Protocol

Study ID: 213497

Official Title of Study: A randomized double-blind, placebo controlled, single ascending and repeat dose, First Time in Human study in healthy participants and stable asthmatics to assess safety, tolerability and pharmacokinetics of GSK3923868 inhalation powder

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Title Page

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Protocol Number: 213497

Compound Number: GSK3923868

Short Title: Safety, tolerability and pharmacokinetics of GSK3923868 inhalation powder in healthy participants and stable asthmatics.

Sponsor Name: GlaxoSmithKline Research & Development Limited

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Version history

This Statistical Analysis Plan (SAP) for study 213497 is based on the protocol dated 24-Sep-2021.

Table 1 SAP Version History Summary

SAP Version	Document Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
1	-	07-Sep-2020	Not Applicable	Original version
2		24-Sep-2021	-Updated 'SABA only' treatment to include treatment with 'intermittent ICS/LABA'	-Population treatment requirements updated in line with updated treatment guidelines.
			-Updated access to unblinded data from complete cohorts to include safety endpoints	-To allow better interpretation of both safety and PK data following the completion of each cohort, to help the design of furture studies.
			-Updated text to define time of unblinding	-To enable modelling of PK data to start after cohort 3.
			-Cohorts 3 and 4 will be pooled and reported together	-As cohorts 3 and 4 are identical [redacted], data from the two cohorts will be pooled and reported together.

1. INTRODUCTION

The purpose of this SAP is to describe the planned analyses to be included in the Clinical Study Report for Study 213497.

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 (including COVID-19 reporting) will be provided in the Output and Programming Specification (OPS) document.

1.1. Objectives, Estimands and Endpoints

1.1.1. Objectives and Endpoints

1.1.1.1. Parts A and B (Healthy participants)

Objectives	Endpoints
Primary	
• To evaluate the safety and tolerability of GSK3923868 following single and repeat inhaled administration in healthy participants.	• Adverse events (AEs) and serious adverse events (SAEs). • Clinically significant laboratory values, vital signs,12-lead electrocardiogram (ECG) and spirometry measurements up to Day 2 of the final treatment period in Part A, and Day 18 in Part B.
Secondary	
• To evaluate the plasma pharmacokinetics of GSK3923868 following single and repeat inhaled administration in healthy participants.	Derived pharmacokinetic parameters as data permit, including (but not limited to): Single dose (Part A, Cohorts 1 & 2): • Area under the plasma GSK3923868 concentration versus time curve from time zero to last quantifiable concentration (AUC(0-t)) and from time zero to infinity (AUC(0-∞)) (if determined). • Maximum observed GSK3923868 plasma concentration (Cmax). • Time to maximum observed plasma drug concentration (Tmax). Repeated dose (Part B, Cohorts 3 & 4): • AUC(0-τ) on Day 1 and Day 14 (τ=24h for once a day dosing regimen) (if determined). • Cmax and Tmax on Day 1 and Day 14.

Objectives	Endpoints
CCI [redacted]	

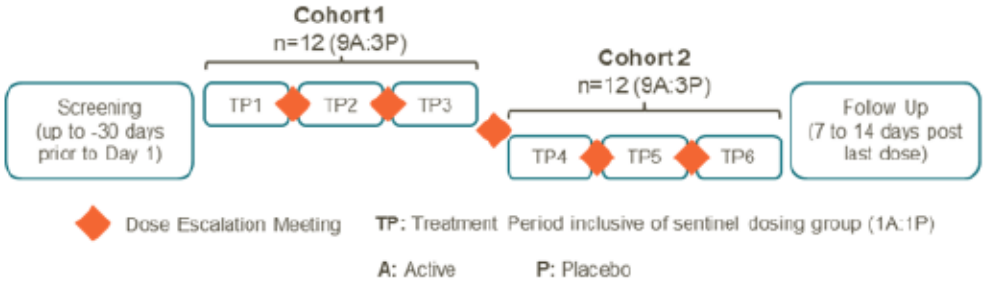
1.1.1.2. Part C (Participants with Asthma)

Objectives	Endpoints
Primary	
• To evaluate the safety and tolerability of GSK3923868 following repeat inhaled administration in participants with asthma.	• AE and SAEs • Clinically significant laboratory values, vital signs, 12-lead ECG and spirometry measurements up to Day 8.
Secondary	
To evaluate the plasma pharmacokinetics of GSK3923868 following repeat inhaled administration in participants with asthma.	• AUC(0-τ) on Day 1 and Day 7 (τ=24h for once a day dosing regimen) (if determined). • Cmax and Tmax on Day 1 and Day 7.

