Statistical Analysis Plan Amendment 01

Study ID: 214075

Official Title of Study: A randomized, double-blind, placebo controlled, single and repeat dose study to assess the safety, tolerability, and pharmacokinetics of inhaled GSK3923868 in participants with Chronic Obstructive Pulmonary Disease (COPD)

Date of Document: 16-Aug-2023

Information Type: Statistical Analysis Plan (SAP)

TITLE PAGE

Protocol Title: A randomized, double-blind, placebo controlled, single and repeat dose study to assess the safety, tolerability, and pharmacokinetics of inhaled GSK3923868 in participants with Chronic Obstructive Pulmonary Disease (COPD)

Study Number: 214075

Compound Number: *GSK3923868*

Abbreviated Title: The safety, tolerability and PK of GSK3923868 in participants with COPD

Sponsor Name: GSK Research & Development Limited

Regulatory Agency Identifier Number(s)

Registry	**ID**

TABLE OF CONTENTS

PAGE

LIST OF TABLES

PAGE

VERSION HISTORY

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
SAP	06 Dec 2022	08-Jul-22	Not Applicable	Original version
Amendment 01	16 Aug 2023	28-Nov-22	Section 6.2.1 updated	Discrepancy between PCI ranges and units provided in SAP and values collected by lab
			Removed wording which mentioned PEF data would be summarised.	PEF is being collected for monitoring purposes only and is not recorded in the eCRF.

1. INTRODUCTION

The purpose of this SAP is to describe the planned analyses to be included in the Clinical Study Report for Study 214075.

1.1. Objectives and Endpoints

Objectives	Endpoints
Primary	
• To assess the safety and tolerability of GSK3923868 following single and repeat inhaled administration in participants with Chronic Obstructive Pulmonary Disease (COPD).	• Occurrence of adverse events (AEs) and serious adverse events (SAEs). • Clinically significant changes in laboratory values, vital signs,12-lead electrocardiogram (ECG) and spirometry measurements up to Follow Up.
Secondary	
• To evaluate the plasma pharmacokinetics of GSK3923868 following single and repeat inhaled administration in participants with COPD.	Derived pharmacokinetic parameters as data permit, including (but not limited to): • Area under the plasma-concentration time curve (AUC): area under the concentration-time curve from time 0 (pre-dose) to 24 hours post dose administration following the first dose (AUC[0-24]) or area under the concentration-time curve from time 0 to the time of the last quantifiable concentration (AUC[0-t]) for single dose and area under the concentration-time curve from time 0 (pre-dose) to 6 hours post dose administration following the first dose (AUC[0-6]) for repeat dose • Maximum observed plasma drug concentration (Cmax), time to maximum observed plasma drug concentration (Tmax)

1.2. Study Design

<table>
<tr><th colspan="2">Overview of Study Design and Key Features</th></tr>
<tr><td>Design Features</td><td>This is a single cohort, randomized, double-blind, placebo controlled single and repeat dose study designed to assess the safety, tolerability and plasma PK of GSK3923868 administered as an inhalation powder blend (GSK3923868 CCI [redacted] for inhalation) using the CCI [redacted] inhaler in participants with stable COPD. This study contains two parts, a single ascending dose followed by 14-days repeat dosing.

The single ascending dose part will assess two dose levels of GSK3923868 or placebo across two treatment periods in a single crossover cohort of participants.

The repeat dose part will assess one dose level of GSK3923868 or placebo in one treatment period in the same cohort of participants.</td></tr>
<tr><td>Study intervention</td><td>The study consists of a single cohort which goes through three treatment periods:

Period 1 is Dose Level 1 of GSK3923868 single dose vs Placebo.

