Information Type:	Statistical Analysis Plan (SAP)

TITLE PAGE

Protocol Title: A Phase 1, randomized, open-label, single dose, 2-treatment arm (200 µg and 800 µg), 4-way cross-over study in healthy participants aged 18 to 55 to compare the pharmacokinetics of salbutamol administered via metered dose inhalers containing propellants HFA-152a (test) and HFA-134a (reference).

Study Number: 219728

Compound Number: AH3365 (Salbutamol)

Sponsor Name: GlaxoSmithKline Research & Development Limited

EU CT Number –2023-508279-36-00.

TABLE OF CONTENTS

PAGE

LIST OF TABLES

PAGE

LIST OF FIGURES

PAGE

VERSION HISTORY

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
SAP	20 May 2024	1.0 (18 Jan 2024)	Not Applicable	Original version
SAP Amendment 1	25 Sep 2024	- Protocol Amendment 1 (02 May 2024)	- Sensitivity Analysis for PK parameters as per FDA and EMA regulatory guideline - Random effect has been removed from linear mixed model for analyzing the exploratory PD endpoints	- If $S_{WR} \geq 0.294$ for Cmax, AUC(0-∞) and AUC(0-last) then Reference Scale Average Bioequivalence (RSABE) will be used to analyse the PK parameters. - Based on derivation of PD parameters, each participant will have single observation for the study therefore random effect is not required while estimating the PD parameters.

1. INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to describe the planned analyses to be included in the CSR for Study 219728. Details of the planned interim analysis (cohort 1), as well as the final analyses, are provided.

1.1. Objectives, Estimands and Endpoints

Objectives	Endpoints
Primary	
• To characterize the PK of single doses of salbutamol in healthy participants delivered via an MDI containing propellant HFA-152a (test), and to compare with an MDI containing propellant HFA-134a (reference) in the following cohorts: **Cohort 1:** Salbutamol HFA-152a MDI 200 µg (test), HFA-134a MDI 200 µg (reference) **Cohort 2:** Salbutamol HFA-152a MDI 800 µg (test), HFA-134a MDI 800 µg (reference)	• AUC(0-30min) • AUC(0-∞) • Cmax
Secondary	
• **Pharmacokinetic:** To characterize the PK of single doses of salbutamol in healthy participants delivered via an MDI containing propellant HFA-152a (test), and to compare with an MDI containing propellant HFA134a (reference) in the following cohorts: **Cohort 1:** Salbutamol HFA-152a MDI 200 µg (test), HFA-134a MDI 200 µg (reference) **Cohort 2:** Salbutamol HFA-152a MDI 800 µg (test), HFA-134a MDI 800 µg (reference)	• Pharmacokinetic: ▪ Tmax ▪ t1/2 ▪ AUC(0-last)
• **Pharmacokinetics:** To measure the intra-participant variability in PK of single doses of salbutamol for healthy participants delivered via an MDI containing propellant in the following cohorts: **Cohort 1:** Salbutamol HFA-152a MDI 200 µg (test), Salbutamol HFA-134a MDI 200 µg (reference)	• **Pharmacokinetics**: ▪ Intra-participant variability of AUC(0-30min), AUC(0-∞), AUC(0-last), and Cmax of HFA-152a (test) ▪ Intra-participant variability CVw of AUC(0-30min), AUC(0-∞), AUC(0-last), and Cmax of HFA-134a (reference)

Objectives	Endpoints
Cohort 2: Salbutamol HFA-152a MDI 800 µg (test), Salbutamol HFA-134a MDI 800 µg (reference)	
• **Safety:** To assess the safety and tolerability of single doses of salbutamol in healthy participants delivered via MDI HFA-152a (test) or propellant HFA-134a (reference) in the following cohorts: **Cohort 1:** Salbutamol HFA-152a MDI 200 µg (test), HFA-134a MDI 200 µg (reference) **Cohort 2:** Salbutamol HFA-152a MDI 800 µg (test), HFA-134a MDI 800 µg (reference)	• **Safety:** ▪ Incidence of AEs and SAEs ▪ Absolute values for 12 lead ECGs recording of HR and QTc intervals at each assessed visit ▪ Change from baseline for postdose 12 lead ECGs recording of HR and QTc intervals at each assessed visit ▪ Absolute values of clinical laboratory parameters at each assessed visit ▪ Absolute values of vital signs (systolic and diastolic blood pressure and pulse rate) at each assessed visit
Exploratory	
• **Pharmacodynamics:** To characterize the PD of single doses of salbutamol in healthy participants delivered via an MDI containing propellant HFA-152a (test), and to compare to an MDI containing propellant HFA-134a (reference) in the following cohorts: **Cohort 1:** Salbutamol HFA-152a MDI 200 µg (test), Salbutamol HFA-134a MDI 200 µg (reference) **Cohort 2:** Salbutamol HFA-152a MDI 800 µg (test), Salbutamol HFA-134a MDI 800 µg (reference)	• **Pharmacodynamics:** ▪ Minimum serum potassium ▪ MHR ▪ Maximum QTc interval

Primary estimand: -

Cohort 1:

Test: Salbutamol HFA-152a MDI 200 µg

Reference: Salbutamol HFA-134a MDI 200 µg

The primary clinical question of interest for Cohort 1 is -

What is the GMR for Cohort 1 in primary PK parameters (AUC(0-30min), AUC(0-∞) and Cmax) of salbutamol HFA-152a and salbutamol HFA-134a in healthy participants after administration of single dose of 200 µg?