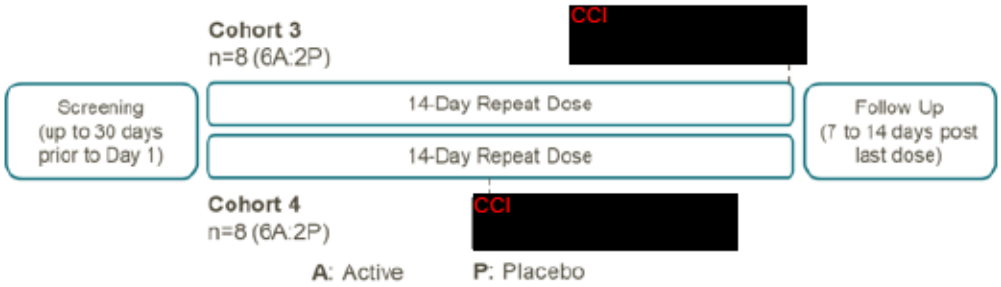
1.2. Study Design

Overview of Study Design and Key Features

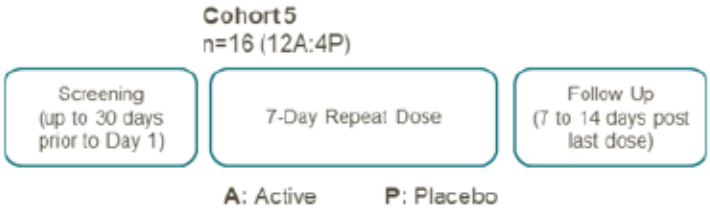
Part A: Single Ascending Dose | Healthy Participants



Part B: Repeat Dose | Healthy Participants



Part C: Repeat Dose | Participants with Asthma



Design Features	A randomized double-blind, placebo controlled, three-part (Parts A, B and C), First Time in Human (FTIH) study to assess safety, tolerability and pharmacokinetics of GSK3923868 inhalation powder In Part A, single ascending doses of GSK3923868 will be assessed in two sequential crossover cohorts (Cohorts 1 and 2, 12 participants per cohort) of healthy participants, each with up to three treatment periods. There will be a minimum of 10 days between doses, before a follow up visit 7-14 days post the final dose.

<table>
<tr><th colspan="2">Overview of Study Design and Key Features</th></tr>
<tr><td></td><td>Part B will assess repeat doses of GSK3923868 for 14 days across two parallel cohorts (Cohorts 3 and 4) of 8 healthy participants (total 16 participants in Part B).

In Part C, further repeat dosing of GSK3923868 for 7 days will be assessed in a single parallel cohort (Cohort 5) of 16 participants with stable asthma. Part C will be randomized according to two strata:1) SABA and/or intermittent ICS/LABA users and 2) ICS or ICS/LABA users.

A Dose Escalation Committee (DEC) will be responsible for the review of emerging safety, tolerability and plasma PK results to determine the progression of single ascending dose levels in each treatment period in Part A and the progression to repeat dose levels in Parts B and C.</td></tr>
<tr><td>Study intervention</td><td>The starting dose in Part A Cohort 1 Period 1 is 50 mcg.

The planned doses for dose escalation in Part A after the first cohort with 50 mcg are 100, 250, 500, 1000, and 3000 mcg. The planned dose for Part B (Cohorts 3 and 4) and Part C is 3000 mcg.

