Reporting and Analysis Plan

Study ID: 213376

Official Title of Study A Two-Part First Time in Human (FTIH) Study to Evaluate Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Single and Repeat Oral Doses of GSK3884464 in a Randomized, Double Blind, Placebo-Controlled, Dose Escalation Study in Healthy Participants

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TITLE PAGE

Protocol Title: A Two-Part First Time in Human (FTIH) Study to Evaluate Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Single and Repeat Oral Doses of GSK3884464 in a Randomized, Double Blind, Placebo-Controlled, Dose Escalation Study in Healthy Participants

Study Number: 213376

Compound Number: GSK3884464

Abbreviated Title: A FTIH study to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of single and repeat doses of GSK3884464 in healthy participants.

Sponsor Name: GlaxoSmithKline Research & Development Limited

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Version history

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
SAP	20 Sep 2021	19-AUG-2021	Not Applicable	Original version
SAP amendment 1	16 Mar 2023	06-APR-2022	All sections: Changes made to align with the latest protocol amendment. Few sections have been rearranged. Section 1.1.1: A table added for the estimands framework. Section 4.3.2, Section 4.4.1.1, Section 4.5.1.2: Definition of statistical models modified. Section 4.3.2: Level of significance changed to 10% for all PK analyses.	Protocol Amendment To ensure clear understanding of the intercurrent events and corresponding strategies To allow for correct and clear description of analyses. Modified as per the suggestion from CPMS team.
			Section 6.1.4: Wording for reporting modified. Section 6.2.1: PCI ranges updated.	To align with the requirements reporting standards. To allow reporting of only the critical parameters.

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
			Section 6.2: List of abbreviations added.	To allow for better understanding and interpretation.

1. INTRODUCTION

The purpose of this SAP is to describe the planned analyses to be included in the Clinical Study Report (CSR) for Study 213376. Details of the final analyses, descriptive study population analyses such as summary of demography and baseline characteristics and additional detail with regards to data handling conventions are provided in this document.

Details about the planned displays are provided in the Output and Programming Specification (OPS) document.

1.1. Objectives, Estimands and Endpoints

Objectives	Endpoints
Primary	
• To characterize the safety and tolerability profile of GSK3884464 in healthy participants.	• Number and percentage of healthy participants with adverse events. • Clinically significant changes from baseline in laboratory values, vital signs, continuous telemetry, 12-lead electrocardiogram (ECG), and echocardiograms (in Part 2 only) up to and including the follow up visit (7-10 days post final dose).
• To characterize the plasma Pharmacokinetics (PK) of GSK3884464 in healthy participants.	• Plasma pharmacokinetic parameters following single oral doses including Area Under the Curve $(AUC)_{(0-t)}$, $AUC_{(0-\infty)}$, maximum concentration (C_{max}), time to maximum observed plasma drug concentration (t_{max}), and terminal half-life ($t_{½}$). • Plasma pharmacokinetic parameters following repeat oral doses including AUC_{τ}, C_{max}, trough plasma concentration (C_{τ}), peak-to-trough (PTT) ratio (C_{max} /C_{τ}), t_{max}, $t_{½}$, accumulation ratios based on AUC_{τ} (R_{AUC}), on C_{max} (R_{Cmax}), and on C_{τ} ($R_{C\tau}$).

Objectives	Endpoints
Secondary	
• To evaluate target engagement following single and repeat oral doses of GSK3884464 in healthy participants.	• Maximum changes from baseline in NQO1 mRNA in whole blood post treatment with GSK3884464 in all parts of the study.
CCI [redacted]	

Objectives	Endpoints
CCI [redacted]	[redacted]

Objectives	Endpoints
CCI [redacted]	[redacted]

1.1.1. Estimands

Table 1 describes the possible intercurrent events and the corresponding strategies to be used. Once a participant discontinues study treatment, they will proceed to follow up. Individual participant data will be included in data listings regardless of the strategy followed for the analyses.

Table 1 Estimands

- Treatment: GSK3884464 or Placebo
- Population: Healthy Volunteers

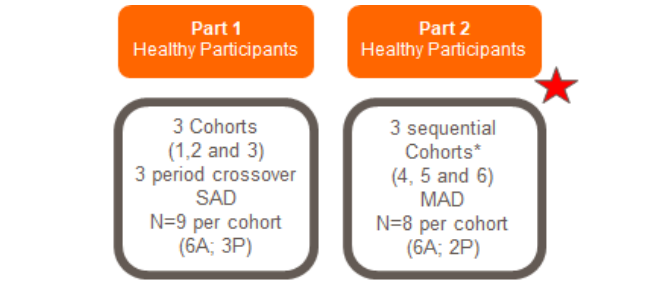
Endpoint	Population Level Summary Measure	Intercurrent Event –Corresponding Estimand Strategy
Primary Objective (1) - To characterize the safety and tolerability profile of GSK3884464 in healthy participants.		
• Number and percentage of healthy participants with adverse events (Part 1 and 2 of the study) • Clinically significant changes from baseline in laboratory values, vital signs, continuous telemetry, 12-lead ECG, and echocardiograms (in Part 2 only) up to and including the protocol defined follow up.	Frequency and percentages; Descriptive summary including mean, median, standard deviation, minimum, maximum, reported separately for each dose.	1) **Study treatment discontinuation** – While-on-treatment strategy will be used. Data until the protocol defined last follow-up day post treatment discontinuation will be considered for analysis. 2) **Use of concomitant/prohibited medication** – Treatment policy strategy. The data post consumption of concomitant/prohibited medications (intercurrent event) will be analysed as is.
Primary Objective (2) - To characterize the plasma PK of GSK3884464 in healthy participants.		
• Plasma PK parameters following single oral doses including $AUC_{(0-t)}$, $AUC_{(0-\infty)}$, C_{max}, t_{max}, and t½.	• Descriptive statistics for log transformed and untransformed data.	1) **Study treatment discontinuation** – While-on-treatment strategy will be used. Data until the protocol defined last follow-up day post treatment discontinuation will be considered for analysis. If

Endpoint	Population Level Summary Measure	Intercurrent Event –Corresponding Estimand Strategy
• Plasma PK parameters following repeat oral doses including AUCτ, C_{max}, C_{τ}, PTT, t_{max}, t½, R_{AUC}, R_{Cmax}, and $R_{C\tau}$. • Other derived PK parameters listed in Table 2 of Section 4.3.1.1.	• Estimate of slope and corresponding 90% Confidence Interval (CI) for dose proportionality and steady state analyses.	a subject withdraws consent during a period, the missing data post withdrawal will not be imputed. The PK parameters of that partially completed period will be calculated as data permits. 2) **Use of concomitant/prohibited medication** – Treatment policy strategy will be used. The data post consumption of concomitant/prohibited medications (intercurrent event) will be analysed as collected. 3) **Site being shut down due to COVID-19** – The missing data after shutdown will be assumed to be missing at random. The PK parameters of the last fully or partially completed period will be calculated as data permits.
Secondary Objective - To evaluate target engagement following single and repeat oral doses of GSK3884464 in healthy participants		
• Maximum changes from baseline in NQO1 mRNA in whole blood post treatment with GSK3884464 in all parts of the study.	• Descriptive statistics for log transformed or untransformed data • Mean and corresponding 90% CI from the fitted model (Section 4.3.2).	1) **Study treatment discontinuation** – While-on-treatment strategy will be used. Data until the protocol defined last follow-up day post treatment discontinuation will be considered for analysis. 2) **Use of concomitant/prohibited medication** – Treatment policy strategy will be used. The data post consumption of concomitant/prohibited medications (intercurrent event) will be analysed as collected.