The primary estimand for Cohort 1 is described by the following attributes:

- The population is healthy male or female participants aged 18 to 55 years.
- The primary PK parameters endpoints are AUC(0-30min), AUC (0-∞) and Cmax.
- Treatment condition is administration of salbutamol as a single 200 µg dose, given as 2 actuations each separated by a 20-second interval, each delivering 100 µg of salbutamol (as salbutamol sulfate) as the ex-valve dose for the HFA-152a MDI or HFA-134a MDI.
- The ICEs and estimand strategies are as follows:
    - Study treatment discontinuation due to any reason (hypothetical strategy).
    - Occurrence of emesis or coughing on dosing (hypothetical strategy).
    - Dosing error: Considered less than or more than prescribed dose (hypothetical strategy).
    - Use of prohibited or rescue medication which impacts PK parameters (hypothetical strategy).

For all ICEs, interest lies in evaluating the primary PK parameters and comparisons of the ratio of 2 formulations for each of the primary PK parameters in a hypothetical scenario in which the participant had not experienced an intercurrent event. This is to minimize potential confounding of ICEs on individual PK parameters across treatment periods.

- The population level summary to be estimated is:

Ratio of adjusted GM (for logarithmic transformed values) of 2 formulations (test/ reference) with 90% CI for each primary PK endpoint.

Cohort 2:

Test: Salbutamol HFA-152a MDI 800 µg

Reference: Salbutamol HFA-134a MDI 800 µg

The primary clinical question of interest for Cohort 2 is -

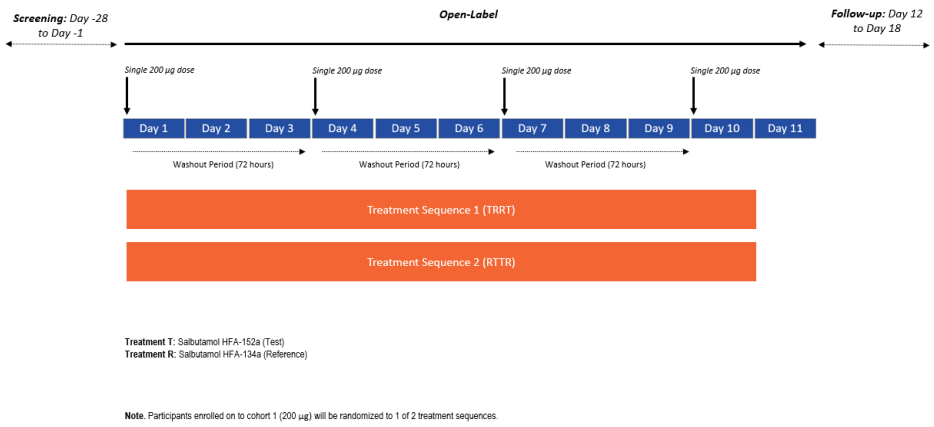
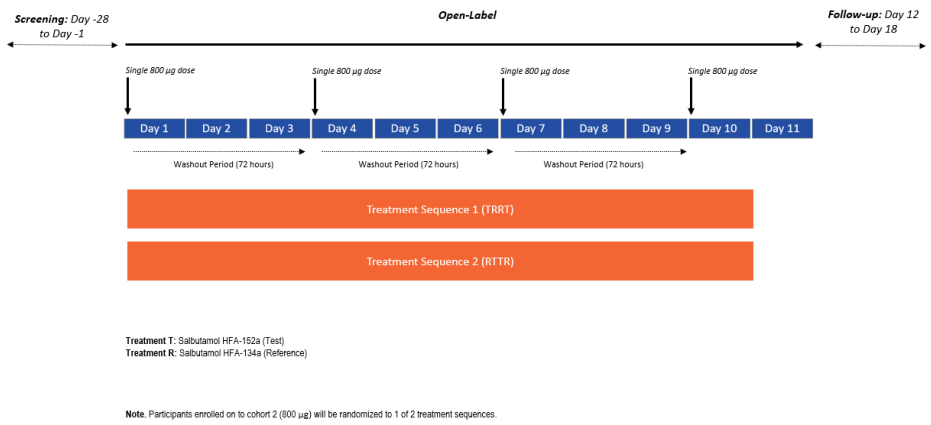
What is the GMR for Cohort 2 in primary PK parameters (AUC(0-30min), AUC(0-∞) and Cmax) of salbutamol HFA-152a and salbutamol HFA-134a in healthy participants after administration of a single dose of 800 µg?