<table>
<tr><th>Screen</th><th>Treatment Period 1 (Dose Level 1 single dose) plus washout</th><th>Treatment Period 2 (Dose Level 2 single dose) plus washout</th><th>Treatment Period 3 (Dose Level 3 repeat dose)</th><th>Follow-up Period</th><th>Total Duration</th></tr>
<tr><td>Up to 30 days before first dose</td><td>6 days (2 days inpatient + 4 days outpatient)</td><td>6 days (2 days inpatient + 4 days outpatient)</td><td>15 days (3 days inpatient + 12 days outpatient)</td><td>7- 14 days post-dose</td><td>64 - 71 days</td></tr>
</table>

Period 2 is Dose Level 2 of GSK3923868 single dose vs Placebo. Escalation to treatment period 2 (Dose Level 2) will occur on an individual participant basis.

Period 3 is Dose Level 3 of GSK3923868 repeat dose vs Placebo, once daily for 14 days. Escalation to treatment period 3 (Dose Level 3) will also occur on an individual participant basis.</td></tr>
</table>

<table>
<tr><th colspan="2">Overview of Study Design and Key Features</th></tr>
<tr><td>Study intervention Assignment</td><td>Participants who meet the study entry criteria will be randomized to receive GSK3923868 or placebo before study intervention administration on Day 1 of Treatment Period 1.
<table>
<tr><th rowspan="2">Treatment Period</th><th rowspan="2">Planned Dose</th><th colspan="4">Cohort 1</th></tr>
<tr><th>(n=3)</th><th>(n=3)</th><th>(n=3)</th><th>(n=3)</th></tr>
<tr><td>1 (Single Dose)</td><td>Dose Level 1 GSK3923868</td><td>A</td><td>A</td><td>A</td><td>P</td></tr>
<tr><td>2 (Single Dose)</td><td>Dose Level 2 GSK3923868</td><td>P</td><td>A</td><td>A</td><td>A</td></tr>
<tr><td>3 (14-Day Repeat Dose)</td><td>Dose Level 3 GSK3923868</td><td>A</td><td>P</td><td>A</td><td>A</td></tr>
</table>
*Note: A: Active, P: Placebo

12 Participants will be randomised into one of the four treatment sequences described in the table above, to achieve 3:1 ratio of Active to Placebo within each period.</td></tr>
<tr><td>Interim Analysis</td><td>There are no formal interim analyses conducted as part of this study.</td></tr>
</table>

2. STATISTICAL HYPOTHESES

No formal statistical hypotheses will be tested. The primary objective is to evaluate the safety and tolerability of GSK3923868 in participants with COPD.

2.1. Multiplicity Adjustment

N/A

3. ANALYSIS SETS

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

Analysis Set	Definition	Analyses Evaluated
Screened	All participants who were screened for eligibility.	Study Population
Enrolled	The All Subjects Enrolled (ASE) population will consist of all participants who enrolled in 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
Randomized	The randomized population will consist of all participants who were randomized.	Study Population
Safety	All randomized participants who received at least 1 dose of study treatment. Participants will be analysed according to the treatment they received.	Safety Study Population
Pharmacokinetic (PK)	All randomized participants in the Safety population who had at least 1 dose of GSK3923868 and at least 1 non-missing PK assessment (Non-quantifiable [NQ] values will be considered as non-missing values). • Participants will be analysed according to the treatment they received.	PK

4. STATISTICAL ANALYSES

4.1. General Considerations

4.1.1. General Methodology

Confidence intervals (CI) will use 95% confidence levels for both summary statistics and statistical analysis, except PK analysis, which will use 90% CI.

Unless otherwise specified, continuous data will be summarized using descriptive statistics: n, mean, standard deviation (std), median, minimum and maximum. Categorical data will be summarized as the number and percentage of participants in each category.

4.1.2. Baseline Definition

Unless otherwise specified, baseline will be the last value/assessment before the first dose of study treatment (Day 1 pre-dose). If there are multiple assessments collected at the same scheduled time, the average of these assessments will be used as the baseline.

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

4.2. Primary Endpoint(s) Analyses

All safety analyses will be performed on the Safety Analysis set, unless otherwise specified.

Primary Endpoints:

- Adverse events (AEs) and serious adverse events (SAEs).
- Clinically significant changes in laboratory values, vital signs,12-lead ECG, and spirometry measurements up to Follow Up.