<table>
<tr><th>Part</th><th>Screening</th><th>Treatment Period</th><th>Washout Period</th><th>Follow-Up</th></tr>
<tr><td>A</td><td rowspan="3">Up to 30 days before the first dose.</td><td>Each cohort will be comprised of three treatment periods (3 days each) with a follow up phone call at 48 hours after each dose.</td><td>Will be at least 10 days between doses for each participant.</td><td rowspan="3">Between 7 to 14 days following the final dose.</td></tr>
<tr><td>B</td><td>Each participant will receive up to 14 days of treatment with additional observation up to 96 hours after their final dose.</td><td>N/A</td></tr>
<tr><td>C</td><td>Each participant will receive up to 7 days of treatment.</td><td>N/A</td></tr>
</table>

The total duration of the study will be approximately 11 weeks in Part A, approximately 9 weeks in Part B and approximately 8 weeks in Part C.</td></tr>
<tr><td>Study intervention Assignment</td><td>In Part A (Cohorts 1 and 2), each cohort has a crossover design with four treatment sequences that participants will be randomized to. Of the four sequences, three include placebo for one of the treatment periods whilst the last contains active for all treatment periods. This gives a 3:1 active:placebo ratio within each treatment period of the cohort (as shown below):</td></tr>
</table>

Overview of Study Design and Key Features	
	<table><tr><th rowspan="2">Treatment Period</th><th colspan="4">Cohort 1</th><th colspan="4">Cohort 2</th></tr><tr><th>(n=3)</th><th>(n=3)</th><th>(n=3)</th><th>(n=3)</th><th>(n=3)</th><th>(n=3)</th><th>(n=3)</th><th>(n=3)</th></tr><tr><td>1</td><td>A</td><td>A</td><td>A</td><td>P</td><td colspan="4">-</td></tr><tr><td>2</td><td>P</td><td>A</td><td>A</td><td>A</td><td colspan="4">-</td></tr><tr><td>3</td><td>A</td><td>P</td><td>A</td><td>A</td><td colspan="4">-</td></tr><tr><td>4</td><td colspan="4">-</td><td>P</td><td>A</td><td>A</td><td>A</td></tr><tr><td>5</td><td colspan="4">-</td><td>A</td><td>P</td><td>A</td><td>A</td></tr><tr><td>6</td><td colspan="4">-</td><td>A</td><td>A</td><td>P</td><td>A</td></tr></table> Part B (Cohorts 3 and 4), follow a parallel group design where participants will be randomized in a 3:1 ratio (active:placebo) to receive study treatment. Part C (Cohort 5) also follows a parallel group design with participants randomized in a 3:1 ratio (active:placebo) to receive study treatment. In addition, Part C will be stratified to ensure 8 SABA and/or intermittent ICS/LABA participants (6 active and 2 placebo) and 8 ICS or ICS/LABA participants (6 active and 2 placebo) are randomized.
Interim Analysis	There are no formal interim analyses conducted as part of this study, however the following in-stream analyses will be performed as described in the sections below.
Dose Escalation Committee	A review of preliminary safety, tolerability and plasma PK data will be conducted by the DEC prior to each dose level in Part A, before initiating repeat dosing in Part B, and before initiating repeat dosing asthmatics in Part C. Safety and tolerability data includes adverse event/serious adverse event (AE/SAE), clinical laboratory values, 12-lead electrocardiogram (ECG), vital signs and spirometry measurements. Additional details are available in the Dose Escalation Plan.
Instream Analysis of PK Data	Once each of Part A (Cohorts 1 and 2) and Part B (Cohorts 3 and 4) have completed, selected members of the GSK team will be formally unblinded to the treatment allocations of the completed participants for PK and safety data from these cohorts to enable the analysis and modelling of PK data to start. The aim of this analysis is to inform internal decision making around dose selection for future studies in the development plan of this compound. This analysis will not impact the conduct or the design of the current study and will be reported separately from this SAP.

2. SUCCESS CRITERIA

Given this study is the FTIH for GSK3923868, no formal statistical hypotheses will be tested. The primary objective is to evaluate the safety and tolerability of GSK3923868 in healthy participants and stable asthmatics.

3. ANALYSIS SETS

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 including those randomized in error. A participant who is recorded as a screen failure and was also randomized will be considered as randomized in error provided that they have not performed any study assessments.	Study Population
Safety	All randomized participants who received at least 1 dose of study intervention. Participants will be analysed according to the treatment they received.	Safety
Pharmacokinetic (PK)	All randomized 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). • Participants will be analysed according to the treatment they received.	PK

3.1. Definitions for Per Protocol Analysis Set

This study does not have a per protocol analysis set.