The estimand for Cohort 2 has the same estimand attributes as Cohort 1 (population, PK endpoints, population-level summary measure, ICE strategy), except for the attribute for the treatment condition:

- Treatment condition is administration of salbutamol as a single 800 µg dose, given as 8 actuations each separated by a 20-second interval, each delivering 800 µg of salbutamol (as salbutamol sulfate) as the ex-valve dose for the HFA-152a MDI or HFA-134a MDI.

Rationale for primary estimands for both cohorts: The test formulation is being developed with an aim to have comparable PK characteristics as the reference formulation. Interest lies in the PK values obtained in the scenarios that the participant been exposed to correct dose as prescribed, and where study treatment discontinuation of the randomized sequence, the occurrence of emesis or coughing on dosing, and prohibited rescue medication usage had not occurred.

1.2. Study Design

Overview of Study Design and Key Features	
Design Features	**Figure 1- Study Design Overview (Cohort 1 – 200 µg dose)**  **Figure 2- Study Design Overview (Cohort 1 – 800 µg dose)**  • This is a randomized, open-label, single dose, 2-sequence, 2-treatment arm, 4-way cross-over (2x2x4) single-center study in healthy participants aged 18 to 55 years. Salbutamol will be administered as either a 200 µg or 800 µg dose, given as 2 or 8 actuations respectively at 20 second intervals, each delivering 100 µg as the ex-valve dose of HFA152a or HFA-134a.

Overview of Study Design and Key Features	
	• The study has planned to enroll a total of 60 participants to either Cohort 1 (200 µg) or Cohort 2 (800 µg) to ensure at least 56 participants in the PK analysis set. • Sequential enrollment approach will be followed for the study. Participants in Cohort 2 will be enrolled once participants in Cohort 1 have completed the study. • Following treatment sequences will be applied in each cohort: - Treatment Sequence 1: TRRT - Treatment Sequence 2: RTTR where T is salbutamol HFA-152a (test) and R is salbutamol HFA-134a (reference). • In Cohort 1, salbutamol will be administered as single 200 µg dose, given as 2 actuations each separated by a 20-second interval, each delivering 100 µg of salbutamol (as salbutamol sulfate) as the ex-valve dose for the HFA-152a MDI or HFA-134a MDI. In Cohort 2, salbutamol will be administered as single 800 µg dose, given as 8 actuations each separated by a 20-second interval, each delivering 100 µg of salbutamol (as salbutamol sulfate) as the ex-valve dose for the HFA-152a MDI or HFA-134a MDI. • Participants will attend a screening visit between Day -28 and Day -1. The intervention period will be 10 days with dosing on Day 1, Day 4, Day 7, and Day 10. Participants will be discharged on Day 11. There will be a follow-up period between Day 12 and Day 18.
Study treatment	• The Experimental treatment group - Salbutamol MDI inhaler containing HFA-152a propellant. • The Reference treatment group - Salbutamol MDI inhaler containing HFA-134a propellant
Study treatment Assignment	• Cohort 1 - A single 200 µg dose, given as 2 x 100 µg (ex-valve) at 20-second intervals in experimental or reference treatment group. • Cohort 2 - A single 800 µg dose, given as 8 x 100 µg (ex-valve) at 20-second intervals in experimental or reference treatment group. • Following treatment sequences will be applied in each cohort: - Treatment Sequence 1: TRRT - Treatment Sequence 2: RTTR where T is salbutamol HFA-152a (test) and R is salbutamol HFA-134a (reference).
Interim Analysis	• An interim analysis is planned for when last participant enrolled for the 200 µg (Cohort 1) completes his/her last visit.

2. STATISTICAL HYPOTHESES

2.1. Multiplicity Adjustment

No multiple adjustment will be performed for the study.

3. ANALYSIS SETS

Analysis Set	Definition / Criteria	Analyses Evaluated
Screened	• All participants who were screened for eligibility.	• All Screened Reason for Screen Failures
Enrolled	• All participants who screen passed and entered in the study (who were randomized or received treatment or underwent a post-screening study procedure) • Note screening failures (who never passed screening even if rescreened) and participants screened but never enrolled into the study (met eligibility but not needed) are excluded from the enrolled analysis set as they did not enter the study	• Study Population
FAS	• All randomized participants who received at least a single dose period of study intervention • Data will be reported according to the randomized study intervention. • Single dose = 2 puffs/actuations for Cohort 1 • Single dose = 8 puffs/actuations for Cohort 2	• Study Population • Exploratory PD objective
Safety	• All participants who received at least one puff/actuation of study intervention. • Data will be reported according to the actual study intervention.	• Estimand for secondary safety objective
Pharmacokinetic (PK)	• All participants in the FAS who had at least 1 non-missing PK assessment (NQ values will be considered as non-missing values). • Data will be reported according to the actual study intervention.	• Estimand for primary and secondary objective of PK parameters

4. STATISTICAL ANALYSES

4.1. General Considerations

The aim of the statistical analysis is to estimate the relative bioavailability of salbutamol HFA-152a (test) and salbutamol HFA-134a (reference) in the following cohorts:

Cohort 1: Salbutamol HFA-152a 200 µg, Salbutamol HFA-134a 200 µg.

