazole and 5-Hydroxyomeprazole Plasma Pharmacokinetic Parameters Based on Actual Time by Treatment		SAC
47.	PK Parameter	PKPL1P	Listing of Midazolam and 1-Hydroxymidazolam Plasma Pharmacokinetic Parameters Based on Actual Time by Treatment		SAC
48.	PK Parameter	PKPL1P	Listing of Digoxin Plasma Pharmacokinetic Parameters Based on Actual Time by Treatment		SAC
49.	PK Parameter	PKPL1P	Listing of Pravastatin Acid and Pravastatin Lactone Plasma Pharmacokinetic Parameters Based on Actual Time by Treatment		SAC
50.	PK Parameter	PKPL1P	Listing of GSK3640254 Plasma Pharmacokinetic Parameters Based on Actual Time by Treatment		SAC
Pharmacodynamic					
51.	PD Concentration	PKCL1P	Listing of CP-1 Plasma Concentration-Time Data by Treatment		SAC
52.	PD Parameter	PKPL1P	Listing of CP-1 Plasma Pharmacodynamic Parameters Based on Actual Time by Treatment		SAC
COVID-19 Related AE					
53.	Safety	PAN12	Listing of COVID-19 Assessments and Symptom Assessment		SAC
54.	Safety	AE9CP	Listing of Adverse Events of COVID-19		SAC