Division	:	Worldwide Development
Information Type	:	Statistical Analysis Plan (SAP)

TITLE PAGE

Protocol Title: A two-period study in healthy male participants to determine the pharmacokinetics, balance/excretion, and metabolism of [^{14}C]-GSK3640254 following a single intravenous radiolabeled microtracer dose (concomitant with a non-radiolabeled oral dose) and a single oral radiolabeled dose

Protocol Number: 213051

Compound Number: GSK3640254

Short Title: PH 1, [^{14}C]-GSK3640254, IV vs oral, ADME study
Sponsor Name: ViiV Healthcare UK Limited

Regulatory Agency Identifier Number(s)

Registry	**ID**
Clinicaltrials.gov	NCT04507321
EudraCT	2019-004444-30
IND	139838

SAP Author(s):

Author	Date
PPD Associate Statistician, Dev Biostats India Stats	04-SEP-2020
PPD Director, Clinical Pharmacology, CPMS	04-SEP-2020

SAP Team Review Confirmations (E-mail Confirmation):

Reviewer	Date of E-mail Confirmation
PPD Principal Statistician, Dev Biostats Stats Dev	04-SEP-2020
PPD Director, Clinical Pharmacology, CPMS	07-SEP-2020
PPD Senior Manager, Programming, Dev Biostats India Prog	07-SEP-2020
PPD Discovery Medicine Scientist Manager GSK Fellow, R&D GCSD	04-SEP-2020
PPD DMPK Project Rep	08-SEP-2020
PPD Physician Product Lead, ViiV Development	09-SEP-2020
PPD Director, Clinical Development, ViiV Research & Development	05-SEP-2020
PPD Principal Clinical Data Manager, RD PCPS GCDO DM ID	04-SEP-2020
PPD Medical Director, SERM, SMG Pharma Safety	07-SEP-2020

SAP Biostatistics Line Approval (Vault TMF eSignature):

Approver
PPD Manager Statistics, Dev Biostats India Stats

TABLE OF CONTENTS

PAGE

VERSION HISTORY

This Statistical Analysis Plan (SAP) for study 213051 is based on the protocol Amendment 01 dated 10-JUN-2020.

Table 1 SAP Version History Summary

SAP Version	Effective Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
1	Refer to Document Date	Amendment 01 dated 10-JUN-2020	Not Applicable	Original version

1. INTRODUCTION

The purpose of this SAP is to describe the planned analyses to be included in the Clinical Study Report for Study 213051. Details of the final analyses are provided.

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

1.1. Changes to the Protocol Defined Statistical Analysis Plan

Changes from the originally planned statistical analysis specified in the protocol are detailed in Table 2

Table 2 Changes to Protocol Defined Analysis Plan

Protocol Defined Analysis	SAP Defined Analysis	Rationale for Changes
• Population for analysis	• Enrolled population- All participants who 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 analysis set as they did not enter the study.	• This population was not present in the protocol. It has been added to SAP as per the requirement for the data display

1.2. Objectives, Endpoints and Estimands

1.2.1. Objectives and Endpoints

Objectives	Endpoints[1]
Primary	
• To determine parent GSK3640254 and total drug-related radioactivity systemic concentrations following a single IV microtracer dose of [^{14}C]-GSK3640254 (with an oral dose of non-radiolabelled	• AUC(0–inf), AUC(0–t), Cmax, tmax and t1/2 of parent and total drug-related material (radioactivity) in plasma and blood.

Objectives	Endpoints[1]
GSK3640254) and oral dose of [^{14}C]-GSK3640254[1]	• Volume of distribution at steady state (Vss) and clearance (CL) of parent after IV dose (Period 1 only). • Renal clearance of parent (CLr) after both IV and oral dose • Oral clearance (CL/F) and apparent volume of distribution (Vz/F) for the parent following oral administration
• To calculate the absolute oral bioavailability of GSK3640254	• Direct estimation of absolute oral bioavailability (F), indirect calculation of fraction of drug escaping first pass hepatic clearance (Fh), fraction absorbed (Fa) and fraction of drug escaping gut metabolism (Fg).
• To determine the rate and extent of excretion of total radioactivity in urine and feces and the total recovery of radioactivity, following IV and oral administrations of [^{14}C]-GSK3640254	• Urinary and fecal cumulative excretion as a percentage of the total radioactive dose
Secondary	
• To evaluate the safety and tolerability of GSK3640254 after single IV and oral doses in healthy participants.	• Characterize observed adverse events, and abnormal laboratory, 12-lead ECG, and vital signs assessments observed.
• To determine the blood:plasma ratio of [^{14}C]-GSK3640254-related materials (total radioactivity) associated with blood cellular components	• Blood:plasma ratio of [^{14}C]-GSK3640254-related materials (total radioactivity).
Exploratory	
• To generate samples that will be used to characterize the metabolite profile of GSK3640254 following a single IV microtracer dose of [^{14}C]-GSK3640254 concomitant with an oral dose of non-radiolabelled GSK3640254 (plasma, urine, feces, duodenal bile) and a single, oral dose of [^{14}C]- GSK3640254 (plasma, urine, feces, duodenal bile).	• Characterization and quantification of metabolites in plasma, urine, feces, and duodenal bile (qualitative identification in bile). These analytical investigations will be conducted, and the results reported under a separate nonclinical GSK protocol.

Objectives	Endpoints[1]
• To evaluate the PK and relative bioavailability of GSK3640254 following administration of the 85 mg suspension compared to the 200 mg tablet	• AUC(0-inf), AUC(0-t) and Cmax

AUC(0–inf): Area under the plasma concentration-time curve from time zero (pre-dose) extrapolated to infinite time, AUC(0–t): Area under the plasma concentration-time curve from time zero (pre-dose) to last time of quantifiable concentration within a participant across all treatments, Cmax: Maximum observed plasma concentration, tmax: time of occurrence of Cmax, t1/2: terminal phase half-life, ECG: electrocardiogram.