4.2.1. Definition of endpoints

Adverse events will be coded using the latest standard Medical Dictionary for Regulatory Affairs (MedDRA dictionary).

Grade 1 AEs are defined as mild. Grade 2 or higher AEs are defined as moderate or severe. This study will report AEs as mild, moderate, or severe.

A study intervention-related AE/SAE is defined as an AE/SAE for which the investigator classifies the possible relationship to study intervention as "Yes". A worst-case scenario approach will be taken to handle missing relatedness data, i.e., the summary table will include events with the relationship to study intervention as 'Yes' or missing.

Spirometry assessments are performed in triplicate with the highest value reported.

Whilst all data collected will be summarized, only measurements which are clinically significant at any timepoint between randomization and follow up will be reported as part of the primary endpoint.

Clinically significant values are defined as:

- Values in the potential clinical interest (PCI) ranges for laboratory values, vital signs, ECGs and spirometry.
- Values that achieve the study stopping criteria (protocol Section 7.1.3) for spirometry

The PCI ranges will be defined in the Section 6.2.1.

4.2.2. Main analytical approach

4.2.2.1. Adverse events and serious adverse events

An adverse event (AE) is considered study intervention emergent if the AE onset date is on or after study intervention start date. All AE summaries will be based on study intervention emergent events unless otherwise specified. SAE summaries will be based on all SAEs reported regardless of whether they meet the definition of study intervention emergent or not.

Adverse event analysis will be based on GSK Core Data Standards.

The proportion of participants reporting AEs will be tabulated by study intervention and by dose.

The following displays for Adverse events ((All AEs, Grade 2 or higher, and SAEs)) will be generated: Overview of Adverse Events, Summary of All Adverse Events, Summary of Taste Adverse Events, Summary of Drug-Related Adverse Events, Summary of Adverse Events Leading to Permanent Discontinuation of Study Treatment, Summary of Adverse Events Leading to Withdrawal from Study. These displays will be tabulated by by System Organ Class and Preferred Term.

Further details of the planned displays will be given in OPS.

4.2.2.2. Laboratory Data, Vital Signs, ECGs

For haematology, clinical chemistry, urinalysis, vital signs, ECG and spirometry data the following information will be summarised:

1) Clinically significant values at each visit

2) Raw and change from baseline values at each visit

Note: The first table is the only one included as part of the primary endpoint. Urinalysis data is only collected when there is an abnormal finding and so it is expected that urinalysis tables/listings will be sparse.

Laboratory Data

For laboratory data, separate tables for haematology, clinical chemistry and urinalysis tests will be produced. Laboratory evaluations including the analyses of Clinical chemistry tests, haematology tests and urinalysis, will be based on GSK Core Data Standards. Liver biochemical parameters will be included with clinical chemistry tests.

The details of the planned displays will be given in the OPS. Incidence of clinically significant laboratory parameters will be reported.

Vital Signs

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

In vital sign assessment, pulse rate, respiratory rate, tympanic temperature, and systolic and diastolic blood pressure will be assessed. Blood pressure and pulse measurement will be taken in the semi supine position.

Incidence of clinically significant vital sign parameters will be reported. Refer the normal ranges of laboratory parameters in the Section 6.2.1

Further details of the planned displays will be given in OPS.

ECG

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

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

Safety ECGs will be performed in semi-supine position after at least 5 minutes rest. The parameters collected are PR, QRS, QT and QTc intervals.

Incidence of clinically significant ECG parameters will be reported. Refer the normal ranges of laboratory parameters in the Section 6.2.1

Further details of the planned displays will be given in OPS.

4.2.2.3. Lung Function Measurements

Spirometry

Spirometry data will include FEV1 measurements.

For spirometry data the following information will be summarised:

1) Clinically significant values at each visit

2) Raw and change from baseline values at each visit

4.3. Secondary Endpoint(s) Analyses

All pharmacokinetic analyses will be performed on the PK Population.