1.2. Study Design

Overview of Study Design and Key Features

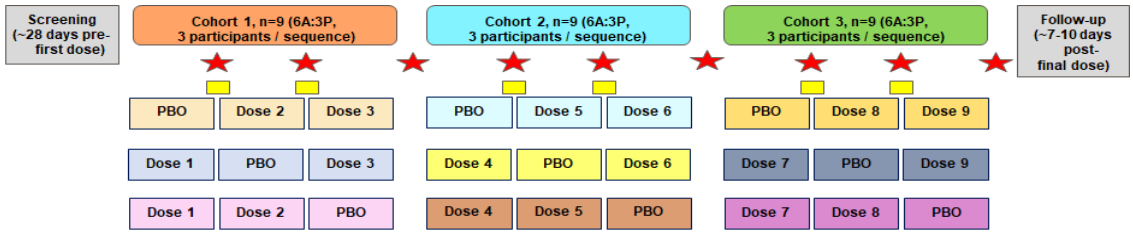
Overall design:



*Part 2, Cohorts 4 and 5 will be 14 days and Cohort 6 will be up to 21 days

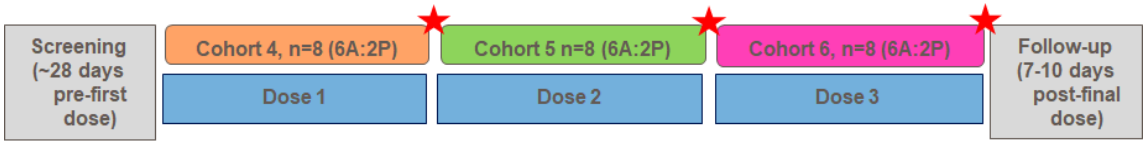
Final Dose Escalation Meeting: Dose escalations will be determined by full safety data, PK data and PD data (if available). Note: Dose escalation meetings will be conducted between cohorts in each Part of the study (as outlined below).

Part 1 – Single Dose:



= Dose escalations will be determined by Safety data, PK data and PD data (if available).
= Wash out
Participants will only participate in one Cohort

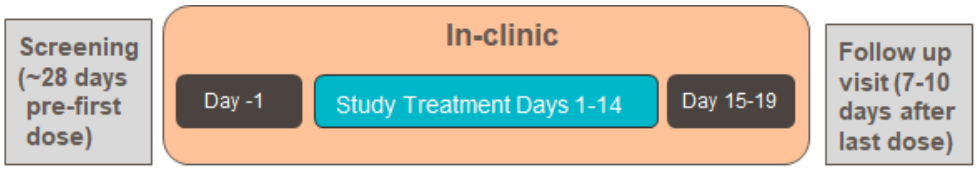
Part 2 – Repeat Dose:



= Dose escalations will be determined by Safety data, PK data and PD data (if available).
Participants will only participate in one Cohort

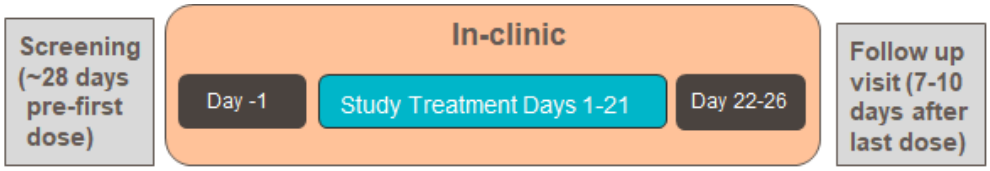
Overview of Study Design and Key Features

Part 2 cohorts 4 and 5:



Cohorts 4 and 5 will be approximately 72 days.

Part 2 cohort 6:



Cohort 6 will be approximately 80 days. Study treatment may be less than 21 days.

Design Features	This FTIH study, 213376, will be a randomized, double-blind, placebo-controlled study of the oral administration of GSK3884464 in healthy participants. As this will be the first time GSK3884464 will be given to humans, the study design may change based on emerging data as the study progresses. The study is planned to have two parts and will be conducted at a single center. **Part 1 (Single Dose):** This will be a 3-period crossover design, single dose (SD), dose escalation study in healthy participants. Participants will receive GSK3884464 or matching placebo as an oral dose. There will be up to three cohorts with 9 participants in each cohort, each cohort will have up to 3 time periods. **Part 2 (Repeat Dose):** This will be a sequential design, 14-day (Cohorts 4 and 5) and up to 21-days (Cohort 6) repeat-dose (RD), dose escalation study in healthy participants. It will consist of up to 3 ascending dose cohorts with 8 participants per cohort. Participants in each cohort will receive GSK3884464 or matching placebo; not all participants will receive placebo.

Overview of Study Design and Key Features	
Study intervention	**Part 1 (Single Dose):** This part will be a 3-period crossover design, SD, dose escalation study in healthy participants. Each participant will participate in up to 3 dosing periods and will receive up to 2 doses of GSK3884464 and 1 dose of placebo in a randomized fashion. There will be a minimum of 7 days (or 5 half-lives, whichever is longer) washout period between dosing in each period. Each cohort will have approximately 9 participants who will be randomized to one of 3 treatment sequences, with 3 participants per sequence in a 1:1:1 ratio. Within each sequence, an increasing dose of GSK3884464 will be administered in each period. Within each period, allocation to GSK3884464 and placebo will be 2:1. **Part 2 (Repeat Dose):** This part will be a sequential design, 14-day (Cohorts 4 and 5) and up to 21-day (Cohort 6) RD, dose escalation study in healthy participants. Each cohort will consist of approximately 8 participants. Participants in each cohort will receive GSK3884464 or matching placebo in a 3:1 ratio.
Study intervention Assignment	**Part 1 (Single Dose):** Each cohort will have approximately 9 participants and will be randomized to one of 3 treatment sequences, with 3 participants per sequence in a 1:1:1 ratio. Within each sequence, an increasing dose of GSK3884464 will be administered in each period. Within each period, allocation to GSK3884464 and placebo will be 2:1. **Part 2 (Repeat Dose):** Each dose cohort will have approximately 8 participants and will be randomized to receive either GSK3884464 or placebo in sequential design using a 3:1 allocation ratio.
Interim Analysis	No formal interim analysis is planned; data may be analyzed at the end of each completed cohort/study Part. Safety and PK data will be reviewed by the Dose Escalation Committee (DEC) before dose escalation in each study part, and between study parts.

2. STATISTICAL HYPOTHESES

The focus of this FTIH study is to evaluate the safety, tolerability, PK and PD of GSK3884464. As such there is no formal hypothesis being tested. However, wherever appropriate, an estimation approach will be taken, and point estimates and CIs will be constructed.

Intercurrent events, the estimand strategy to handle such events and the changes to the respective analyses to implement the strategies are highlighted in Section 1.1.1.

3. ANALYSIS SETS

Analysis Set	Definition / Criteria	Analyses Evaluated
Enrolled	• All participants who sign the informed consent form (ICF).	• Study Population
Randomized	• All participants who were randomly assigned to treatment in the study. • This population will be based on the treatment the participant was randomized to.	• Study Population
Safety	• All randomized participants who take at least 1 dose of study intervention. • Participants will be analysed according to the intervention they actually received.	• Safety
PK	• All participants in the Safety population who had at least one non-missing PK assessment (Non-quantifiable [NQ] values will be considered as valid PK assessments). • This population will be based on the treatment the participant actually received.*	• PK
PD	• Participants in the Safety population with baseline and at least one post baseline PD measure (e.g., NQO1 mRNA)	• PD

*Subjects on active only will be included in the PK analysis set.