[1] For measured concentrations of GSK3640254 in plasma, the nomenclature **[^{14}C]-GSK3640254** describes the parent GSK3640254 concentration derived via analysis by liquid chromatography (LC) + AMS, whereas **GSK3640254** describes the parent GSK3640254 concentration derived via liquid chromatography-tandem mass spectrometry (LC-MS/MS).

AUC(0-inf), AUC(0-t), Cmax, tmax and t1/2 of parent and total drug-related material (radioactivity) will only be collected in plasma.

1.2.2. Estimands

Table 3 Estimands

Objective	Estimand Category	Estimand Variable/ Endpoint	Analysis Set	Intercurrent Event Strategy	Population Level Summary Measure
Primary Objective: To determine parent GSK3640254 and total drug-related radioactivity systemic concentrations following a single IV microtracer dose of [^{14}C]-GSK3640254 (with an oral dose of non-radiolabelled GSK3640254) and oral dose of [^{14}C]-GSK36402541	Primary 1	AUC(0-inf), AUC(0-t), Cmax, tmax and t1/2 of parent and total drug-related material (radioactivity) in plasma	PK	Subject withdrawal or AE occurrence (treatment policy)	No adjustments will be made for the occurrence of any intercurrent events. Estimation will be done based upon observed data.
	Supplementary 1	Volume of distribution at steady-state (Vss) and clearance (CL) of parent after IV dose (Period 1 only)	PK	See Primary 1	
	Supplementary 2	Renal clearance of	PK	See Primary 1	

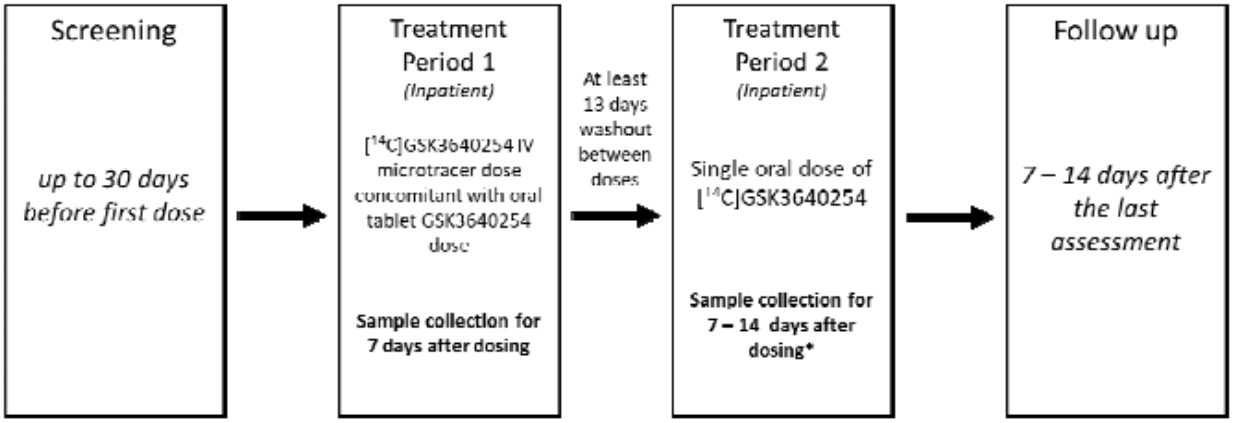
Objective	Estimand Category	Estimand Variable/ Endpoint	Analysis Set	Intercurrent Event Strategy	Population Level Summary Measure
		parent (CLr) after IV and oral administration			
	Supplementary 3	Oral clearance (CL/F) and apparent volume of distribution (Vz/F) for the parent following oral administration	PK	See Primary 1	
To calculate the absolute oral bioavailability of GSK3640254	primary 2	Direct estimation of absolute oral bioavailability (F), indirect calculation of fraction of drug escaping first pass hepatic clearance (Fh),	PK	See Primary 1	

Objective	Estimand Category	Estimand			
		Variable/ Endpoint	**Analysis Set**	**Intercurrent Event Strategy**	**Population Level Summary Measure**
		fraction absorbed (Fa) and fraction of drug escaping gut metabolism (Fg).			
To determine the rate and extent of excretion of total radioactivity in urine and feces and the total recovery of radioactivity, following IV and oral administrations of [^{14}C]-GSK3640254	Primary 3	Urinary and fecal cumulative excretion as a percentage of the total radioactive dose		See Primary 1	
Key Secondary objective : To determine the blood:plasma ratio of [^{14}C]-GSK3640254-related materials (total radioactivity)	Secondary	Blood:plasma ratio of [^{14}C]-GSK3640254-related materials (total radioactivity).	PK	See Primary 1	

Objective	Estimand Category	Estimand			
		Variable/ Endpoint	Analysis Set	Intercurrent Event Strategy	Population Level Summary Measure
associated with blood cellular components					

1.3. Study Design

Overview of Study Design and Key Features



*If radioactivity in the 24 hour interval collections immediately prior to discharge is still >1%, faecal samples will be collected by participants at home after Day 15 (day of discharge/follow up)

Design Features	• Open-label • Single center • Non-randomised • 2-period, single-sequence • Mass balance study • Approximately 6 healthy male participants will be enrolled • A screening visit (up to 30 days before first dose) • Two inpatient treatment periods (Treatment Periods 1 and 2), with at least 13 days between doses. A follow-up visit 7 – 14 days after the last assessment in Treatment Period 2
Study intervention	
Study intervention Assignment	Approximately six participants will be enrolled to achieve at least 4 participants completing the two treatment periods. On Day 1 of Treatment Period 1, after an overnight fast of at least 8 h, each participant will take a single 200 mg oral dose (2 x 100 mg tablets) of GSK3640254 with a moderate fat meal (approximately 600 calories with approximately 30% of calories from fat); the IV infusion of 100 µg of [^{14}C]-GSK3640254 (approximately 3.7 kBq; 100 nCi) will begin 5 h after oral dose and continue over 1 h. On Day 1 of Treatment Period 2, after an overnight fast of at least 8 h, each participant will receive approximately 85 mg [^{14}C]-GSK3640254 (approximately 3.15 MBq; 85 µCi) as an oral suspension with a moderate fat meal (approximately 600 calories with approximately 30% of calories from fat).
Interim Analysis	There will be no formal interim analyses.