For PK endpoints, all analysis will be performed by Part i.e., Part A (Periods 1 and 2, single dose) and Part B (Period 3, repeat dose), except dose proportionality, which will be carried out using data from the three periods.

From the plasma concentration-time data, the following pharmacokinetic parameters will be determined if data permitting, for each dose of GSK3923868:

- Treatment period 1 & 2 (single ascending doses): AUC(0-t), AUC(0-24), AUC(0-6), Cmax and Tmax
- Treatment period 3 (repeat dose): Cmax, Tmax and AUC(0-6) on Day 1 and Day 14

4.3.1. Key secondary endpoint(s)

4.3.1.1. Definition of endpoints

Parameter	Parameter Description
AUC(0-t)	Area under the concentration-time curve from time zero to the time of the last quantifiable concentration (C(t)) will be calculated using the linear trapezoidal rule for each incremental trapezoid and the log trapezoidal rule for each decremental trapezoid.
AUC (0-24)	Area under the concentration-time curve over the dosing interval.
Cmax	Maximum observed concentration, determined directly from the concentration-time data over the dosing interval.
Tmax	Time to reach Cmax, determined directly from the concentration-time data over the dosing interval/
AUC (0-6)	Area under the concentration-time curve from time 0 to 6-hour post dose.

NOTE: Additional parameters may be included as required.

4.3.1.2. Main analytical approach

Plasma GSK3923868 concentration-time data will be analyzed by non-compartmental methods with WinNonlin. Calculations will be based on the actual sampling times recorded during the study.

Pharmacokinetic data will be presented in graphical and/or tabular form and will be summarised descriptively.

4.3.1.3. Dose Proportionality

The following pharmacokinetic statistical analyses will only be performed if sufficient data are available (i.e., if more than 5 subjects have well defined plasma profiles). If the dose with limited data is at the lower end of the dose range, the data will be excluded, and the appropriate analysis conducted on the rest of the data. However, if there are non-calculable PK parameter data at intermittent doses no statistical analyses will be performed. The assessment of dose proportionality will utilise Period 1,2 and the first dose of Period 3 data only.

Dose proportionality will be assessed using power method as primary, and ANOVA as supportive method:

Pharmacokinetic Statistical Analyses for Dose Proportionality: Power Method
Endpoint(s)
• AUC(0-6), Cmax • Each endpoint to be assessed separately.
Model Specification
• $\log_e(Y) = \beta \times \log_e(dose) + \log_e(\alpha)$ where Y is the pharmacokinetic parameter and $\log_e(\alpha)$ is an intercept term.
Model Results Presentation
• The coefficient of the slope with 90% confidence intervals, on the log scale, will be calculated, using the pooled estimate of variance, and used to assess dose proportionality. • Point estimates and confidence intervals for the slope will be reported to 2 decimal places

Pharmacokinetic Statistical Analyses for Dose Proportionality: ANOVA Method
Endpoint(s)
• AUC(0-6), Cmax • Each endpoint to be assessed separately.
Model Specification
• The PK parameter will be dose-normalised prior to loge-transformation by multiplying by reference dose / dose • Dose will be fitted as a fixed effect, subject as a random effect using DDFM=KR. • The reference dose will be chosen based on the lowest clinically relevant dose over which PK can be adequately described, with each other dose as the test doses in the construction of the ratio μ(test)/μ(reference).
Model Results Presentation

Pharmacokinetic Statistical Analyses for Dose Proportionality: ANOVA Method
• Point estimates for the adjusted means on the $\log_e$ scale, the mean difference between each dose (test) and the reference dose and associated 90% confidence interval will be constructed using the residual variance. These will not be presented. • The point estimate and confidence interval will then be exponentially back-transformed to allow the presentation of the adjusted (least square) geometric means for each treatment (dose), and point estimates and associated 90% confidence intervals for the ratio test/reference. • Point estimates and 90% confidence intervals for AUC, Cmax will be reported to 2 decimal places. Ratios and 90% CIs will be plotted by dose. • Plots will also be provided showing the adjusted geometric mean ratio of test to reference treatment (dose) for AUC(0-6), and Cmax together with 90% confidence interval.