4. STATISTICAL ANALYSES

4.1. General Considerations

4.1.1. General Methodology

Analyses planned will be mainly descriptive in nature involving frequencies and percentages for categorical variables and number of subjects (n), mean, standard deviation, median, minimum and maximum for continuous variables. Where appropriate, statistical modelling will be performed and point estimates with CIs will be constructed (for e.g., analysis of evaluation of dose proportionality, steady state).

4.1.2. Baseline Definition

Unless stated otherwise, the baseline value will be the latest pre-dose assessment 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. When pre-dose data is completely missing for a subject, then no derivation will be performed, and the baseline will be set to missing.

For each period within a cohort, the period baseline is defined in a similar manner, by considering the latest available non-missing pre-dose assessment in that period.

Where pre-dose data is captured multiple times, the baseline will be defined as the mean of the assessments (e.g., Triplicate measurements for all BP readings.)

4.2. Safety Analyses

The primary objectives of this study include the assessment of the safety and tolerability of single and repeat ascending doses in healthy participants.

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

The intercurrent events mentioned in Section 1.1.1. along with the corresponding estimand strategies will be considered for these analyses.

4.2.1. Extent of Exposure

The extent of exposure will be summarised using GSK Core Data Standards. Further details of the planned displays are given in the OPS.

4.2.2. Adverse Events

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

Events, Drug-related Adverse Events. Further details of the planned displays are given in the OPS.

4.2.2.1. Adverse Events of Special Interest (AESI)

For this study, AESI represent moderate or severe increases in liver function analyses. Further details of the planned displays are given in the OPS and will be reported as data permit.

4.2.2.2. COVID-19 Assessment and COVID-19 AEs

A standardized MedDRA Query (SMQ) will be used to identify all COVID-19 AEs.

If required, some additional (optional) COVID-19 displays may be reported. Further details of the planned displays are given in the OPS.

4.2.3. Additional Safety Assessments (if applicable)

4.2.3.1. Laboratory Data

Laboratory evaluations including the analyses of Chemistry laboratory tests, Haematology laboratory tests, Urinalysis, Core Urine Monitoring Assessments, Renal, Liver function tests, fasting serum insulin and other biomarkers will be based on GSK Core Data Standards. Based upon the concern ranges in Section 6.2.1, the laboratory test results will be categorized according to the normal range as low (below the lower limit), normal (within the normal range) and high (above the upper limit). Summary statistics for change from baseline will also be tabulated. The details of the planned displays are given in the OPS.

4.2.3.2. Vital Signs

The analyses of vital signs will be based on GSK Core Data Standards, unless otherwise specified.

Mean Arterial Pressure (MAP) will be derived (Section 4.5.1.2) and reported in the summaries for vital signs.

BMI will be computed for all the visits where weight information is available, using height from the screening visit. Derivation will be done using the standard formula.

Further details of the planned displays and derivations are given in the OPS.

4.2.3.3. ECG

The analysis of 12 lead ECG and 24-hour telemetry along with any ECG findings will be reported according to the GSK Core Data Standards.

The QTc data analysis will use the collected values based on the following Fridericia formula:

$$QTcF = \frac{QT}{\sqrt[3]{RR}}$$

Where RR is the duration of RR interval and a represents the time elapsed between two successive R waves of the QRS signal on the ECG.

The changes in QTc values will be categorized into the clinical concern ranges which are specific to changes in QTc as mentioned in Section 6.2.1. A summary of change in QTc value will display the number and percentage of subjects with a change within each range for the worst-case post-baseline. Subjects with missing baseline values will be excluded from this summary.

Further details of the planned displays are given in the OPS.

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4.3. Primary Pharmacokinetic Analyses

The primary objectives of this study include the assessment of the PK of GSK3884464 following single and repeat ascending doses in healthy participants.

All PK analyses will be based on the PK population, unless otherwise specified.

4.3.1. Definition of endpoints/estimands

4.3.1.1. Derived Pharmacokinetic Parameters

PK parameters will be calculated using standard non-compartmental analysis (NCA) according to current working practices and using the currently supported version of WinNonlin (version 8.2 or higher). All calculations of non-compartmental parameters will be based on actual sampling times for the final analysis.

For plasma PK parameter derivation, NQ values before the first measurable concentration will be assigned a value of zero, while single NQ values between measurable concentrations, consecutive NQ values between measurable concentrations and any subsequent measurable concentrations, and NQ values after the last measurable concentration will be set to missing.

PK parameters listed in Table 2 will be determined from the plasma concentration time data, provided there is enough evaluable data available for the calculations. Additional plasma PK parameters may be derived as data permit.

Table 2 Derivations for plasma PK parameters

Parameter	Parameter Description
Part 1:	
C_{max}	Maximum observed concentration, determined directly from the concentration-time data.
C_{max}/D	Maximum observed concentration normalized by dose: $$C_{max}/D = \frac{C_{max}}{Dose}$$
T_{max}	Time to reach C_{max}, determined directly from the concentration-time data.
T_{last}	Time of last quantifiable concentration
$t_{1/2}$	Apparent terminal half-life will be calculated as: $$t_{1/2} = \frac{ln2}{\lambda_z}$$ NOTE: λ_z is the terminal phase rate constant.
$AUC_{(0\text{-}24h)}$*	Area under the concentration-time curve from time zero to 24 hours post-dose.
$AUC_{(0\text{-}t)}$	Area under the concentration-time curve from time zero to the time of the last quantifiable concentration (C(t)) will be calculated using the linear trapezoidal rule for each incremental trapezoid and the $\log_e$ trapezoidal rule for each decremental trapezoid (linear up/log down calculation method in Phoenix WinNonlin).
$AUC_{(0\text{-}\infty)}$	Area under the concentration-time curve extrapolated to infinity will be calculated as: $$AUC_{(0-\infty)} = AUC_{(0-t)} + \frac{C(t)}{\lambda_z}$$ NOTE: λ_z is the terminal phase rate constant and C(t) is the last quantifiable concentration and λ_z is the terminal phase rate constant.
$AUC_{(0\text{-}\infty)}/D$	Area under the concentration-time curve extrapolated to infinity normalized by dose: $$AUC_{(0-\infty)}/D = \frac{AUC_{(0-\infty)}}{Dose}$$
CL/F	The apparent clearance will be calculated as Dose/$AUC_{(0\text{-}\infty)}$
$\%AUC_{ex}$	The percentage of $AUC_{(0\text{-}\infty)}$ obtained by extrapolation will be calculated as follows:

Parameter	Parameter Description
	$\%AUC_{ex} = \frac{AUC_{(0-\infty)} - AUC_{(0-t)}}{AUC_{(0-\infty)}} \times 100$ NOTE: % of the extrapolated area should not exceed 20%. Any value of $\%AUC_{ex} > 20\%$ should be flagged and excluded from summary statistics if >40%. Derived parameter ($AUC_{(0-\infty)}$, $AUC_{(0-\infty)}/D$ and CL/F) values should be flagged or excluded from statistical analysis accordingly.
λ_z	λ_z is the terminal phase rate constant. A minimum number of three data points in the terminal phase will be used starting at any post- C_{max} data point, only those data points that are judged to describe the terminal log-linear decline will be used in regression. NOTE: • The adjusted correlation coefficient (R^2 adjusted) in general should be greater than 0.85. Any value < 0.85 will be flagged but may be used at the PK Scientist's discretion. • The interval used to determine λ_z should be equal or greater than 2- fold the estimated $t_{1/2}$ or otherwise flagged and used at the PK Scientist's discretion. All the derived parameters that include λ_z in their calculation (i.e., $t_{½}$, $AUC_{(0-\infty)}$, $AUC_{(0-\infty)}/D$, $\%AUC_{ex}$, CL/F) will need to be flagged or excluded from statistical analysis accordingly.
λ_z upper limit	The upper limit on time for values to be included in the calculation of λ_z.
λ_z lower limit	The lower limit on time for values to be included in the calculation of λ_z.
λ_z number of points	The number of time points used in computing λ_z.
Part 2:	
C_τ	Trough concentration prior to dosing, determined directly from concentration-time data at Day 2, 4, 7, 11, 14, and 15 for Part 2 Cohorts 4 and 5 and at Day 2, 4, 7, 11, 18, 21, and 22 for Part 2 Cohort 6. NOTE: Day 15 (Cohorts 4 and 5) and Day 22 (Cohort 6) trough concentrations are determined from concentration-time data at the end of dosing period for protocol defined last dosing day (24h post Day 14 or 21 doses, in case of QD dosing).
C_τ/D	Trough concentration prior to dosing on last dosing day normalized by dose: $C_\tau/D = \frac{C_\tau\ (Day\ N)}{Dose}$ where N is the protocol defined last dosing day.

Parameter	Parameter Description
C_{max}	Maximum observed concentration, determined directly from the concentration-time data after dosing on Day 1 and protocol defined last dosing day.
C_{max}/D	Maximum observed concentration after dosing on protocol defined last dosing day normalized by dose: $$C_{max}/D = \frac{C_{max}\ (Day\ N)}{Dose}$$ where N is the protocol defined last dosing day.
T_{max}	Time to reach C_{max}, determined directly from the concentration-time data after dosing on Day 1 and protocol defined last dosing day.
$AUC_{(0\text{-}24)}$*	Area under the concentration-time curve from time zero to 24 hours post-dose on Day 1.
AUC_{τ}	Area under the concentration-time curve over the dosing interval will be calculated after dosing on the protocol defined last dosing day, using the linear trapezoidal rule for each incremental trapezoid and the $\log_e$ trapezoidal rule for each decremental trapezoid (linear up/log down calculation method in Phoenix WinNonlin).
AUC_{τ}/D	Area under the concentration-time curve over the dosing interval normalized by dose: $$AUC_{\tau}/D = \frac{AUC_{\tau}}{Dose}$$
$AUC_{(0\text{-}\infty)}$**	Area under the concentration-time curve extrapolated to infinity on Day 1 will be calculated as: $$AUC_{(0-\infty)} = AUC_{(0-t)} + \frac{C(t)}{\lambda_z}$$ NOTE: λ_z is the terminal phase rate constant and C(t) is the last quantifiable concentration on Day 1.
$t_{1/2}$	Apparent terminal half-life will be calculated after dosing on Day 1**, and on the protocol defined last dosing day: $$t_{1/2} = \frac{ln2}{\lambda_z}$$ NOTE: λ_z is the terminal phase rate constant.
λ_z	λ_z is the terminal phase rate constant (after dosing on Day 1** and after dosing on last dosing day). A minimum number of three data points in the terminal phase will be used starting at any post- C_{max} data point, only those data points that are judged to describe the terminal log-linear decline will be used in regression. NOTE: • The adjusted correlation coefficient (R^2 adjusted) in general should be greater than 0.85. Any value < 0.85 will be flagged but may be used at the PK Scientist's discretion.

Parameter	Parameter Description
	• The interval used to determine λ_z should be equal or greater than 2- fold the estimated $t_{1/2}$ or otherwise flagged and used at the PK Scientist's discretion. All the derived parameters that include λ_z in their calculation (i.e., $t_{½}$) will need to be flagged or excluded from statistical analysis accordingly.
λ_z upper limit	The upper limit on time for values to be included in the calculation of λ_z.
λ_z lower limit	The lower limit on time for values to be included in the calculation of λ_z.
λ_z number of points	The number of time points used in computing λ_z.
R_{AUC}	Accumulation ratio based on AUC_τ will be calculated as: $$R_{AUC} = \frac{AUC_\tau}{AUC_{(0-24)}}$$
R_{Cmax}	Accumulation ratio based on C_{max} will be calculated as: $$R_{Cmax} = \frac{C_{max}(Day\ N)}{C_{max}\ (Day\ 1)}$$ where N is the protocol defined last dosing day.
$R_{C\tau}$	Accumulation ratio based on C_τ will be calculated as the ratio of C_τ for last dose (pre-dose on Day N) and C_τ after first dose (concentration at 24 h post- Day 1 dose, in case of QD regimen): $$R_{C\tau} = \frac{C_\tau(Day\ N)}{C_\tau\ (Day\ 2)}$$ where N is the protocol defined last dosing day.
PTT	Peak-to-trough ratio at steady-state will be calculated as: $$PTT = \frac{C_{max}(Day\ N)}{C_\tau(Day\ N)}$$ where N is the protocol defined last dosing day.

*Other partial areas might be evaluated based on the dosing interval to be used in Part 2. AUC_{0-24} is relevant in case of QD repeat dosing regimen.
**These Day 1 parameters might not be calculable, depending on half-life.

4.3.2. Main analytical approach

The intercurrent events mentioned in Section 1.1.1. along with the corresponding estimand strategies will be considered for the PK analyses.

The summaries and models defined in this section will be reported only as data permits.

4.3.2.1. Descriptive Statistics

The following summaries for log transformed (base e) as well as untransformed data will be provided for PK parameters listed in Table 2. All data will be summarised by dose:

- **Untransformed data:** N (number of subjects in the population), n (number of subjects used for the analysis), arithmetic mean, 90% CI for the arithmetic mean, SD, median, minimum, maximum.
- **Log transformed data:** N (number of subjects in the population), n (number of subjects used for the analysis), geometric mean, 90% CI for the geometric mean, SD of $\log_e$-transformed data and %CVb or %CVw (except t_{max} and t_{last}).

4.3.2.2. Dose proportionality (Part 1 and 2):

Part 1 (SD): Dose proportionality will be assessed by visual inspection of dose normalised $AUC_{(0-\infty)}$ ($AUC_{(0-\infty)}$/D) and dose normalized C_{max} (C_{max}/D) values versus dose for all cohorts together.

Part 2 (RD): Dose proportionality will be assessed by visual inspection of dose normalised AUC_τ (AUC_τ/D), C_{max} (C_{max}/D), and C_τ (C_τ/D) values for protocol defined last dosing day versus dose for all cohorts together.

Dose proportionality may also be assessed using the power model as described below:

Endpoints:

Part 1: Dose normalized $AUC_{(0-\infty)}$, C_{max}

Part 2: Dose normalized AUC_τ, C_{max}, C_τ

Part 1: Terms fitted in the model

Model specification: $\log_e(y) = \log_e(\alpha) + \beta_1 \times \log_e(dose) + \beta_2 \times \text{period} + \beta_3 \times \text{sequence}$

Where y is the endpoint of interest, dose is the actual dose received, β_1 is the coefficient associated with dose, β_2 and β_3 are the coefficients associated with period and sequence respectively, and α is the subject-specific random effect.