Cohort 2: Salbutamol HFA-152a 800 µg, Salbutamol HFA-134a 800 µg.

No formal hypothesis will be tested in either cohort for each PK parameter (AUC(0-30min.), AUC (0-∞), Cmax and AUC(0-last)).

Statistical analysis will be presented as per estimands for primary and secondary objectives. ICEs and strategies for primary and secondary estimands are defined in Sections 1.1. and 4.3.1.1.

PK analysis will be the responsibility of CCI [redacted] CCI [redacted]. Plasma concentration-time data will be analyzed by noncompartmental methods with WinNolin 8.3.

4.1.1. General Methodology

Participants who prematurely withdraw from study will not be replaced.

Unless specified otherwise, 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. No imputation of study data will be applied. Percentages will be presented as per GSK statistical display principles.

4.1.2. Baseline and Change from Baseline Definition

Baseline definition: -

For all endpoints baseline value will be defined as per Table 1 and Table 2

Table 1 Baseline Definition for Laboratory PD and Safety Parameters and Safety Endpoints

	Baseline To be used in Analysis/Summaries			
	Period 1	Period 2	Period 3	Period 4
Laboratory PD and Safety parameters - Serum potassium (PD) and Glucose (safety) **Safety endpoints** - 12-lead ECG [1] [2] Vital Signs	Predose Day 1	Predose Day 4	Predose Day 7	Predose Day 10

[1] Taken in triplicate.
[2] Mean of the triplicate 12-lead ECG measurement from the Day 1 assessment (pre-dose).
For safety endpoints, if a pre-dose observation of day i (where i = 1,4,7 and 10) is missing in a given period, then the day-1 or screening (latest available observation) value may be used as baseline.

Table 2 Baseline Definition for Clinical Laboratory Assessment

Parameter	Study Assessments Considered as Baseline		Baseline To be used in Analysis/Summaries
	Screening/Day -28 to -1	Day -1	
Clinical Laboratory Parameters			
Hematology	x	x	Day -1
Clinical chemistry	x	x	Day -1
Urinalysis	x	x	Day -1

If day -1 clinical laboratory assessment is missing for any endpoint, then latest data prior to day -1 (pre-dose) will be considered as baseline.

If either baseline or post-baseline data is missing, then change from baseline will be set to missing at that timepoint for all parameters.

Change from baseline definition: -

Change from baseline will be calculated as given follows: -

Change from baseline = Post-randomization assessment value – Baseline assessment value at each dosing period.

4.2. Primary Endpoint(s) Analyses

Primary estimands (refer Section 1.1) for primary endpoints will be implemented for the primary analysis.

4.2.1. Definition of primary endpoints

The Primary endpoints are defined in Section 1.1.

The definitions of primary PK parameters are described in Table 3.

Table 3 Primary Pharmacokinetic Parameters

PK Parameters	Descriptions
AUC(0-30min)	Area under the plasma concentration-time curve up to 30 minutes postdose and trapezoidal methods will be used to calculate it.
AUC(0-∞)	Area under the plasma concentration-time curve from time 0 to infinity calculated as: AUC(0-∞) = AUC(0-last) +C(last)/k(el), where C_{last} is the last measurable plasma concentration and K(el) is the elimination rate constant.
Cmax	Maximum observed plasma concentration

4.2.2. Main analytical approach

The primary pharmacokinetic (PK) endpoints will be analyzed for Cohort 1 and Cohort 2 using PK analysis set.

For the log_e transformed data of AUC(0-30min), AUC(0-∞) and Cmax, descriptive statistics (N, n, GM, 95% CI of GM, SD (log_e), between- subject coefficient of variation (CV_b in %)) will be presented, where $\%CV_b=100*(SQRT(EXP(SD^2)-1))$ and SD is the standard deviation on the log_e scale.

For the untransformed data of AUC(0-30min), AUC(0-∞) and Cmax, descriptive statistics (N, n, AM, 95% CI of AM, SD) median, minimum and maximum) will be computed.

AUC (0-∞)) will be reported with <20% of AUC(0-inf) of this area coming from extrapolation. It will be acceptable to include data from profiles with >20% extrapolated if at least 80% of the profiles in the study have <20% of the of the AUC(0-inf) as extrapolated area. It will be unacceptable to use AUC(0-inf) data if >40% of the AUC has been extrapolated, except in specific situations which will be justified in the study report.