2. STATISTICAL HYPOTHESES / SUCCESS CRITERIA

This study is not designed for statistical testing and therefore has no formal statistical hypothesis.

Study objective will be evaluated descriptively and through estimation.

2.1. Multiple Comparisons and Multiplicity

No adjustments for multiple comparison will be made.

3. SAMPLE SIZE DETERMINATION

No formal sample size calculation has been performed for this study. However, the sample size reflects an accepted industry standard for human ADME studies using 14Cradiolabelled drug. Additionally, the design of the study in terms of the concomitant administration of intravenous with oral administration (Period 1) inherently reduces variability in the parameters determined, versus a cross-over design for absolute bioavailability assessment, while enabling cross-over to Period 2 in the same participants The primary objective of the study is to gain a better understanding of the compound's pharmacokinetic, excretory, and metabolic profile and 4 to 6 participants are deemed sufficient for this purpose. Six participants will be enrolled into the study. To minimize the number of participants exposed to radiation; those participants that discontinue early will not be replaced unless the total number of participants who complete both Periods 1 and 2 drops below 4.

4. ANALYSIS SETS

Analysis Set	Definition / Criteria	Analyses Evaluated
Screened	• All participants who were screened for eligibility. This will be the population for reporting screened population data.	• Study Population
Enrolled	• All participants who 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 analysis set as they did not enter the study.	• Study Population
Safety	• All participants who take at least 1 dose of study intervention. Participants will be analysed according to the treatment they received. This will be the population for reporting safety and study population data.	• Study / Safety Population
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 Population

4.1. Protocol Deviations

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

Protocol deviations will be tracked by the study team throughout the conduct of the study.

These protocol deviations will be reviewed to identify those considered as important as follows:

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

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.

To facilitate presenting protocol deviations that occurred due to the COVID-19 pandemic, the description of protocol deviations occurring because of COVID-19 will include the standard text “COVID-19” as per the Data Management guidance issued on “COVID-19 Designation of protocol deviations”.

After a discussion with the study team, the following analyses will be included:

[1] Protocol deviations that occurred due to the COVID-19 pandemic

[2] List which subjects were impacted due to the COVID-19 pandemic and how their participation was impacted

[3] Summarize the number of missed visits due to the COVID-19 pandemic

[4] Summarize the number of missed assessments for key endpoints due to the COVID-19 pandemic (if not fully described based on the summary of missed visits)

[5] Summarize the number of visits where assessments were performed using alternative methods due to the COVID-19 pandemic.

5. STATISTICAL ANALYSES

5.1. General Considerations

5.1.1. General Methodology

Confidence intervals will use 95% confidence levels unless otherwise specified.

Summary tables (except for Safety and PK analyses) will provide the following descriptive

statistics:

- Continuous data (normal data): n, mean, standard deviation (SD), median, interquartile

range, minimum and maximum.

- Continuous data (log normal data): n, geometric mean, standard deviation (SD) on the log

scale, and between subject variability(%CVb)

- Categorical data: number and percentage of participants in each category.

5.1.2. Baseline Definition

For all endpoints the baseline value will be the latest pre-dose assessment in each treatment period (Prior to the oral dose) in each treatment period), 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. For subjects who did not receive study treatment during the study, baseline will be defined as the latest, non-missing collected value. Day 1 pre-dose ECGs for each treatment period will be performed in triplicate. In such case of triplicate measurement for pre-dose average will be used as baseline.

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

5.2. Primary Endpoint(s) Analyses

The PK analyses will be based on the pharmacokinetic analysis set.

The plasma pharmacokinetic concentrations will have different nomenclatures dependent on the method of measuring. For measured concentrations of GSK3640254 in plasma, the nomenclature [^{14}C]-GSK3640254 describes the parent GSK3640254 concentration derived via analysis by liquid chromatography (LC) + Accelerator Mass Spectrometry (AMS), whereas GSK3640254 describes the parent GSK3640254 concentration derived via liquid chromatography-tandem mass spectrometry (LC-MS/MS). It is expected that, for period 1, the radiolabelled iv dose will be measured using LC+AMS and will be labelled "[^{14}C]-GSK3640254", the non-radiolabelled oral dose will be measured using LC-MS/MS and will be labelled "GSK3640254". For period 2, the radiolabelled oral dose will be measured using LC-MS/MS and will be labelled "GSK3640254". For the reporting of displays a footnote will be added to detail the nomenclature used to discriminate between labelled and non-labelled drug (and the analytical methods used to provide the data).

Total radioactivity measurements in urine samples and faecal homogenates will be determined by Liquid Scintillation Counting (LSC) and/or by AMS. Total radioactivity measurements from plasma derived from blood will be analysed, as appropriate, by AMS in Treatment Period 1 and by LSC and/or by AMS, for Treatment Period 2, as detailed in the SRM.

The reconciliation of the Plasma PK Case Report Form (CRF) and SMS2000 data will be provided by DM(GSK) and the analytical CROs – Pharmaron, and Covance will also perform reconciliation and provided via their analytical reports.

Derivation of plasma pharmacokinetic parameters for [^{14}C]- GSK3640254, total radioactivity and GSK3640254 will be performed by, or under the direct auspices of, Clinical Pharmacology Modelling and Simulation (CPMS), GlaxoSmithKline.

Derivation of urine/faeces total radioactivity parameters will be performed by the analytical CROs – Pharmaron, and Covance via their analytical reports.

5.2.1. Definition of endpoint(s)

- AUC(0-inf), AUC(0-t), Cmax, tmax and t1/2 of parent and total drug-related material (radioactivity) in plasma.
- Volume of distribution at steady-state (Vss) and clearance (CL) of parent after IV dose (Period 1 only)
- Renal clearance of parent (CLr) after IV and oral administration
- Oral Clearance (CL/F) and apparent volume of distribution (Vz/F) for the parent following oral administration
- Direct evaluation of absolute bioavailability (F), indirect calculation of fraction of drug escaping first pass hepatic clearance (Fh), fraction absorbed (Fa) and fraction of drug escaping gut metabolism (Fg)
- Urinary and fecal cumulative excretion of total radioactivity as a percentage of the total radioactive dose (Period 1 and Period 2)

5.2.1.1. Drug concentration measures

Refer to the Output and Programing Specification (OPS) document for Data Display Standards & Handling Conventions for Pharmacokinetic Data.