Response: log transformation of the endpoint of interest (base e)

Fixed continuous covariate: $\log_e(dose)$

Fixed effects: Period, Sequence

Random: Subject (intercept only)

Kenward-Roger method for approximating the denominator degrees of freedom.

Part 2: Terms fitted in the model

For part 2, dose proportionality will be assessed and reported only on Day 14 for cohort 4,5 and on Day 21 for cohort 6, hence, no random effects are required in the model for Part 2.

Model specification: $\log_e(y) = \log_e(\alpha) + \beta \times \log_e(dose)$

Where y is the endpoint of interest, dose is the actual dose received, β is the coefficient associated with dose and $\log_e(\alpha)$ is the intercept.

Response: Log transformation of the endpoint of interest (base e)

Fixed continuous covariate: $\log_e(dose)$

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.

For both Part 1 and 2, the beta estimates and corresponding 90% CIs of $\log_e$(dose) will be presented. Given that the endpoints are dose normalised, note that a beta coefficient ≈ 0 implies dose proportionality.

4.3.2.3. Steady state analysis (Part 2)

A preliminary assessment of time to achieve steady state will be made based on visual inspection of trough concentration levels (Cτ, collected at pre-dose as per Table 2) on Y-axis versus collection day on X-axis, by dose. The time points (days) to be included in the statistical analysis will be determined from assessment of the figure

Terms fitted in the model:

Response: Log transformed (base e) trough plasma concentration (Cτ)

Fixed continuous covariate: Visit

Random: Subject effect (intercept only)

Kenward-Roger method for approximating the denominator degrees of freedom will be used.

Distributional assumptions underlying the model used for analysis will be examined by obtaining a normal probability plot of the residuals and a plot of the residuals versus the fitted values (i.e., checking the normality assumption and constant variance assumption of the model respectively) to gain confidence that the model assumptions are reasonable.

The slope (beta estimate) along with the corresponding 90% CIs for the slope for each dose will be presented. A slope of 0 will indicate steady state.

4.4. Secondary Endpoint(s) Analyses

All analyses for secondary endpoint(s) will be based on the PD population, unless otherwise specified. The intercurrent events mentioned in Section 1.1.1. along with the corresponding estimand strategies will be considered for the analyses.

4.4.1. Secondary endpoint

The secondary endpoint is the maximum fold change from baseline of NQO1 mRNA in whole blood post treatment with GSK3884464 in Parts 1 and 2 of the study.

The summaries and models defined in this section will be reported only as the data permits.

4.4.1.1. Main analytical approach

For Parts 1 and 2, the maximum fold change from baseline mRNA expression data will be analysed together for all cohorts. The data will be inspected visually. If the maximum fold change from baseline in NQO1 mRNA expression is not normally distributed, log (base e) transformation will be applied. Fold-change from baseline of NQO1 mRNA will be calculated as the absolute NQO1 mRNA observation divided by the baseline NQO1 mRNA observation (pre-dose).

In Part 1, maximum fold-change value for each subject and dose will be computed from all observations collected in each period separately. In Part 2, maximum fold-change values at Day 1, 7, and Day 14 (Cohorts 4 and 5) or Day 21 (Cohort 6) will be computed from all observations collected on those days. The following will be fitted in the model.

Part 1: Terms fitted in the model

Response: Maximum fold change from baseline in NQO1 mRNA expression (log transformed (base e) if not normally distributed)

Fixed effect: Treatment (placebo and active doses of GSK3884464) as categorical variable, Period, Sequence

Fixed continuous covariate: Age

Random: Subject effect (intercept only)

Kenward-Roger method for approximating the denominator degrees of freedom will be used.

Part 2: Terms fitted in the model

The model will be fitted by visits (Day 1, Day 7, and Day 14 (Cohorts 4 and 5) and Day 21 (Cohort 6)). A mixed model will not be fit for Part 2 data.

Response: Maximum fold change from baseline in NQO1 mRNA expression (log transformed (base e) if not normally distributed)

Fixed effect: Treatment (placebo and active doses of GSK3884464) as categorical variable

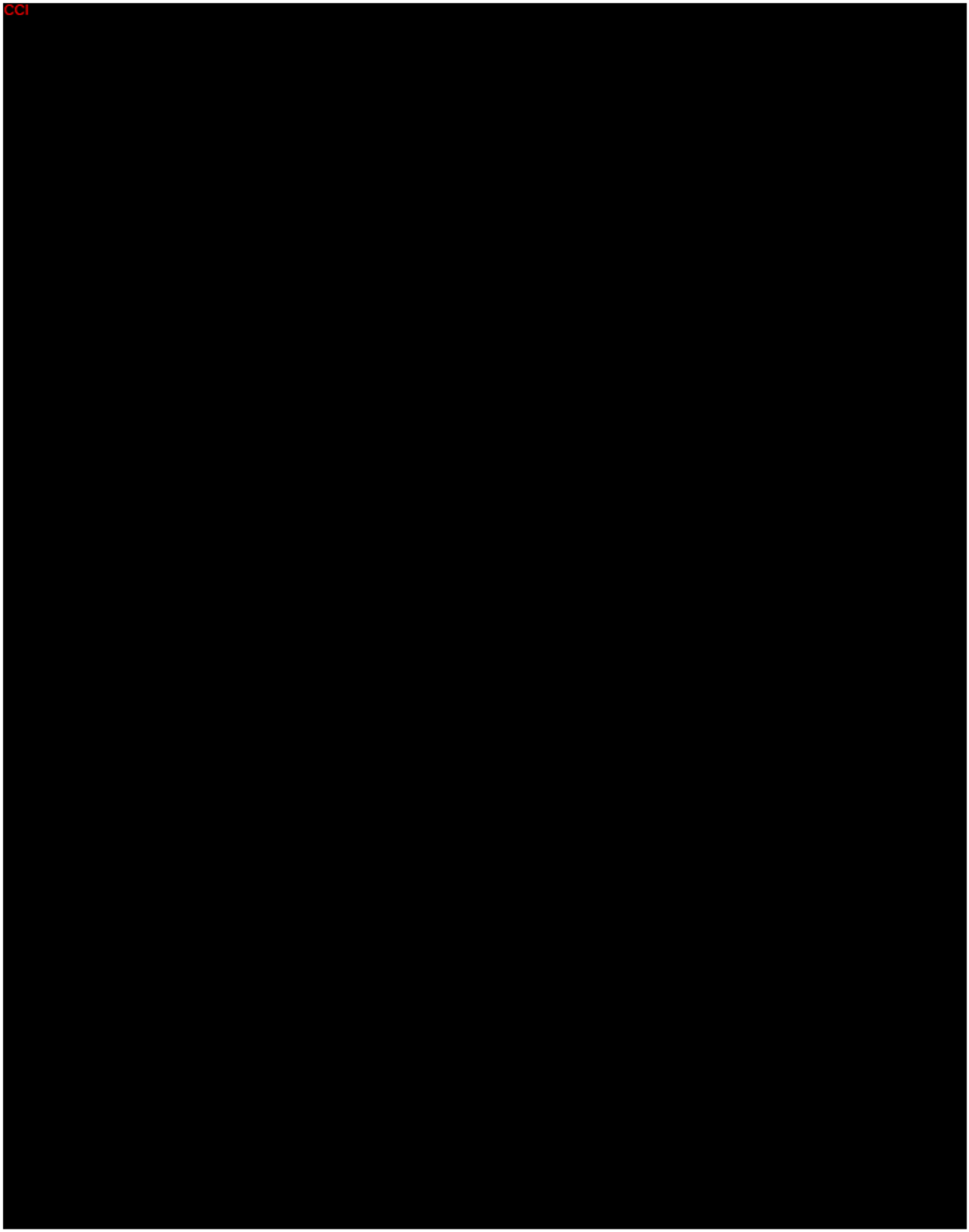
Fixed continuous covariate: Age

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.