4. STATISTICAL ANALYSES

4.1. General Considerations

4.1.1. General Methodology

The Safety Analysis Set will be used for all outputs except for pharmacokinetic (PK) CCI [redacted] endpoints which will use the Pharmacokinetic Analysis Set.

All cohorts will be presented separately, except Cohorts 3 and 4 which will be combined, unless otherwise stated. In addition, for Part A, all outputs excluding study population will be summarised according to treatment and dose level of GSK3923868.

In the case of wrong stratification assigned at the time of randomization, the analyses will be performed based on the data collected in the eCRF, not the assigned stratum at randomization.

Confidence intervals will use 95% confidence levels for both summary statistics and statistical analysis, unless otherwise stated.

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

For all endpoints the baseline value will be the latest pre-dose with a non-missing value, including day 1 pre-dose and those from unscheduled visits prior to the first dose of study treatment. For Part A, baseline will be defined as the latest pre-dose assessment at the start of each treatment period.

Baseline QTcF will be calculated as the average of the three pre-dose measurements on Day 1.

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

4.1.3. Multicentre Studies

Due to the small sample size of this first time in human study, if multiple centres are utilised for recruitment purposes, all data will be pooled and no summaries will be provided by site or country.

4.1.4. 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.

4.2. Primary Endpoints Analyses

The safety analyses will be based on the Safety Analysis Set, unless otherwise specified.

Primary Endpoints:

- Adverse events (AEs) and serious adverse events (SAEs).
- Clinically significant laboratory values, vital signs, 12-lead electrocardiogram (ECG) and spirometry measurements up to Day 2 of the final treatment period in Part A, and Day 18 in Part B.
- Clinically significant laboratory values, vital signs, 12-lead ECG and spirometry measurements up to Day 8 in Part C.

4.2.1. Definition of endpoints

Adverse events will be coded using the 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.

Clinically significant values are defined as:

- Values in the potential clinical interest (PCI) ranges for laboratory values, vital signs and ECGs
- Values that achieve the study stopping criteria (protocol section 7.2.5) for spirometry

The same PCI ranges will be used for both healthy volunteers and stable asthmatics, with all ranges being defined in the OPS.

4.2.2. Main analytical approach

4.2.2.1. Adverse events and serious adverse events

Adverse events analyses including the analysis of adverse events (AEs) and Serious AEs (SAEs) will be based on GSK Core Data Standards. All summaries will be tabulated by study intervention, cohort and dose, except for Cohorts 3 and 4. As cohorts 3 and 4 are identical in every aspect except the timing of bronchoscopy assessment, data from the two cohorts will be pooled and reported together.

An overview summary of AEs, including counts and percentages of participants with any AE, AEs related to study intervention, moderate and severe AEs, moderate and severe AEs related to study intervention, AEs leading to permanent discontinuation of study intervention, study intervention related AEs leading to permanent discontinuation of study intervention, AE leading to dose reductions, AEs leading to dose delays, SAEs, SAEs related to study intervention, fatal SAEs, and fatal SAEs related to study intervention as well as bronchoscopy related AEs will be produced.

The frequency and percentage of AEs will be summarized and displayed in two ways: 1) in descending order by preferred term (PT) only and 2) in descending order by system organ class (SOC) and PT.

All SAEs will be tabulated based on the number and percentage of participants who experienced the event.

Separate summaries will also be provided for study intervention-related AEs and SAEs, AEs leading to permanent discontinuation of study intervention and study intervention related AEs leading to permanent discontinuation of study intervention. These summary tables will be displayed by PT.

4.2.2.2. Laboratory Data, Vital Signs, ECGs and Spirometry

For laboratory data, separate tables for haematology, clinical chemistry and urinalysis tests will be produced. Liver biochemical parameters will be included with clinical chemistry tests.Vital signs data will include semi supine systolic and diastolic blood pressure, pulse rate, respiratory rate and temperature measurements.

ECG data will include PR, QRS, QT and QTcF intervals.

Spirometry data will include FEV_1 and FVC measurements.

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. CCI [redacted]

In order to detect potential bronchospasms, an additional table for spirometry values will be produced which summarises the changes between daily pre- and post-dose FEV_1 and FVC values.