Plasma GSK3640254, [^{14}C]- GSK3640254 and blood and Plasma total radioactivity concentration-time data will be listed for each participant and standard summary statistics will be calculated (i.e. arithmetic mean, standard deviation, median, minimum and maximum) by treatment and planned sampling time.

Individual participant, mean and median plasma GSK3640254, [^{14}C]- GSK3640254 and total radioactivity concentration-time profiles will be plotted for each treatment on both a linear and semi-log scale.

For urine and feces, the total radioactivity excreted in urine and feces per sample or collection interval will be listed by subject. The cumulative total and the cumulative percentage of the total radioactive dose will be calculated and listed by subject. The concentration of radioactivity in urine, feces and fecal homogenates will be expressed as ng equivalents/g.

5.2.1.2. Derived Pharmacokinetic Parameters

5.2.1.2.1. Derived plasma pharmacokinetic parameters

PK Parameters will be calculated by standard non-compartmental analysis according to current working practices and using the currently supported version of WinNonlin version 6.3 or above. All calculations of non-compartmental parameters will be based on actual sampling times. PK parameters listed will be determined from plasma GSK3640254, [^{14}C]-GSK3640254, total radioactivity as data permits and unless otherwise stated.

Table 4 Derived Pharmacokinetic Plasma 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.
λz	The first order rate constant associated with the terminal (log-linear) portion of the concentration-time curve.
AUC(0-∞)	Area under the concentration-time curve extrapolated to infinity will be calculated as: $$AUC(0-\infty) = AUC(0-t) + \frac{C(t)}{\lambda z}$$
%AUCex	The percentage of AUC (0-∞) obtained by extrapolation (%AUCex) will be calculated as: $$\frac{[AUC(0-\infty) - AUC(0-t)]}{AUC(0-\infty)} * 100$$
Cmax	Maximum observed concentration, determined directly from the concentration-time data.
tmax	Time to reach Cmax, determined directly from the concentration-time data.
$t_{1/2}$	Apparent terminal half-life will be calculated as: $$t1/2 = \ln 2 / \lambda z$$
CL	Total clearance calculated as: $$CL = \frac{Dose(IV)}{AUC(0-\infty)}$$ Treatment Period 1, analyte [^{14}C]-GSK3640254 only and where the Dose(IV) is the actual IV dose provided by Covance, Harrogate
Vss	Volume of distribution at steady-state, calculated as:

Parameter	Parameter Description
	$$Vss = CL * MRTiv$$ Where CL is total clearance and MRT is the mean residence time, calculated as AUMC(0-∞) [Area under the first moment curve]/AUC(0-∞)

CLr	If plasma AUC(0-∞) is calculable, then
	$$CLr = \frac{Cumulative\ Ae[Urine]\ for\ Period\ 1}{Plasma\ AUC(0 - ¥)}$$
	If plasma AUC(0-∞) is not calculable, then
	$$CLr = \frac{Cumulative\ Ae[Urine]\ for\ Period\ 1}{Plasma\ AUC(0 - t)}$$
	Where cumulative urine Ae from excretion data for treatment Period 1 and AUC from NCA PK analysis of Treatment Period 1, analyte [^{14}C]-GSK3640254 only

ML(iv)	Metabolite load following intravenous administration, calculated as: $$ML(iv) = \frac{[Total\ Radioactivity\ AUC(0 - \infty) - [14C]GSK3640254\ AUC(0 - \infty)]}{Total\ Radioactivity\ AUC(0 - \infty)}$$ Treatment Period 1
ML(po)	Metabolite load following oral administration, calculated as: $$ML(po) = \frac{[Total\ Radioactivity\ AUC(0 - \infty) - GSK3640254\ AUC(0 - \infty)]}{Total\ Radioactivity\ AUC(0 - \infty)}$$ Treatment Period 2 Note: GSK3640254 AUC(0-∞) may be updated depending on the sample analysis conducted but refers to the parent GSK3640254 from oral dose
Fg	Fraction metabolized by gut wall as a fraction of the oral dose, calculated as: $$Fg = 1 - [ML(po) - ML(iv)]$$

Parameter	Parameter Description
$CL_{h,iv,blood}$	Hepatic blood clearance, calculated as: $CL_{h,iv,blood} = CL_{h,iv,plasma}$ * blood to plasma ratio Where $CL_{h,iv,plasma}$ is the hepatic plasma clearance calculated as: $CL_{h,iv,plasma} = CL - CLr$
E_h	Hepatic extraction ratio, calculated as: $E_H = CL_{h,iv,blood} / Q_h$ Where Qh = hepatic blood flow (literature value of 1660 mL/min, Edginton, 2006) Note: if assumption that hepatic CL accounts for 100% of the clearance (i.e. CLr is negligible), then E_h = CL*blood to plasma ratio*Qh
F_h	$F_h=1-E_h$
Fa	Fraction absorbed following an oral dose, calculated as follows $$Fa = \frac{F(0-\infty)]/(1-EH)}{Fg}$$
Dose(iv)	Radiometric IV dose calculated by Covance
Dose(oral)	Radiometric oral dose calculated by Covance
F(0-∞)	Oral absolute bioavailability based on AUC(0-∞), calculated as: $$F(0-\infty) = \frac{\text{GSK3640254 AUC}(0-\infty)(\text{oral})}{\text{Dose(oral)}} * \frac{\text{Dose(iv)}}{[14C]GSK3640254\ AUC(0-\infty)(iv)}$$ Per Subject