For both parts, for non-transformed data, adjusted means with corresponding 95% CI and treatment differences with placebo along with corresponding 95% CI's will be presented. If the data is log-transformed, back-transformed adjusted geometric means with corresponding 95% CIs and back-transformed ratio of the geometric means for each treatment with placebo along with 95% CI will be presented. For part 2, all results will be presented separately for each visit [Day 1, 7, Day 14 (Cohorts 4 & 5) and Day 21 (Cohort 6)].

The maximum changes from baseline will also be descriptively summarized. Plots will be reported as per GSK Core Data Standards. The details of the planned displays are given in the OPS.

CCI



CCI

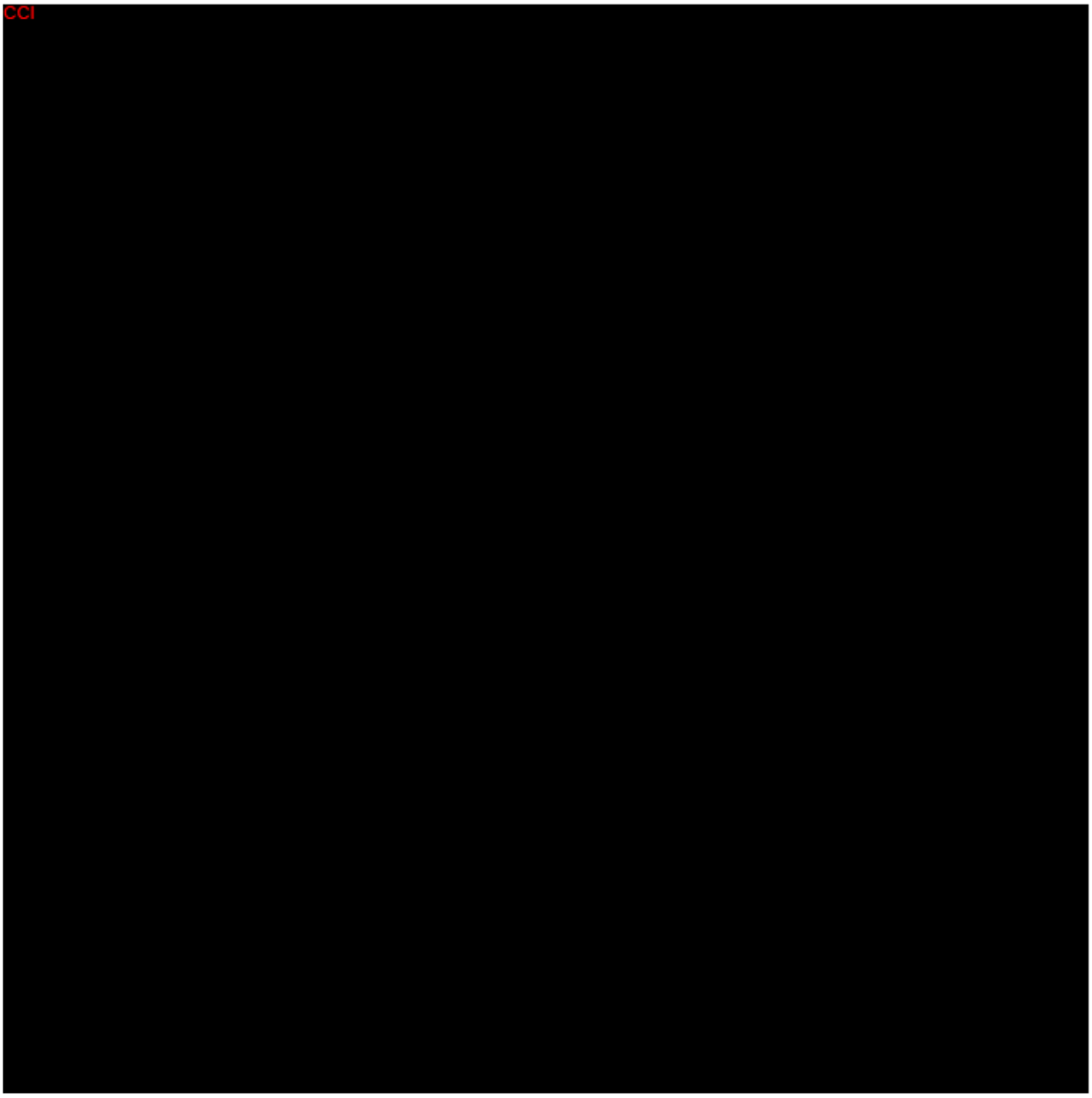
[redacted]

CCI

[redacted]

[1] Where MAP is calculated as: DBP + 1/3(SBP – DBP)

CCI



4.6. Interim Analyses

No formal interim analyses were planned during the course of the study. Based on emerging blinded study data and internal safety board recommendation (GSB), an ad-hoc unblinded safety analysis was performed to assess safety, PK and PD of GSK3884464 after completion of Cohort 4. The details about this analysis are added in the Ad-hoc Safety Analysis Charter (TMF – 15049788). The results dissemination plan and details of all unblinded members involved are archived in a Note-to-file (TMF – 14918703).

4.7. Changes to Protocol Defined Analyses

Changes from the originally planned statistical analysis specified in the protocol are detailed in Table 4.

Table 4 Changes to Protocol Defined Analysis Plan

Protocol Defined Analysis	SAP Defined Analysis	Rationale for Changes
Analysis for Secondary Endpoint(s): The normalized mRNA expression data will be analysed with a mixed effect model with subject as random effect, and treatment, visit and treatment by visit as fixed effect.	Analysis for Secondary Endpoint(s): For both parts, the normalized maximum change from baseline mRNA expression data will be analysed with a mixed effect model with, dose, and **age** as fixed effects and subject as random visit.	Age added as a covariate as per the study team's suggestion

5. SAMPLE SIZE DETERMINATION

A sufficient number of participants will be screened to achieve up to 51 randomly assigned to study intervention and up to 51 evaluable participants. It is estimated that Part 1 will have 27 evaluable participants; Part 2 will have 24 evaluable participants (6 for each of the three repeat doses levels and 6 for placebo). Additional participants/cohorts may be enrolled to allow for evaluation of additional dose levels. If participants prematurely discontinue during the study, additional replacement participants may be enrolled at the discretion of the Sponsor. These replacement participants will be assigned to the same treatment/treatment sequence as the corresponding participant who prematurely discontinued from the study.

The sample size has been assessed based on the evaluation of fold change from baseline (FCFB) of NQO1 expression, a secondary endpoint in the study to the end of repeated dosing. Assuming the within subject CV of 50% and based on 6 participants each in GSK3884464 and placebo treatment arms.

- If the true ratio of FCFB between GSK3884464 and placebo is 5-fold, then there is 69% probability that the observed ratio is greater than 4.2 -fold; if the true ratio is 6-fold, then the probability is 83%; if the true ratio is greater than 7-fold then the probability is greater than 90%. This provides high confidence of observing a clinically meaningful effect in the expected range (>5-fold) of target engagement in NQO1.

If the true ratio of FCFB between GSK3884464 and placebo is 1-fold, then the false positive rate that the observed ratio is greater than 4.2-fold is <0.1%.