Statistical model for the analysis of primary PK parameters - AUC(0-30min), AUC(0-∞) and Cmax

For each cohort, following log_e-transformation, AUC(0-30min.), AUC(0-∞) and Cmax will be separately analyzed using mixed effect model approach with fixed effect terms for sequence, period and treatment group. Participants will be treated as random effects in the model. Factor analytic (FA(02))variance and covariance structures will be assumed. If the above model fails to converge, other covariance structures (e.g., UN, CS, AR (1), VC etc.) might be investigated. The point estimates and their associated 90% CI will then be back-transformed to provide point estimates and 90% CI for the ratios (GMR) of HFA-152a MDI (test)/HFA-134a MDI (reference).

If an intercurrent event (ICE) (as described in Section 1.1) happens during a specific treatment period, and this event affects the measurement of individual pharmacokinetic (PK) concentrations (pharmacokinetic data), then the data points for those affected individuals in the treatment period will be set to missing.

Criteria Necessary to Declare Average Bioequivalence (ABE)

If for the reference product, S_{WR} <0.294 or C_{WR}<30%, then ABE approach will be used for the acceptance range limit of BE (refer Table 4).

CCI

CCI

CCI

4.3. Secondary Endpoint(s) Analyses

Secondary PK endpoints will be analyzed using the secondary estimands (refer to Section 4.3.1.1). Secondary safety endpoints will be analyzed considering safety estimand (refer to Section 4.3.1.1).

4.3.1. Secondary endpoints

The secondary endpoints are defined in Section 1.1.

The definitions of secondary PK parameters are described in Table 5.

Table 5 Secondary Pharmacokinetic Parameters

PK Parameters	Descriptions
Tmax	Time to Cmax
t1/2	Apparent terminal phase half-life
AUC(0-last)	Area under the plasma concentration-time curve up to last time with concentrations above the LLOQ. AUC(0-last) is calculated by a combination of linear and logarithmic trapezoidal methods.

4.3.1.1. Definition of estimands

Estimand for Pharmacokinetic (PK)

Cohort 1:

Test: Salbutamol HFA-152a MDI 200 µg

Reference: Salbutamol HFA-134a MDI 200 µg

The secondary clinical question of interest for Cohort 1 is:

What is the summarized PK profile in Cohort 1 using descriptive statistics for Tmax and t1/2 and GMR for AUC(0-last) between salbutamol HFA-152a and salbutamol HFA-134a in healthy participants after administration of single dose of 200 µg?

The secondary estimand for Cohort 1 has the same estimand attributes as the primary estimand (refer Section 1.1) for Cohort 1 (population, treatment condition, ICE strategy), except for the estimand attributes of PK endpoints and population-level summary measure:

- The secondary PK parameters endpoints are Tmax, t1/2, AUC(0-last).
- The population level summaries to be estimated are:
  - AM with 95% CI for Tmax and GM with 95% CI for t1/2.
  - Ratio of adjusted GM (for logarithmic transformed values) of 2 formulations (test/reference) with 90% CI for AUC(0-last).

Cohort 2:

Test: Salbutamol HFA-152a MDI 800 µg

Reference: Salbutamol HFA-134a MDI 800 µg

The secondary clinical question of interest for Cohort 2 is -

What is the summarized PK profile in Cohort 2 using descriptive statistics for Tmax and t1/2 and GMR for AUC(0-last) between salbutamol HFA-152a and salbutamol HFA-134a in healthy participants after administration of single dose of 800 µg?

The secondary estimand for Cohort 2 has the same estimand attributes as the primary estimand (refer Section 1.1) for Cohort 2 (population, treatment condition, ICE strategy), except for the estimand attributes of PK endpoints and population-level summary measure:

- The secondary PK parameters endpoints are Tmax, t1/2, AUC(0-last).
- The population level summaries to be estimated are:
  - AM with 95% CI for Tmax and GM with 95% CI for t1/2.
  - Ratio of adjusted GM (for logarithmic transformed values) of 2 formulations (test/reference) with 90% CI for AUC(0-last).

Estimand for Intra-participant variability of pharmacokinetic (PK) parameters

Cohort 1:

Test: Salbutamol HFA-152a 200 µg

Reference: Salbutamol HFA-134a 200 µg

The secondary clinical question of interest for Cohort 1 is -

What is the intra-participant variability of the PK profile of Cohort 1 using CV_{WR} for AUC (0-30min), AUC (0-∞), Cmax and AUC (0-last) PK parameters for salbutamol HFA-152a and salbutamol HFA-134a in healthy participants after administration of a single dose of 200 µg?

This secondary objective is to establish whether either the reference or test product is considered a high variable product at the 200 µg dose level (CV_{WR}>30%).