For ECGs, a figure plotting the baseline QTcF and the worst-case post-baseline values will be produced. The figure will have reference lines at 480 and 500 msec for both the ordinate and the abscissa axes. There will be diagonal reference lines at equality (i.e. a 45 degree line), at equality plus 30 msec, and at equality plus 60 msec.

4.3. Secondary Endpoints Analyses

All pharmacokinetic analyses will be performed on the Pharmacokinetic Analysis Set. For PK endpoints, all analysis will be performed by Part i.e. Part A (Cohorts 1 and 2 combined), Part B (Cohorts 3 and 4 combined) and Part C (Cohort 5).

Derived pharmacokinetic parameters as data permit, including (but not limited to):

Part A, Cohorts 1 & 2:

- Area under the plasma GSK3923868 concentration versus time curve from time zero to last quantifiable concentration (AUC(0-t)) and from time zero to infinity (AUC(0-∞)) (if determined).
- Maximum observed GSK3923868 plasma concentration (Cmax).
- Time to maximum observed plasma drug concentration (Tmax).

Part B, Cohorts 3 & 4:

- AUC(0-□) on Day 1 and Day 14 (□=24h for once a day dosing regimen) (if determined).

- Cmax and Tmax on Day 1 and Day 14.

Part C, Cohort 5:

- AUC(0-□) on Day 1 and Day 7 (□=24h for once a day dosing regimen) (if determined).

- Cmax and Tmax on Day 1 and Day 7.

4.3.1. Definition of endpoint(s)

If the AUC(0-τ) or AUC(0-Inf) is not calculatable due to non-quantifiable plasma GSK3923868 data, AUC(0-t') may be calculated instead. t' is the common timepoint for all subjects for the corresponding dose or cohort.

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-□)	Area under the concentration-time curve over the dosing interval.
AUC(0-Inf)	Area under the concentration-time curve extrapolated to infinity will be calculated as follows: AUC = AUC(0-t) + C(t)/λz.
Cmax	Maximum observed concentration, determined directly from the concentration-time data over the dosing interval.
C□	Trough concentration
Tmax	Time to reach Cmax, determined directly from the concentration-time data.
t½	Apparent terminal half-life will be calculated as: t½ = ln2 / λz (NOTE: λz is the terminal phase rate constant).

NOTE: Additional parameters may be included as required.

4.3.2. Main analytical approach

Plasma GSK3923868 concentration-time data will be analysed 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 form and will be summarised descriptively. Analysis of dose proportionality (Part A), steady state assessment and dose accumulation (Parts B and C) will be conducted.

4.3.2.1. 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. A minimum of 3 doses will be required to assess dose proportionality. The assessment of dose proportionality will utilise Part A data only.

Dose proportionality will be assessed using the following two methods:

Pharmacokinetic Statistical Analyses for Dose Proportionality: Power Method
Endpoint(s)
• AUC(0-Inf) (if determined, otherwise use AUC(0-t)), 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-Inf) (if determined, otherwise use AUC(0-t')), 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. • Separate lines will be fitted for each cohort by including terms for cohort and cohort*$\log_e$(dose). If the slopes are not significantly (p-value<0.05) different from each other, the interaction term will be removed and a single slope estimate obtained. If the slopes are significantly different from each other, a separate slope estimate and associated 90% confidence interval will be reported for each cohort. • 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
• 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

Pharmacokinetic Statistical Analyses for Dose Proportionality: ANOVA Method
(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. Treatment 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-∞) or AUC(0-t'), and Cmax together with 90% confidence interval.