6. SUPPORTING DOCUMENTATION

6.1. Appendix 1 Study Population Analyses

The study population analyses will be based on the Safety population, unless otherwise specified. Please see Section 3 for more information on analysis sets.

Study population analyses including analyses of participant's disposition, protocol 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 given in the OPS.

6.1.1. Participant Disposition

A summary of participant status and reason for study withdrawal will be provided. This display will show the number and percentage of participants who completed the study and who prematurely withdrew from the study, including reasons for study withdrawal. A participant is considered to have completed the study if they have completed study assessments until the end of the study as per the schedule of assessments, including the follow up visit.

A summary of study intervention status will be provided. This display will show the number and percentage of participants who have discontinued study intervention and a summary of the reasons for discontinuation of study intervention. A summary of the number of participants in each of the analysis sets described in the Section 3 will be provided.

The data for phase conclusion in each period of Part 1 will be derived based on the subject visit and treatment information.

All the data will be summarized based on GSK Core Data Standards.

6.1.2. Demographic and Baseline Characteristics

The demographic characteristics (e.g., age, race, ethnicity, sex, height, baseline body weight and BMI (derived)) will be summarized using descriptive statistics.

The summary of disease history and characteristics will be provided. Past medical conditions and current medical conditions as of screening will be summarized respectively. Substance use, including smoking history, tobacco use, alcohol and drug history will be summarized.

All the data will be summarized based on GSK Core Data Standards.

6.1.3. Protocol Deviations

Important protocol deviations 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 (where possible without knowing the study intervention details) are captured and categorised in the protocol deviations dataset.
- This dataset will be the basis for the summaries of important protocol deviations.

6.1.4. Prior and Concomitant Medications

Concomitant medications will be coded using both the GSK Drug and WHO Drug dictionaries. However, the summary will be based on GSK Drug dictionary only. Medications will be coded using the GSK Drug coding dictionary (current version at the time of Data Base Release (DBR)). The number and percentage of participants reporting the use of each concomitant medication will be summarized by GSK-Drug Anatomical Therapeutic Chemical (ATC) classification level 1, 2, 3 (body system) and ingredient. Drugs that are composed of a combination of ingredients will be displayed according to the ATC classifications of the ingredients, not of the combination.

Concomitant medications include any medication that was taken at some point during the on-intervention period as defined in Section 6.2.2.

6.1.5. Study Intervention Compliance

A summary of overall compliance for GSK3884464 based on the exposure data will be summarized using descriptive summary for Part 2.

Study intervention Compliance (%) = [Total cumulative actual dose / Total cumulative scheduled dose] *100.

6.2. Appendix 2 Data Derivations Rule

6.2.1. Criteria for Potential Clinical Importance

A laboratory value that is outside the reference range is considered either high abnormal (value above the upper limit of the reference range) or low abnormal (value below the lower limit of the reference range). Note: a high abnormal or low abnormal laboratory value is not necessarily of clinical concern.

Criteria specified below will be used to flag for potential clinical importance:

Clinical Chemistry

Laboratory Parameters	Units	Category	Clinical Concern Range	
			Lower	Upper
Albumin	g/L		< 30	
Calcium	mmol/L		< 2.0	> 2.75
Creatinine	umol/L			> 1.3xULN
Creatinine	umol/L	Change from baseline		Increase of 40
Glucose (Fasted)	mmol/L		< 3.0	> 7.5
Magnesium	mmol/L		< 0.4	> 1.03
Phosphate	mmol/L		< 0.7	> 1.6
Potassium	mmol/L		< 3.0	> 5.3
Sodium	mmol/L		< 130	> 149

Liver Functions

Test Analyte	Units	Category	Clinical Concern Range	
			Lower	Upper
Alkaline phosphatase	U/L			> 2 x ULN
AST/SGOT	U/L			> 2 x ULN
ALT/SGPT	U/L			> 2 x ULN
Gamma GT	IU/L			1.5 X ULN
Total Bilirubin	µmol/L			> 1.5 x ULN
TROPONIN T (HIGH SENSITIVITY)	ng/L			>14
NTPRO BNP	pmol/L			>47

Haematology

Laboratory Parameter	Units	Category	Clinical Concern Range	
			Lower	Upper
Hematocrit	%	Male		>51
		Female		>45
		Δ from BL	N/A	> 7.5%
Hemoglobin	g/L	Male	<100	>175
		Female	<95	>150
		Δ from BL	N/A	> 25g/L
Lymphocytes	$x10^9$/ L		<0.97	
Neutrophils	$x10^9$/ L		<1.5	
Platelet Count	$x10^9$/ L		<100	>550
While Blood Cell Count (WBC)	$x10^9$/ L		<2	>18
Red Blood Cell Count (RBC)	$x10^{12}$/L	Male	<3.0	
		Female	<2.5	

ECG

ECG Parameter (Absolute)	Units	Clinical Concern Range	
		Lower	Upper
Absolute QTcF during the study (i.e. post dose)	msec		>450
Absolute PR Interval	msec	<120	>220
Absolute QRS Interval	msec	<75	>110
Change from Baseline			
Increase from Baseline QTc	msec		>60

Vital Signs

Vital Sign Parameter (Absolute)	Units	Clinical Concern Range	
		Lower	Upper
Systolic Blood Pressure	mmHg	<85	>160
Diastolic Blood Pressure	mmHg	<45	>100
Pulse Rate (Heart Rate)	bpm	<50	>100
temperature	°C	<35	>38
Respiratory rate	Breaths/min	<10	>25

6.2.2. Study Period

Assessments and events will be classified according to the time of occurrence relative to the study intervention period.

Pre-Intervention is defined as time prior to the first dose of study intervention, i.e.
Part 1: Ref Date < Study Intervention Start Date of Period 1 in each Cohort
Part 2: Ref Date < Study Intervention Start Date in each Cohort

On-Intervention is defined as time from first dose to last date plus lag days, i.e.
Part 2: Study Treatment Start Date and time ≤ Date and time ≤ Study Treatment End Date and time + 7 days, in each cohort.

Post-Intervention is defined as any time post dosing, i.e.
Part 1: Study Intervention Start Date and Time ≤ Ref Date < Next Study Intervention Start Date and Time, in each Period within a Cohort. It will additionally include any events occurring in the washout period before start of the next treatment dose.
Part 2: Date and time > Study Treatment End Date and time + 7 days, in each cohort

Note: For the last period in each cohort, events occurring during the follow-up (7-10 days) will be attributed to the last dose level.

6.2.3. Study Day and Reference Dates

The safety reference date is the study intervention start date and will be used to calculate study day for safety measures.

The study day is calculated as below:

- Assessment Date = Missing → Study Day = Missing
- Assessment Date < Reference Date → Study Day = Assessment Date – Ref Date
- Assessment Data ≥ Reference Date → Study Day = Assessment Date – Ref Date + 1

6.2.4. Assessment Window

Refer to section '**Time Deviation Windows for Study Assessments**' (Table 4) of the Study Reference Manual.

6.2.5. Multiple measurements at One Analysis Time Point

Unless otherwise specified, when multiple assessments are done for a single timepoint, the mean of the measurement will be calculated first and summary statistics will be based on the calculated mean. This will apply to both baseline and post baseline assessments.

If multiple assessments are taken from the same type of lab, the worst case will be used.