The secondary estimand for Cohort 1 has the same estimand attributes as the primary estimand for Cohort 1 (population, treatment condition, ICE strategy), except for the estimand attributes of PK endpoints and population-level summary measure:

- The secondary PK parameters endpoints for HFA-152a (test) and HFA-134a (reference) are:
  - Intra-participants variability in AUC(0-30min)
  - Intra-participants variability in AUC(0-∞)
  - Intra-participants variability in Cmax
  - Intra-participants variability in AUC(0-last)
- The population level summaries to be estimated for HFA-152a (test) and HFA-134a (reference) are:
  - Intra(within)- participants CV_{WR} (%) for AUC(0-30min), AUC(0-∞), Cmax and AUC(0-last)

Cohort 2:

Test: Salbutamol HFA-152a 800 µg

Reference: Salbutamol HFA-134a 800 µg

The secondary clinical question of interest for Cohort 2 is -

What is the intra-participant variability in PK profile of Cohort 2 using CV_{wR} for AUC(0-30min), AUC(0-∞), Cmax and AUC(0-last) PK parameters for salbutamol HFA-152a and salbutamol HFA-134a in healthy participants after administration of single dose of 800 µg?

This secondary objective is to establish whether either the reference or test product is considered a high variable product at the 800 µg dose level (CV_{WR} >30%).

The secondary estimand for Cohort 2 has the same estimand attributes as the primary estimand for Cohort 2 (population, treatment condition, ICE strategy), except for the estimand attributes of PK endpoints and population-level summary measure:

- The secondary PK parameters endpoints for HFA-152a (test) and HFA-134a (reference) are:
  - Intra-participants variability in AUC(0-30min)

- Intra-participants variability in AUC(0-∞)
- Intra-participants variability in Cmax
- Intra-participants variability in AUC(0-last)

- The population level summaries to be estimated for HFA-152a (test) and HFA-134a (reference) are:
  - Intra(with-in)- participants CV_{WR} (%) for AUC(0-30min), AUC(0-∞), Cmax and AUC(0-last)

Rationale for supporting secondary estimands of PK parameters for both cohorts:
Rational for supporting secondary estimands of PK parameters for both cohorts is the same as primary estimands (refer Section 1.1).

Estimands for Safety

Cohort 1:

Test: Salbutamol HFA-152a MDI 200 µg

Reference: Salbutamol HFA-134a MDI 200 µg

The clinical question of interest for the safety secondary objective in Cohort 1 is -

What is the safety and tolerability profile of single doses 200 µg of salbutamol in Cohort 1 healthy participants delivered via MDIs?

The secondary safety estimand for Cohort 1 is described by the following attributes:

- The population is healthy male or female participants aged 18 to 55 years.
- The secondary safety endpoints are:
  - Incidence of AEs and SAEs
  - Absolute values for 12-lead ECGs recording of HR and QTc intervals at each assessed visit
  - Change from baseline for postdose 12-lead ECGs recording of HR and QTc intervals at each assessed visit
  - Absolute values of clinical laboratory parameters at each assessed visit
  - Absolute values of vital signs (systolic and diastolic blood pressure and pulse rate) at each assessed visit.
- Treatment condition is administration of salbutamol as a single 200 µg dose, given as 2 actuations each separated by a 20-second interval, each delivering 100 µg of salbutamol (as salbutamol sulfate) as the ex-valve dose for the HFA-152a MDI or HFA-134a MDI.
- The ICEs and estimand strategies are as follows:

  - Study treatment discontinuation due to any reason (treatment policy strategy). Interest lies in the group of participants irrespective of whether they completed the study intervention.
  - Occurrence of emesis or coughing on dosing (treatment policy strategy).
  - Dosing error: Considered less than or more than prescribed dose (treatment policy strategy).
  - Use of prohibited or rescue medication which impacts the PK parameters (Treatment policy strategy).
- The population level summaries to be estimated are:
  - Number and percentages for incidence of AEs and SAEs
  - Mean of absolute values for 12-lead ECGs recording of HR and QTc intervals at each assessed visit
  - Mean of change from baseline values for postdose 12-lead ECGs recording of HR and QTc intervals at each assessed visit
  - Mean of absolute of clinical laboratory parameters including vital signs (systolic and diastolic blood pressure and pulse rate) at each assessed visit

Cohort 2:

Test: Salbutamol HFA-152a MDI 800 µg

Reference: Salbutamol HFA-134a MDI 800 µg

The clinical question of interest for the safety secondary objective in Cohort 2 is -

What is the safety and tolerability profile of single doses 800 µg of salbutamol in Cohort 2 healthy participants delivered via MDIs?

The secondary safety estimand for Cohort 2 has the same estimand attributes as Cohort 1 (population, PK endpoints, population-level summary measure, ICE strategy), except for the attribute for the treatment condition:

- Treatment condition is administration of salbutamol as a single 800 µg dose, given as 8 actuations each separated by a 20-second interval, each delivering 100 µg of salbutamol (as salbutamol sulfate) as the ex-valve dose for the HFA-152a MDI or HFA-134a MDI.