4.3.2.2. Accumulation and Steady State Assessment

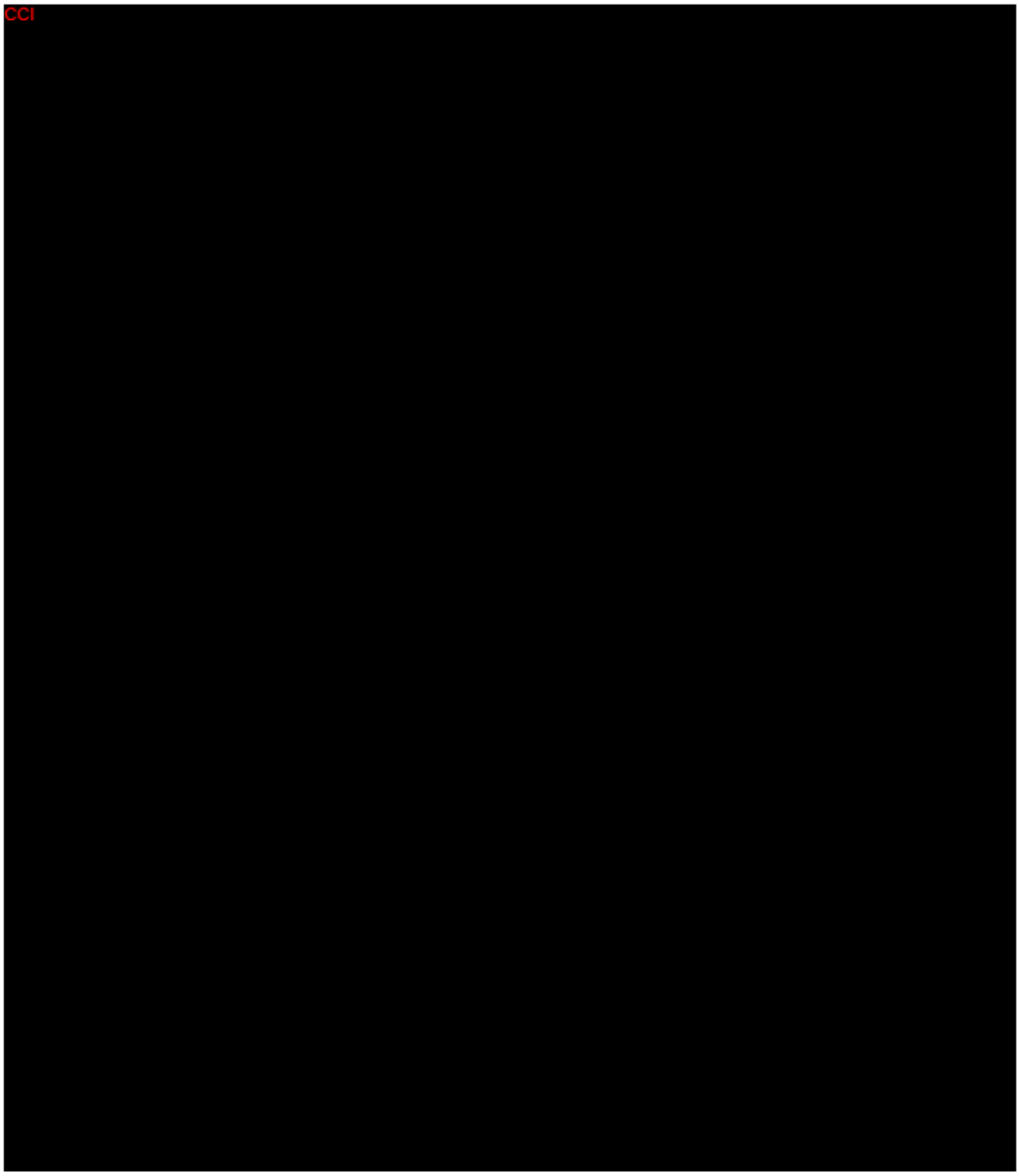
The assessment of accumulation and steady state will be performed following repeated dosing of GSK3923868 in Parts B and C only.

Pharmacokinetic Statistical Analyses
Endpoint(s)
• Accumulation: AUC(0-τ), Cτ (if data permit), Cmax on Day 14 (Part B), Day 7 (Part C) compared to Day 1 • Steady State: Cτ from Day 1 to Day 14 (Part B) or Day 7 (Part C) • 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 treatment will be put on a separate page.

4.3.2.3. Population PK Model

A population PK dataset may be generated to support subsequent population PK modelling. Population PK dataset will include PK data [CCI redacted] from all subjects in this study (Parts A, B and C). The population PK data file will be produced by or under the auspices of Clinical Statistics (Programming).

A population PK model (POP PK) may be developed with all available data as appropriate and may be reported separately.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[redacted]

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[redacted]

4.5. Other Analyses

The other analyses will be based on the Safety Analysis Set, unless otherwise specified.

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

For Part A, exposure to study drug will be calculated separately for each treatment period/treatment received.