4.3.1.4. Accumulation Assessment

The assessment of accumulation will be performed following repeated dosing of GSK3923868 in Period 3 only.

Pharmacokinetic Statistical Analyses
Endpoint(s)
• AUC(0-6), Cmax on Day 14 compared to Day 1 • Each endpoint to be assessed separately following a log-transformation.
Model Specification
• A mixed effect model will be fitted with day as a fixed effect and subject as a random effect. • The Kenward & Roger (KR) degrees of freedom approach will be used. • Day 14 will be compared to Day 1 in order to estimate the accumulation ratio(s) • The accumulation ratio(s) and 90% confidence interval will be calculated by back-transforming the difference between the least square means for the two days and associated 90% confidence interval.
Model Results Presentation
• Point estimates and confidence intervals for the ratios will be reported to 2 decimal places • Scatter plots of each endpoint against day will be produced. The data points for each subject will be joined with straight lines • Boxplots of each endpoint against day will be produced. Each endpoint will be put on a separate page.

4.3.1.5. Model Checking Diagnostics

Model checking diagnostics for dose proportionality and dose accumulation analysis will include the following:

- The Kenward and Roger method for approximating the denominator degrees of freedom and correcting for bias in the estimated variance-covariance of the fixed effects will be used.
- An unstructured covariance structure for the R matrix will be used by specifying

'type=UN' on the REPEATED line.
    - In the event that this model fails to converge, alternative correlation structures may be considered such as CSH or CS.
    - Akaike's Information Criteria (AIC) will be used to assist with the selection of covariance structure.
- 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.

4.3.1.6. Population PK Model

A population PK model (POP PK) may be developed with all available data from this and historical studies as appropriate and will be reported separately.

4.4. Exploratory endpoints Analyses

N/A

4.5. Safety Analyses

The safety analyses will be based on the Safety Analysis Set, unless otherwise specified. The safety analyses have been detailed in Section 4.2 .

4.5.1. Extent of Exposure

Number of days of exposure to study drug will be calculated based on the formula:

Duration of Exposure in Days = Treatment Stop Date – (Treatment Start Date) + 1

Subjects who were randomized but did not report a treatment start date (i.e., were randomized in error) will be categorised as having zero days of exposure.

The cumulative dose will be based on the formula:

Cumulative Dose = Sum of (Number of Days x Total Daily Dose)

Duration of exposure and cumulative dose will be calculated only for Period 3(Repeat dose).

4.5.2. Adverse Events

Refer to Section 4.2.2.1

4.5.2.1. Adverse Events of Special Interest

There are no AEs of Special Interest in the study.

4.5.2.2. Impact of COVID-19 Pandemic on Safety Results

If required, additional COVID-19 displays would be reported if the pandemic has a major impact on trial and interpretation of the trial data.

4.5.3. Additional Safety Assessments

Refer to Section 4.2.2.2 and Section 4.2.2.3

4.6. Other Analyses

N/A

4.7. Interim Analyses

No interim analysis has been planned for this study.

4.8. Changes to Protocol Defined Analyses

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

Table 1 Changes to Protocol Defined Analysis Plan

Protocol Defined Analysis	SAP Defined Analysis	Rationale for Changes
• Spirometry measurements will be summarised for FEV1 and FVC.	• Spirometry measurements will be summarised for FEV1 only.	• The changes are detailed correctly in SoA section of the protocol, but not in the Stats section of the protocol. Hence going by the SoA.

5. SAMPLE SIZE DETERMINATION

No formal statistical techniques were used to calculate the sample size for this study.

The number of participants included is deemed an adequate number to provide an assessment of safety and tolerability and pharmacokinetics measurements.

Sufficient participants with COPD will be screened and randomized to receive GSK3923868 or placebo in a 3:1 ratio with the intention of a minimum of 8 and a maximum of 12 participants to complete the study.