Rationale for estimands supporting secondary safety objectives in both cohorts: This is a study in healthy volunteers with short follow-up duration. Therefore, all AEs, SAEs, 12 lead ECGs, laboratory parameters and vital signs data are of interest, regardless of ICEs to support completeness of reporting and transparency of the clinical study.

Counts and Percentages will be presented for intercurrent events for primary and secondary endpoints.

4.3.1.2. Main analytical approach

The secondary pharmacokinetic (PK) endpoints will be analyzed for Cohort 1 and Cohort 2 using PK analysis set.

For the log_e transformed data of t1/2 and AUC(0-last), descriptive statistics (N, n, GM, 95% CI of GM, , SD (log_e), between- subject coefficient of variation (CV_b in %)) will be presented, where $\%CV_b=100*(SQRT\ (EXP(SD^2)-1))$ and SD is the standard deviation on the log_e scale.

For the untransformed data of Tmax, t1/2 and AUC(0-last), descriptive statistics (N, n, AM, 95% CI of AM, SD, median, minimum, and maximum) will be presented. All PK parameters will be summarized by study treatment.

Statistical model for the analysis of secondary PK endpoint - AUC(0-last)

For each cohort, following log_e-transformation, AUC(0-last) will be analyzed using a mixed effect model approach with fixed effect for sequence, period, treatment group and participants as random effects. Factor Analytic (FA(02)) variance and covariance structures will be assumed. If the above model fails to converge, other covariance structures (e.g. UN, CS, AR (1), VC etc.) might be investigated. The point estimates and their associated 90% CI will then be back-transformed to provide point estimates and 90% CI for the ratios (GMR) of HFA-152a MDI (test)/HFA-134a MDI (reference).

Statistical model for estimating the intra-participants (with-in) variability for PK parameters – AUC (0-30min), AUC (0-∞), Cmax and AUC (0-last)

For each cohort, following log_e-transformation, AUC (0-30min.), AUC (0-∞), Cmax and AUC (0-last) will be analyzed using a mixed effect model approach with fixed for period, treatment group and participants as random effects. Factor Analytic (FA(02)) variance and covariance structures will be assumed. If the above model fails to converge, other covariance structures (e.g. UN, CS, AR (1), VC etc.) might be investigated. SD in log_e scale and coefficient of variation (CV_{WR})for intra (within)-participants will be computed, where $\%CV_{WR}=100*(SQRT\ (EXP\ (\sigma^2_{wR})-1))$ and σ^2_{wR} is the mean squares error (MSE) or residual in log_e scale from the statistical mixed model.

Statistical model for estimating the inter-participants (intra participants for test and reference) variability for PK parameters – AUC (0-30min), AUC (0-∞), Cmax and AUC (0-last)

For each cohort, following log_e-transformation, AUC (0-30min.), AUC (0-∞), Cmax and AUC (0-last) will be analyzed using a mixed effect model approach with fixed for period, treatment group and treatment group as random effects. Factor Analytic (FA(02)) variance and covariance structures will be assumed. If the above model fails to converge, other covariance structures (e.g. UN, CS, AR(1), VC etc.) might be investigated. SD in log_e scale and coefficient of variance (CV) for inter-participants will be calculated.

- Total participants variability will be calculated as the sum of intra (within)-participants and inter-participants variability.

If an intercurrent events (ICEs) (as described in Section 4.3.1.1 - intra-participants variability of PK parameters) happens during a specific treatment period, and this event affects the measurement of individual pharmacokinetic (PK) concentrations (pharmacokinetic data), then the data points for those affected individuals in the treatment period will be set to missing.

Graphs for Pharmacokinetic (PK) parameters -

- Individual plasma concentration - time plots (linear and semi-logarithmic) by subjects
- Individual plasma concentration - time plots (linear and semi-logarithmic) by treatment group
- Median (range) plasma concentration - time plot (linear and semi-logarithmic) by treatment group
- Mean (± SD) plasma concentration - time plots (linear and semi-logarithmic) by treatment group
- Mean (± SD) plasma concentration - time plots (linear and semi-logarithmic)

To present the descriptive statistics and plots for PK parameters, refer the GSK statistical analysis SOPs.

Listing for PK concentration and PK parameters (AUC(0-30min), AUC(0-∞), Cmax, Tmax, t1/2 and AUC(0-last)) will be generated using PK analysis set.

4.3.2. Handling missing data of PK parameters

CCI [redacted] CCI [redacted] (refer protocol Section 8.5 for detailed information). Refer GSK statistical analysis SOPs for the rules of handling missing PK parameters data and below LLOQ value.

Outliers - Any participants excluded from the summaries and/or statistical analyses will be documented along with the reason for exclusion in the clinical study report.