6.2.6. Handling of Partial Dates

<table>
<tr><th>Element</th><th>Reporting Detail</th></tr>
<tr><td>General</td><td>

Partial dates will be displayed as captured in participant listing displays.
However, where necessary, display macros may impute dates as temporary variables for sorting data in listings only. In addition, partial dates may be imputed for 'slotting' data to study phases or for specific analysis purposes as outlined below.
Imputed partial dates will not be used to derive study day, time to onset or duration (e.g., time to onset or duration of adverse events), or elapsed time variables (e.g., time since diagnosis).

</td></tr>
<tr><td>Adverse Events</td><td>

Missing or Partial start/end date and time are not expected for Adverse events.

</td></tr>
<tr><td>Concomitant Medications/ Medical History</td><td>

Partial dates for any concomitant medications recorded in the CRF will be imputed using the following convention:

<table>
<tr><td>Missing start day</td><td>If study intervention start date is missing (i.e., participant did not start study intervention), then set start date = 1st of month.

Else if study intervention start date is not missing:

o If month and year of start date = month and year of study intervention start date, then

▪ If stop date contains a full date and stop date is earlier than study intervention start date, then set start date= 1st of month.
▪ Else set start date = study intervention start date.</td></tr>
<tr><td>Missing start day and month</td><td>If study intervention start date is missing (i.e., participant did not start study intervention), then set start date = January 1.</td></tr>
</table>
</td></tr>
</table>

Element	Reporting Detail		
			Else if study intervention start date is not missing: o If year of start date = year of study intervention start date, then ▪ If stop date contains a full date and stop date is earlier than study intervention start date, then set start date = January 1. ▪ Else set start date = study. intervention start date.
	Missing end day		A '28/29/30/31' will be used for the day (dependent on the month and year).
	Missing end day and month		A '31' will be used for the day and 'Dec' will be used for the month.
	Completely missing start/end date		No imputation
Age	Age will not be imputed.		

6.2.7. Early PK Access Key Activities

Items	Details	Roles with Authorized Access	Secured Area
Early PK Access Starting Milestone	PK Cutoff Milestone Or PK Last Subject Last Visit	CPMS Lead/Modeller including CPMS modelers/programmers from vendors BIB Lead	NA
Creation of PopPK/PD with Scrambled Subject ID	PopPK/PD	CPMS Lead/Modeler including CPMS modelers/programmers from vendors	NA
Development of PopPK/PD Preliminary Model	PopPK/PD Preliminary Model	CPMS Lead/Modeler including CPMS modelers from vendors	NA

Items	Details	Roles with Authorized Access	Secured Area
Ad-hoc safety analysis (includes unblinded PK/PD data)	Post completion of Cohort 4	Independent unblinded SDTM, Biostats and key study team members (TMF – 15049788)	Server 175 - /arenv/arprod/gsk3884464/ mid213376/trt_safety_01

6.2.8. Abbreviations

Δ	Change from baseline
ΔΔ	Placebo-corrected change-from-baseline
CCI [redacted]	
AE	Adverse event
AESI	Adverse Events of Special Interest
ATC	Anatomical Therapeutic Chemical
AUC	Area under the curve
BIB	Bioanalysis, Immunogenicity and Biomarkers
BL	Baseline
BMI	Body mass index
BP	Blood Pressure
CI	Confidence Interval
COVID-19	Coronavirus disease
CPMS	Clinical Pharmacology Modelling and Simulation
CSR	Clinical study report
CV	Coefficient of Variation
DEC	Dose Escalation Committee
DBP	Diastolic Blood Pressure
DBR	Database Release
ECG	Electrocardiogram
CRF	Case Report Form
FCFB	Fold Change from Baseline
FTIH	First time in human
CCI [redacted]	
GOF	Goodness of Fit
GSB	Global Safety Board
GSK	GlaxoSmithKline

HARP	Harmonisation For Analysis & Reporting Project
HR	Heart Rate
ICF	Informed Consent Form
LDL	Low-density lipoprotein
CCI [redacted]	
CCI [redacted]	
MAP	Mean Arterial Pressure
MedDRA	Medical Dictionary for Regulatory Activities
mRNA	Messenger RNA
NCA	Non-Compartmental Analysis
CCI [redacted]	
NQ	Non-quantifiable
NQO1	NAD(P)H dehydrogenase (quinone 1)
CCI [redacted]	
OPS	Outputs and Programming Specifications
PCI	Potential Clinical Importance
PD	Pharmacodynamic
PK	Pharmacokinetic
PopPK	Population Pharmacokinetic
PR	PR interval of the ECG
PTT	Peak to trough
QRS	QRS interval of the ECG
QT	QT Interval of the ECG
QTc	Corrected QT interval
QTcF	Corrected QT interval using Fridericia's formula
RD	Repeat dose
RNA	Ribonucleic acid
S&P	Statistics and Programming
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SD	Single dose
SDTM	Study Data Tabulation Model
SMQ	Standardized MedDRA Query (SMQ)
TMF	Trial Master File
CCI [redacted]	
VPCs	Visual Predictive Checks
WHO	World Health Organization

6.2.9. Trademarks

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7. REFERENCES

Axelsson AS, et al. Sulforaphane reduces hepatic glucose production and improves glucose control in patients with type 2 diabetes. *Sci. Transl Med*. 2017; 9:eaah4477.(2017).

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

Dinkova- Kostova AT, Kostov RV, Canning P. KEAP1, the cysteine-based mammalian intracellular sensor for electrophiles and oxidants. *Arch Biochem Biophys.* 2017; 617:84-93.

Drazner MH. The progression of hypertensive heart disease. *Circulation* 2011; 123:327-334 (2011).

European Medicines Agency. "Guideline on the investigation of drug interactions" *Committee for Human Medicinal Products (CHMP)* (2012).

GlaxoSmithKline Document Number 2020N459103_01. Prediction of human PK parameters for GSK3884464. 19-Jan-2021

GlaxoSmithKline Document Number 2021N467036. Preliminary Predictions for Enzyme Inhibition/Induction Mediated, and Transporter Inhibition-Mediated Perpetrator Drug-Drug Interactions by GSK3884464 Using Physiologically Based Pharmacokinetic Modelling. 27 May 2021

GlaxoSmithKline Document Number 2021N473852_00. Pharmacodynamic Simulations for GSK3884464 in Humans based on non-clinical data. 05-May-2021

GlaxoSmithKline Document Number RPS-CLIN-000167. GSK3884464 Investigator's Brochure. 07-Jun-21.

Guiney WJ, Beaumont C, Thomas SR, Robertson DC, McHugh SM, Koch A, Richards D. Use of Entero-Test, a simple approach for non-invasive clinical evaluation of the biliary disposition of drugs. Br J Clin Pharmacol. 2011;72:133–142

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

Shah KS, et al. Heart failure with preserved, boarderline and reduced ejection fraction: 5 year outcomes. *J Am Coll Cardiol.* 2017; 70:2476–2486.

Sharma RS, et al. Experimental nonalcoholic steatohepatitis and liver fibrosis are ameliorated by pharmacologic activation of Nrf2 (NF- E2 p45-related factor 2). *Cell Mol Gastroenterol Hepatol*. 2018; 5:367–398.

Shimizu I & Minamino T. Physiological and pathological cardiac hypertrophy. *J Mol Cell Cardiol.*2018; 97:245-262.

Tecfidera Pharmaceuticals (Revised February 2020). Bardoxylone. *Prescribing Information.* https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/204063lbl.pdf

US Food and Drug Administration. "In Vitro Drug Interaction Studies – Cytochrome P450 Enzyme – and Transporter-Mediated Drug–Drug Interaction Studies: Guidance for Industry." *US Food and Drug Administration, Silver Spring, MD* (2020).