In total, up to 9 participants are planned to receive each dose of active drug in each period. If the true adverse outcome rate is 5%, the chance of observing at least one adverse event at a given dose is 37%. If the true adverse outcome rate is 20%, the chance of observing at least one adverse event at a given dose level is 87%. For sample size of 6 participants on active drug in each period, if the true adverse outcome rate is 5%, the chance of observing at least one adverse event at a given dose is 27%. If the true adverse outcome rate is 20%, the chance of observing at least one adverse event at a given dose level is 74%.

This level of predictivity is deemed adequate within this phase of development.

6. SUPPORTING DOCUMENTATION

6.1. Appendix 1 Study Population Analyses

Unless otherwise specified, the study population analyses will be based on the Enrolled Analysis Set. A summary of the number of participants in each of the participant level analysis set will be provided.

6.1.1. Participant Disposition

A summary of the number and percentage of participants who completed the study as well as those who prematurely withdrew from the study will be provided. Reasons for study withdrawal will be summarized. For those who have neither completed nor withdrawn, they will be categorized as on study intervention or in follow up.

A summary of study intervention status will be provided. This display will show the number and percentage of participants who have completed the scheduled study intervention, are ongoing with study intervention, or have discontinued study intervention prematurely, as well as primary reasons for discontinuation of study intervention.

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

6.1.2. Demographic and Baseline Characteristics

The demographic characteristics including age, gender, ethnicity, height/weight at screening and race will be summarized with descriptive statistics.

Past medical conditions and current medical conditions as of screening will be summarized respectively.

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 the latest version of WHO Drug dictionaries. The summary of concomitant medications will be provided by ingredient, i.e., multi-ingredient medications will be summarized for each individual ingredient rather than a combination of ingredients. The summary will be created using ingredient base names, i.e., ingredients with the same base name but different salt will appear under one base name in the summary. Anatomical Therapeutic Chemical (ATC) classifications will not appear in the summary.

Concomitant medications include any medication that was taken at some point during the on-intervention period as defined in Section 6.8 of the protocol.

6.2. Appendix 2 Data Derivations Rule

6.2.1. Criteria for Potential Clinical Importance

- **Laboratory Values**

Haematology				
Laboratory Parameter	**Units**	**Category**	**Clinical Concern Range**	
			Low Flag (< x)	High Flag (>x)
Platelet Count	10^9/L		31	900
RBC Count	10^12/L		4.2	5.9
Hemoglobin	g/L	Male	90	180
		Female	90	180
Hematocrit	fraction of 1			1.5*ULN
RBC Indices				
MCV	fL		0.75*LLN	1.5*ULN
MCH	pg		28	32
%Reticulocytes	%		na	2*ULN
WBC Count with differentials				
Lymphocytes	10^9/L		0.6	6
Neutrophil Count	10^9/L		1.5	12
Monocytes	10^9/L		na	2
Eosinophils	10^9/L		na	0.5
Basophils	10^9/L		na	2*ULN

Clinical Chemistry				
Laboratory Parameter	**Units**	**Category**	**Clinical Concern Range**	
			Low Flag (< x)	High Flag (>x)
Albumin	g/L		32	50
Calcium	mmol/L		2.2	3.24
Creatinine	umol/L	Male 40-49 years	69	106
		Male 50-59 years	67.2	106
		Male 60-69 years	67.2	106
		Male 70+ years	59.2	106
		Female 40-49 years	52.2	106
		Female 50-59 years	53	106
		Female 60-69 years	53	106
		Female 70+ years	55.7	106
Glucose	mmol/L		4.0	7.8
BUN	mmol/L		2.5	15
Potassium	mmol/L		3.5	5.2
Sodium	mmol/L		136	145

Liver Function			
Test Analyte	**Units**	**Category**	**Clinical Concern Range**
Alanine Aminotransferase (ALT) / Serum Glutamic-Pyruvic Transaminase (SGPT)	U/L	High	≥2x ULN
Aspartate Aminotransferase (AST) / Serum Glutamic-Oxaloacetic Transaminase (SGOT)	U/L	High	≥2x ULN
Alkaline phosphatase	U/L	High	≥2x ULN
T Bilirubin	µmol/L	High	≥ 1.5x ULN
Direct Bilirubin	µmol/L		0 – 6