Parameter	Parameter Description
	Note: Radiometric dose will be used for IV. GSK3640254 AUC(0-∞) (0ral) refers to the parent GSK3640254 from oral dose, but may be updated depending on the sample analysis
F(0-t)	Oral absolute bioavailability based on AUC(0-t), calculated as: $$F(0-t) = \frac{\text{GSK3640254 AUC}(0-\text{t})(\text{oral})}{\text{Dose(oral)}} * \frac{\text{Dose(iv)}}{[14C]GSK3640254\ AUC(0-t)(iv)}$$ Per Subject Note: Radiometric dose will be used for IV. GSK3640254 AUC(0-t) (0ral) refers to the parent GSK3640254 from oral dose, but may be updated depending on the sample analysis
CL/F	Apparent oral clearance, calculated as: $$CL/F = \frac{Dose}{AUC(0-\infty)}$$
Vz/F	Apparent volume of distribution based on the terminal phase $$Vz/F = \frac{Dose}{[\lambda z * AUC(0-\infty)]}$$
GSK3640254/ Total radioactivity ratio for Cmax	Cmax Ratio = Exp {[loge(GSK3640254 Cmax] - [loge(Total radioactivity Cmax]} Per subject for radiolabelled oral dose. GSK3640254 may be updated depending on the sample analysis conducted but refers to the parent GSK3640254 from oral dose
GSK3640254/ Total radioactivity ratio for AUC(0-∞)	Cmax Ratio = Exp {[loge(GSK3640254 AUC(0-∞)] - [loge(Total radioactivity AUC(0-∞)]} Per subject for radiolabelled oral dose. GSK3640254 may be updated depending on the sample analysis conducted but refers to the parent GSK3640254 from oral dose
GSK3640254/ Total radioactivity	Cmax Ratio = Exp {[loge(GSK3640254 AUC(0-t)] - [loge(Total radioactivity AUC(0-t)]}

Parameter	Parameter Description
ratio for AUC(0-t)	Per subject for radiolabelled oral dose. GSK3640254 may be updated depending on the sample analysis conducted but refers to the parent GSK3640254 from oral dose
[^{14}C]-GSK3640254/ Total radioactivity ratio for Cmax	Cmax Ratio = Exp {[loge([^{14}C]-GSK3640254 Cmax] - [loge(Total radioactivity Cmax]} Per subject for radiolabelled IV dose
[^{14}C]-GSK3640254/ Total radioactivity ratio for AUC(0-∞)	Cmax Ratio = Exp {[loge([^{14}C]-GSK3640254 AUC(0-∞)] - [loge(Total radioactivity AUC(0-∞)]} Per subject for radiolabelled IV dose
[^{14}C]-GSK3640254/ Total radioactivity ratio for AUC(0-t)	Cmax Ratio = Exp {[loge([^{14}C]-GSK3640254 AUC(0-t)] - [loge(Total radioactivity AUC(0-t)]} Per subject for radiolabelled IV dose

Notes:

- Additional parameters may be included as required
- Lambda_z is the terminal phase rate constant
- The following PK parameters AUC(0-∞), AUC(0-t), %AUCex, Cmax, tmax, t1/2, CL, Vdss, Vz/F and CL/F, will be derived in Phoenix and sent to S&P. The radiometric IV and oral doses will be calculated by Covance and sent to S&P. Additional parameters will be derived by S&P including CLr, ML(iv), ML(po), Fg, E_h,F_h Fa, F(0-∞), F(0-t) and the [^{14}C]-GSK3640254/total radioactivity ratios.

5.2.1.2.2. Derived urine and fecal pharmacokinetic parameters

- Derivation of urine and faecal radioactivity parameters will be the responsibility, or under the direct auspices, of the DMPK department within GSK.
- When summarizing urine and faecal parameters, 'NS' (i.e., no sample provided as subject not voided at particular collection period) or 'NQ' values for these parameters will be imputed with zero.

Table 5 Derived urine and faeces pharmacokinetic parameters

Parameter	Parameter Description
Ae[urine]	Total radioactivity recovered in the urine (Ae[urine]) calculated for each collection interval per subject and treatment period as: Ae[urine]= (concentration in urine sample x collected sample weight) for each urine collection interval, eg 0-24, 24-48, etc.
Cumulative Ae[urine]	Cumulative total radioactivity recovered in the urine (Cumulative Ae[urine]) calculated for each cumulative collection interval per subject and treatment period as: Cumulative Ae[urine] = summation of Ae[urine] For each urine collection with the cumulative urine collection interval
Fe%[urine]	% of total dose excreted as total radioactivity (Fe%[urine]) for each collection interval per subject and treatment period, estimated as: Fe%[urine]=(Ae[urine]) for each collection period)/Dose*100. Where the dose is the radiolabelled [^{14}C]-GSK3640254, that is in period 1 radiometric iv dose, in period 2 radiometric oral dose
Cumulative Fe%[urine]	Cumulative % of total dose excreted as total radioactivity (Cumulative Fe%[urine]) for each cumulative collection interval per subject and treatment period, estimated as: Cumulative Fe%[urine]= summation of Fe[urine] Where the dose is the radiolabelled [^{14}C]-GSK3640254, that is in period 1 radiometric iv dose, in period 2 radiometric oral dose
Ae[faeces]	Total radioactivity recovered in the urine (Ae[faeces]) calculated for each collection interval per subject and treatment period as: Ae[urine]= (concentration in urine sample x collected sample weight) for each urine collection interval, eg 0-24, 24-48, etc.
Cumulative Ae[faeces]	Cumulative total radioactivity recovered in the urine (Cumulative Ae[faeces]) calculated for each cumulative collection interval per subject and treatment period as:

Parameter	Parameter Description
	Cumulative Ae[faeces] = summation of Ae[faeces] For each urine collection with the cumulative urine collection interval
Fe%[faeces]	% of total dose excreted as total radioactivity (Fe%[faeces]) for each collection interval per subject and treatment period, estimated as: Fe%[urine]=(Ae[faeces]) for each collection period)/Dose*100. Where the dose is the radiolabelled [^{14}C]-GSK3640254, that is in period 1 radiometric iv dose, in period 2 radiometric oral dose
Cumulative Fe%[faeces]	Cumulative % of total dose excreted as total radioactivity (Cumulative Fe%[faeces]) for each cumulative collection interval per subject and treatment period, estimated as: Cumulative Fe%[faeces]= summation of Fe[faeces] Where the dose is the radiolabelled [^{14}C]-GSK3640254, that is in period 1 radiometric iv dose, in period 2 radiometric oral dose
Ae[total]	Total radioactivity recovered in total excretum (sum of urine and faecal exvretion) Ae[total] will be estimates by collection interval for each subject and treatment period as: Ae[total]=Ae[urine]+ Ae[faeces]
Cumulative Ae[total]	Total radioactivity recovered in total excretion (sum of urine and faecal excretion), cumulative Ae[total] will be estimates by cumulative collection interval per subject and treatment period as: Cumulative Ae[total]= summation of Ae[total] for each total excretion collection within the cumulative total excretion collection interval, eg 0-24, 0-48, etc
Fe%[total]	% of total dose excreted as total radioactivity (Fe%[total]) for each collection period will be estimated for each subject and treatment period as: Fe%[total]= Fe%[urine]+ Fe%[faeces]

Parameter	Parameter Description
Cumulative Fe%[total]	Cumulative % of total dose excreted as total radioactivity (Cumulative Fe%[total]) for each cumulative collection period will be estimated for each subject and treatment period as: Cumulative Fe%[total]= Cumulative Fe%[urine]+ Cumulative Fe%[faeces] for each total excretion collection within the cumulative total excretion collection interval, eg 0-24, 0-48, etc

Notes: additional parameters may be included as required

5.2.2. Main analytical approach

A primary objective is to determine parent GSK3640254 and total drug-related radioactivity systemic concentrations following a single IV microtracer dose of [^{14}C]-GSK3640254 (with an oral dose of non-radiolabelled GSK3640254) and oral dose of [^{14}C]-GSK36402541. To assess this, the plasma PK parameters: AUC(0–inf), AUC(0–t), Cmax, tmax and t1/2 of parent and total drug-related material (radioactivity) will be summarized and listed. The volume Vss and clearance (CL) of parent after IV dose (Period 1 only) , renal clearance of parent (CLr) after both IV and oral dose, oral clearance (CL/F) and apparent volume of distribution (Vz/F) for the parent following oral administration will also be summarized and listed.

To assess the absolute oral bioavailability of GSK3640254 absolute oral bioavailability (F), F_h F_a and F_g will be summarized and listed.

To determine the rate and extent of excretion of total radioactivity in urine and feces and the total recovery of radioactivity, following IV and oral administrations of [^{14}C]-GSK3640254 the PK parameters: Ae and Fe% will be summarized and listed for urine faeces and total (Urine + Faeces)

Table 6 Statistical methodology specification

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

Pharmacokinetic Statistical Analyses (Absolute Bioavailability assessment in Treatment Period 1)
Primary Endpoint / Variables
• AUC(0-t), AUC (0-∞) PK parameters of Plasma GSK3640254 (**radiolabeled/non-radiolabeled**) from IV and oral dose in Period 1 will be analyzed after $\log_e$ transformation (PK parameters should be divided by corresponding dose)
Model Specification
• Will be statistically analyzed using a mixed model (MM) for Period1. • Terms fitted in the mixed effect ANOVA model will include: o Fixed effect : Treatment (IV dose/Oral dose in Period1) o Random Effect : Subject • The Kenward and Roger method for approximating the denominator degrees of freedom and correcting for bias in the estimated variance-covariance of the fixed effects will be used. • Point estimates for the adjusted means on the loge scale, the mean difference between treatments and associated 90% confidence interval for the contrast (test-reference) will be constructed using the residual variance.
Model Checking & Diagnostics
• Dose normalized PK parameters should be used for the analysis. • For the Mixed Model analysis, Model assumptions will be applied, but appropriate adjustments maybe made 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 point estimate and confidence interval obtained from MM analysis will be exponentially back transformed to obtain Adjusted (least square) geometric means for each treatment. • Point estimates (Absolute Bioavailability of GSK3640254) and associated 90% confidence interval for the ratio IV dose/Oral dose along with within-subject variability (%CVw) will be reported. • Plots showing the adjusted geometric mean ratio(F) of IV dose to Oral dose in Period1 for AUC (0-∞) and AUC(0-t) together with 90% confidence intervals will be provided.

5.3. Secondary Endpoint(s) Analyses

The PK analyses will be based on the pharmacokinetic analysis set.

5.3.1. Definition of Pharmacokinetic endpoint(s)

- Blood: plasma ratio of [^{14}C]-GSK3640254 – related materials (total radioactivity)

5.3.1.1. Derived plasma pharmacokinetic parameters

The blood: plasma ratio of total radioactivity will be calculated in period 2 according to the following equation:

Ratio Cb_Cp= Radioactivity Concentration in blood (Cb)/ Radioactivity Concentration in plasma (Cp)

5.3.2. Main analytical approach

The blood: plasma ratio of total radioactivity (Cb/Cp) will be calculated at each time point and will be summarized and reported by Pharmaron.

5.4. Exploratory Endpoint(s) Analyses

The PK analyses will be based on the pharmacokinetic analysis set.

5.4.1. Definition of Pharmacokinetic endpoint(s)

- Characterization and quantification of metabolites in plasma, urine, faecal and duodenal bile (qualitative identification in bile). These analytical investigations will be conducted, and the results reported under a separate nonclinical GSK protocol
- AUC (0-∞), AUC(0-t), and Cmax for the evaluation of the PK and the relative bioavailability of GSK3640254 following administration of the 85mg suspension compared to the 200 mg tablet

5.4.1.1. Metabolite profiling analyses in plasma, urine, feces and bile

The metabolic profiling/structural characterization aspect of this work will be performed by GSK (or a GSK representative) in a separate DMPK study report. Data from the quantification of unchanged GSK3640254 in urine following IV administration will be used in the estimate of renal clearance, as detailed above.