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)

4.6. Interim Analyses

4.6.1. Dose Escalation Committee (DEC)

A review of preliminary safety, tolerability and plasma PK data will be conducted by the DEC prior to each dose level in Part A, before initiating repeat dosing in Part B, and before repeat dosing asthmatics in Part C.

Safety and tolerability data will be provided by the site at the end of each dosing session, along with analysis of the plasma PK data which will be performed using nominal sampling times.

To minimize the risk of unblinding during DEC meetings, individual PK data will be scrambled such that the blind is maintained. Summary statistics will also be provided for plasma PK parameters (Cmax and AUC). The data may be unblinded should a safety concern arise during the blinded review.

Additional details are available in the Dose Escalation Plan.

4.6.2. Instream Analysis of PK Data

Once Cohort 3 has completed, selected members of the GSK sponsor staff team will be formally unblinded to the treatment allocations of participants who completed the study to enable the analysis and modelling of PK data to start. Once Cohort 4 has completed, the same sponsor staff will also be unblinded to the treatment allocations of the completed participants from Cohort 4 to incorporate their data into the ongoing PK analysis and modelling. Access to unblinded subject-level data will be restricted to members of the Statistics and Programming and Clinical Pharmacology Modelling and Simulation teams, DMPK Modelling and Computational Science.

The aim of this analysis is to inform internal decision making around dose selection for future studies in the development plan of this compound. This analysis will not impact the conduct or the design of the current study and will be reported separately from this SAP.

4.7. Changes to the Protocol Defined Statistical Analysis Plan

There were no changes or deviations to the originally planned statistical analysis specified in the protocol (Dated: 24-Sep-2021).

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, and thereby to allow progression to larger clinical studies.

A minimum of 5 participants receiving each dose of active drug (either as a single or repeat dose) are required for the dose escalation meetings. With 5 participants, if the true adverse outcome rate is 5%, the chance of not observing any adverse events at a given dose is 77%. If the true adverse outcome rate is 20%, the chance of not observing any adverse events at a given dose level is 33%.

For Part A, sufficient healthy adult participants will be screened to ensure a total of 12 participants per cohort are randomized with the aim to achieve approximately 12 per cohort completed.

In total for Part A, 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 not observing any adverse events at a given dose is 63%. If the true adverse outcome rate is 20%, the chance of not observing any adverse events at a given dose level is 13%.

In Part B, sufficient healthy adult participants will be screened to ensure 8 participants are randomized to each of the two cohorts, with the aim to achieve approximately 8 completed in each cohort.

For Part C, sufficient participants with asthma will be screened to ensure 16 participants are randomised, with the aim to achieve 16 completers. Part C will be randomised according to two strata, SABA and/or intermittent ICS/LABA users and ICS or ICS/LABA users.

In Parts B and C, 12 participants are planned to receive each dose of active drug. The corresponding probabilities for 12 participants with true event rates of 5% and 20% are 54% and 7%, respectively.

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

CCI [redacted]

CCI

For Parts A, B and C if participants prematurely discontinue in the study, they will be replaced at the discretion of the sponsor Medical Monitor in consultation with the Principal Investigator.

6. SUPPORTING DOCUMENTATION

6.1. Appendix 1 Abbreviations and Trademarks

6.1.1. List of Abbreviations

Abbreviation	Description
AE	Adverse Event
CCI	
CI	Confidence Interval
CPMS	Clinical Pharmacology Modelling & Simulation
CS	Clinical Statistics
CSR	Clinical Study Report
%CV	Coefficient of Variation
DEC	Dose Escalation Committee
DP	Decimal Places
eCRF	Electronic Case Record Form
CCI	
FTIH	First Time in Human
GSK	GlaxoSmithKline
IA	Interim Analysis
MMRM	Mixed Model Repeated Measures
OPS	Output and Programming Specification
PCI	Potential Clinical Importance
PK	Pharmacokinetic
PP	Per Protocol
PT	Preferred Term
PopPK	Population PK
QC	Quality Control
QTcF	Frederica's QT Interval Corrected for Heart Rate
SAP	Statistical Analysis Plan
SOC	System Organ Class

6.1.2. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
None

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NONMEM
SAS
WinNonlin

7. REFERENCES

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