- **ECG**

ECG Parameters	**Unit**	**Clinical Concern range**	
		Lower(<x)	Upper(>x)
Absolute			
Absolute QTc Interval	msec		> 600
Absolute PR Interval	msec	< 85	> 240
Absolute QRS Interval	msec	< 70	> 120
Change from Baseline			
Increase from Baseline QTc	msec		> 60

- **Vital Signs**

Vital Parameters (Absolute)	Unit	Clinical Concern range	
		Lower(<x)	Upper(>x)
Heart rate	bpm	35	110
Respiratory Rate	breaths/pm	8	20
Systolic blood pressure	mmHg	95	160
Diastolic Blood Pressure	mmHg	55	100
Temperature	°C	35.6	37.7

- **Spirometry**

Any participant experiencing a reduction in FEV1 at the 1-hour post-dose compared to daily pre-dose value of > 20%.

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.

On-Intervention is defined as time from first dose to last dose date plus 14 days. If time of assessment or study intervention is not collected, the following assessment on the first dose date will be assumed to be taken prior to the first dose and therefore considered pre-intervention: ECG, Lab, and vital signs, and first dose date is considered on-intervention for AE and concomitant medication.

Post-Intervention is defined as any time post on-intervention window, i.e., > last dose date + 14 days.

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 5 (**STUDY ASSESSMENTS AND PROCEDURES**) in the Study Reference Manual (SRM).

6.2.5. Multiple measurements at One Analysis Time Point

When triplicate ECG assessments are taken, 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.

For lab tests on a study day, if more than one assessment is taken on the same day, the test from a central lab will be taken over the test from a local lab. 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). In addition, imputed dates are not used for deriving the last contact date in overall survival analysis dataset.</td></tr>
<tr><td>Adverse Events</td><td>• Partial dates for AE recorded in the CRF will be imputed using the following conventions:
<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:</td></tr></table></td></tr>
</table>

Element	Reporting Detail	
		• 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. Else set start date = 1st of month.
	Missing start day and month	If study intervention start date is missing (i.e. participant did not start study intervention), then set start date = January 1. Else if study intervention start date is not missing: • 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. Else set start date = January 1.
	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	No Imputation
	Completely missing start/end date	No imputation
Concomitant Medications/ Medical History	• Partial dates for any concomitant medications recorded in the CRF will be imputed using the following convention:	
	Missing start day	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: • 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.

Element	Reporting Detail	
		– Else set start date = study intervention start date. Else set start date = 1st of month.
	Missing start day and month	If study intervention start date is missing (i.e., participant did not start study intervention), then set start date = January 1. Else if study intervention start date is not missing: • 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. Else set start date = January 1.
	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

6.2.7. Abbreviations

Abbreviation	Description
AE	Adverse Event
BL	Baseline
CI	Confidence Interval
CPMS	Clinical Pharmacology Modelling & Simulation
CS	Clinical Statistics
CSR	Clinical Study Report
%CV	Percent Coefficient of Variation
DP	Decimal Places
eCRF	Electronic Case Record Form
IA	Interim Analysis
MMRM	Mixed Model Repeated Measures
OPS	Output and Programming Specification
PCI	Potential Clinical Importance
PK	Pharmacokinetic
PT	Preferred Term
PopPK	Population PK
QC	Quality Control
QTcF	Frederica's QT Interval Corrected for Heart Rate
SAP	Statistical Analysis Plan

Abbreviation	Description
SOC	System Organ Class

6.2.8. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
NONE

Trademarks not owned by the GlaxoSmithKline Group of Companies
WinNonlin

7. REFERENCES

GSK Document Number TMF-14593236, A randomized, double-blind, placebo controlled, single and repeat dose study to assess the safety, tolerability, and pharmacokinetics of inhaled GSK3923868 in participants with Chronic Obstructive Pulmonary Disease (COPD). 2020