5.4.1.2. Derived plasma pharmacokinetic parameters

The PK parameters for GSK3640254 following oral administration of a 200 mg tablet or of 85 mg suspension will be reported as described in Section 5.2. Subsequently, the following parameters will be used for the assessment of the relative bioavailability of GSK3640254 following administration of the 85 mg suspension compared to the 200 mg tablet as described in Section 5.4.2.

5.4.2. Main analytical approach

Table 7 Statistical methodology specification

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

Endpoint / Variables
Derived PK parameters: • $AUC_{(0\text{-}inf)}$ • $AUC_{(0\text{-}t)}$ • C_{max}
Model Specification
• To evaluate the relative bioavailability of GSK3640254 following administration of the 85 mg suspension compared to the 200 mg tablet, the PK parameters will be analysed using a mixed effect model as described below: $\log_e(\text{PK parameter}) = \beta_0 + \gamma_i + \tau_j + \varepsilon_{ij}$ where, β_0: intercept γ_i: random effect for i^{th} participant, following $N(0, {}^2)$ τ_j: treatment effect (j = 85 mg suspension or 200 mg tablet Treatment) ε_{ij}: random error for participant i, treatment effect j, following $N(0, \sigma_w^2)$. • The model parameters will be estimated using Restricted Maximum Likelihood with the Newton-Raphson algorithm. • The Kenward-Roger degree of freedom approach will be used. • Given the random effect for subject "i", the random error is assumed to be independently distributed within the subject. • The least square means for each treatment formulation (85 mg suspension and 200 mg tablet) will be estimated based on the fitted model. The mean difference between the treatment formulations (85 mg suspension and 200 mg tablet) and its 90% CIs will be also estimated using the within-subject variance. • The estimates of least square means for each treatment formulation, the treatment difference between treatment formulations and the 90% CIs will be exponentially back-transformed to obtain the estimates of geometric means of $AUC_{(0\text{-}t)}$, $AUC_{(0\text{-}inf)}$ and C_{max} for each treatment formulation, the ratio of geometric means (85 mg suspension and 200 mg tablet) and its 90% CIs, respectively. • Within-subject variability (%CVw) for the PK parameters will be estimated using within-subject variance from the analysis model as follows: $\%CVw\ (\%) = [\exp(\sigma_w^2) - 1]^{1/2} \times 100$

Model Checking & Diagnostics
In case there is a problem with model convergence, the arithmetic means for log_e-transformed $AUC_{(0-t)}$ and C_{max} and the treatment differences 85 mg suspension and 200 mg tablet) within each participant will be calculated using only data from the participants who have completed both the periods for 85 mg suspension and 200 mg tablet. The mean treatment difference and paired-t test based 90% CIs for treatment difference in log_e scale will be estimated. The results will be provided in an exponentially back-transformed scale.
Model Results Presentation
Based on the relative bioavailability, the bioequivalence between 85 mg suspension and 200 mg tablet will be evaluated as follows: • The bioequivalence is established when the 90% CI of the ratio for $AUC_{(0-t)}$, $AUC_{(0-inf)}$ and C_{max} between treatment formulations (85 mg suspension and 200 mg tablet) are within the range of 0.80 to 1.25.

5.5. (Other) Safety Analyses

The safety analyses will be based on the Safety analysis set, unless otherwise specified.

5.5.1. Extent of Exposure

Extent of exposure to GSK3640254 will be summarized.

Duration of exposure in days = Treatment stop date –(Treatment start date)+ 1. For Period1 consider oral start date and IV stop date for duration of exposure. Participants who were allocated to treatment but did not report a treatment start date will be categorized as having zero days of exposure. It will be listed.

5.5.2. Adverse Events

Adverse events analyses including the analysis of adverse events (AEs), Serious AEs (SAEs) and other significant AEs will be based on GSK Core Data Standards.

The following categories and subcategories will be used:

- AE

  - Any AEs
    - Maximum Grade
  - Drug-related AEs
    - Grade
  - AEs leading to
    - Permanent discontinuation
    - Withdrawal
  - Common AEs
  - Common non-serious AEs

- SAE

- Any SAEs
  - Grade
- Drug-related SAEs
- Fatal SAEs

Each summary will contain:

- the number of participants with the AE

- the percentage of participants with the AE

- the number of events of the AE

AEs will be displayed by

- Column: Treatment arm or intensity.

- Row: in descending order by SOC and PT, or PT only

A summary of number and percentage of participants with any adverse events by maximum grade will be produced.

The frequency and percentage of AEs (all grades) will be summarized and displayed in two ways: 1) in descending order by PT only and 2) in descending order by SOC and PT.

Adverse events will be coded using the standard Medical Dictionary for Regulatory Affairs (MedDRA dictionary) and graded by the investigator according to the DAIDS (Version 2.1) grading table

5.5.2.1. Adverse Events of Special Interest

The identification and classification of the adverse events of special interest (AESI) will be done programmatically by GSK Biostatistics team.

Table 8 presents the AESI groups. Groups which are not SMQs are made up of a selection of preferred terms (PTs) defined by GSK. The complete list, including the PTs which contribute to each of the groups will be provided by Pharma Safety using the MedDRA version current at the time of reporting.

The summary of event characteristics will be provided for each AESI., including the number of events and occurrences.

Table 8 Adverse Event of Special Interest (AESI)

AESI Group	SMQ	Other
QT prolongation	Torsade de pointes/QT prolongation (SMQ)	Cardiac Disorders SOC; seizures
Gastrointestinal intolerability/toxicity	Narrow ± Broad PTs from three sub-SMQs within the Gastrointestinal nonspecific inflammation and dysfunctional conditions SMQ	
Psychiatric events	Psychosis and psychotic disorders (SMQ; narrow terms); Suicide/self-injury sub-SMQ (narrow terms); Depression (excl suicide and self-injury) sub-SMQ (narrow terms)	Additional PTs for symptoms and complications of Psychiatric events including bipolar disorder, anxiety and sleep disorders
Nervous system disorders		PTs from HLGTs for symptoms and complications of Nervous system disorders
Skin and subcutaneous tissue disorders		Selection of PTs from different HLGTs.

5.5.3. Additional Safety Assessments

The safety data to be summarised are as follows:

Routine laboratory data for haematology, clinical chemistry and urinalysis will be collected, as well as data from additional tests (see Table 6 of the protocol). The key laboratory data to be summarized are as follows:

- Haematology: Platelet Count, red blood cell (RBC) Count, haemoglobin, haematocrit, RBC Indices mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH) Absolute and %Reticulocytes, WBC count with Differential: Neutrophils, Lymphocytes Monocytes, Eosinophils, Basophils
- Clinical chemistry: Urea Creatinine, Uric acid Fasting glucose etc…

- Routine Urinalysis: Routine Urinalysis, pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick
- Microscopic examination (if leukocyte esterase, nitrites, blood or protein is abnormal)
- Screening only Tests: -
    - Alcohol breath test, urine cotinine test
    - Carbon Monoxide (CO) breath test
    - Drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines)
    - Serology (HIV antigen/antibody immunoassay, HBsAg, and hepatitis C virus antibody with reflexive HCV RNA)

5.5.3.1. Laboratory Data

Separate summary tables for haematology, and chemistry laboratory tests will be produced. Liver function laboratory tests will be included with chemistry lab tests.

Shift tables of worst-case increase from baseline will be provided for all the laboratory tests and will be used to detect any laboratory parameter clinical important changes:

- For lab test gradable by DAIDS grading table: worst-case grade increase from baseline grade

- For lab tests not gradable by DAIDS grading table, worst-case changes from baseline relative to normal range.

- For urinalysis, worst-case results post-baseline relative to baseline

Summaries of hepatobiliary laboratory events including possible Hy's law cases will be provided in addition to what has been described above. The summary will be produced for worst-case postbaseline only.

5.5.3.2. Vital Signs

Values of vital signs (temperature, systolic and diastolic blood pressure, pulse rate and respiratory rate as well as the change from baseline will be summarized by scheduled visit using mean, median, standard deviation, minimum and maximum.

Shift tables of worst-case results from baseline to potential clinical importance (PCI) criteria will be provided for systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate and will be used to detect any clinical important changes.

5.5.3.3. ECG

A 12-lead ECG will be performed at Screening to calculate the heart rate and measurements such as PR, QRS, and QT (uncorrected) intervals. QTcF will be calculated (machine read or manually). ECG after Screening will be performed as clinically indicated.

5.5.3.4. 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, and summaries will be based on subjects with COVID-19 adverse event:

- Number of subjects with suspected, probable or confirmed for COVID-19 infection
- Number of subjects who had a SARS-COV-2 diagnostic 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 SAE or AE of COVID-19 infection
- Severity, duration, and outcome of COVID-19 AEs

Further display details are provided in OPS.

5.6. Interim Analyses

No interim analyses will be performed.

6. SUPPORTING DOCUMENTATION

6.1. Appendix 1 Abbreviations and Trademarks

6.1.1. List of Abbreviations

AE	Adverse Event
ADME	Absorption, distribution, metabolism, and excretion
AMS	Accelerator Mass Spectrometry
AUC(0–inf)	Area under the concentration-time curve from time zero (pre-dose) extrapolated to infinite time
AUC(0–t)	Area under the concentration-time curve from time zero (pre-dose) to last time of quantifiable concentration within a participant across all treatments
BIB	Bioanalysis, Immunogenicity and Biomarkers
BMI	Body mass index
BP	Blood Pressure
C_{max}	Maximum observed concentration
CIOMS	Council for International Organizations of Medical Sciences
CL	Clearance
CL/F	Oral clearance
CLr	Renal clearance
cm	Centimeter
CRO	Contract research organization
DAIDS	Division of AIDS
DMPK	Drug metabolism and pharmacokinetics
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
F	Absolute bioavailability
Fa	Fraction absorbed
Fh	Fraction of drug escaping first pass hepatic clearanc
Fg	Fraction of drug escaping gut metabolism
IDSL	Integrated Data Standards Library
IEC	Independent Ethics Committee
IMP	Investigational medicinal product
INR	International normalized ratio
IRB	Institutional Review Board
IV	Intravenous
IVIVT	In vitro / In vivo Translation - Investigative Safety & Drug Metabolism, GSK
kDa	Kilodalton
kg	Kilograms
kg/m^2	Kilograms per meter square

LSC	Liquid Scintillation Counting
µSv	Microsievert
MAD	Multiple Ascending Dose
mg	Milligrams
PK	Pharmacokinetic(s)
POC	Proof of concept
QD	Once daily
QTc	Corrected QT interval
QTcF	QT duration corrected for heart rate by Fridericia's formula
QTL	Quality tolerance limit
RNA	Ribonucleic acid
RBC	Red blood cell
SAE	Serious Adverse Event
t_{max}	Time of occurrence of C_{max}
t½	Terminal phase half-life
TQT	Thorough QT
UK	United Kingdom
ULN	Upper Limit of Normal
VH	ViiV Healthcare group of companies
Vss	Volume of distribution at steady state
Vz/F	Apparent volume of distribution
WHO	World Health Organisation
λz	Lambda-z (Terminal Phase Rate Constant)

6.1.2. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
HARP

Trademarks not owned by the GlaxoSmithKline Group of Companies
SAS

7. REFERENCES

European Medicines Agency (EMA). Science Medicines Health, Heads of Medicines Agencies. Guidance on the Management of Clinical Trials During the COVID-19 (Coronavirus) Pandemic. April 2020b. Available from: https://ec.europa.eu/health/sites/health/files/files/eudralex/vol10/guidanceclinicaltrials_covid19_en.pdf

International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals M3 (R2). 2009. https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Multidisciplinary/M3_R2/Step4/M3_R2__Guideline.pdf. Accessed 15 February 2019.

Signature Page for 213051 TMF-2098747 v1.0

Reason for signing: Approved	Name: PPD Role: Approver Date of signature: 11-Sep-2020 04:34:47 GMT+0000

Signature Page for TMF-2098747 v1.0