4.4. Exploratory Endpoint(s) Analyses

The exploratory pharmacodynamics (PD) endpoints are -

- Minimum serum potassium
- MHR
- Maximum QTc interval

The exploratory pharmacodynamics (PD) endpoints will be analyzed for Cohort 1 and Cohort 2 using FAS. All PD parameters will be summarized by study treatment.

Statistical model for the analysis of exploratory PD endpoints in each cohort

Following log_e-transformation, minimum serum potassium, MHR and maximum QTcF interval will be analyzed using mixed effect model approach with fixed effect for period, treatment group. The point estimates and their associated 90% CI will then be back-transformed to provide point estimates and 90% CI for the ratios (GMR) of HFA-152a MDI (test)/HFA-134a MDI (reference).

For the untransformed data of pharmacodynamics (PD) parameters (minimum serum potassium, MHR (Maximum HR, maximum QTc interval)), descriptive statistics (N, n, AM, 95% CI of AM, SD) median, minimum and maximum) will be computed for FAS.

4.5. Safety Analyses

Safety analysis set will be used for the analysis of safety endpoints. Secondary safety estimand to analyses safety endpoints (refer Section 4.3.1.1.) will be implemented for Cohort 1 and Cohort 2. Safety analysis will be summarized by study treatment.

Details of the planned displays for safety data are provided in Output programming specifications (OPS) and will be based on GSK Data Standards and statistical principles.

4.5.1. Extent of Exposure

The exposure data will be reported for Cohort 1 and Cohort 2.

For each treatment and period, dose administration and exposure data for all participants will be generated in the listing for Safety analysis set.

4.5.2. Adverse Events

The applicable definition of an AE and SAE are in the study protocol Sections 8.4 and 10.3.

All reported AEs will be coded using the standard GSK dictionary, (MedDRA ≥ 26.1 version).

An AE is considered study treatment emergent (on-treatment) if the AE onset date is on or after study treatment start date and on or before study treatment stop date plus 1 day (inclusive) follow-up or worsens (change in AE severity from lower severity to higher severity category) relative to the pre-study treatment state.

AEs occurring following dosing in a specific period but before dosing in the next period will be attributed to that specific period. If the time is missing for an AE on a dosing day then the AE will be attributed to the treatment given on that day.

Overview of AEs:

The following points will be presented in a summary table for overview of AEs in overall (on and post-treatment) and on-treatment period.

- Total number of AEs reported with the number of participants who experienced at least one AE
- AE by maximum severity intensity
- Drug-related AE and SAE, non-fatal SAE, drug-related non-fatal SAE
- SAE leading to death
- AE leading to discontinuation of study treatment and AE leading to withdrawal from study

AEs and SAEs by SOC and PT:

The below summaries (counts and percentages) will be produced for AEs and SAEs by system organ classes (SOC) and (PT) for overall (on- and post-treatment) and on-treatment period.

- Summary of AEs by SOC and PT
- Summary of SAEs by SOC and PT
- Summary of SAEs by SOC and PT with number of subjects and occurrences

Common AEs:

The following summaries (counts and percentages) will be displayed for common (≥10% incidence, before rounding) AEs for overall (on- and post-treatment) and on-treatment period.

- Summary of common (>=10%) AEs by PTs
- Summary of common (>=10%) Non-SAEs by SOCs and PTs with number of subjects and occurrences

AEs and SAEs related to study treatment:

Relationship to study treatment, as indicated by the investigator, is classified as “not related” or “related”. AEs with a missing relationship to study treatment will be recorded as “related” to study treatment. If a participant reports the same AE more than once within an SOCs/PTs, the AE with the worst-case relationship to study treatment will be used in the corresponding relationship summaries.

The following summaries (counts and percentages) will be presented for drug-related AEs and SAEs for on-treatment period.

- Summary of drug-related AEs by overall frequency
- Summary of drug-related SAEs by overall frequency

Summary of serious fatal and non-fatal drug-related AEs will be generated by overall frequency. Summary of non-serious drug-related AEs by overall frequency will also be created.

AEs and SAEs by severity:

Adverse event severity is categorised as mild, moderate, severe. Adverse events starting after the first dose of study treatment with a missing severity will be classified as severe. If a participant reports an AE more than once within an SOCs/PTs, the AE with the worst-case (maximum) severity will be used in the corresponding severity summaries.

The following summaries (counts and percentages) will be produced for severity of AEs and SAEs by SOCs, PTs, and maximum severity in overall (on- and post-treatment) and on-treatment period.

- Summary of AEs by SOC and PT and maximum severity
- Summary of SAEs by SOC and PT and maximum severity

The below summaries (counts and percentages) for AEs and SAEs leading to permanent discontinuation of study treatment by SOCs and PTs will be generated in overall (on- and post-treatment) and on-treatment period.

- Summary of AEs leading to permanent discontinuation of study treatment or withdrawal from study by SOC and PT
- Summary of SAEs leading to permanent discontinuation of study treatment or withdrawal from study by SOC and PT

Adverse events analyses including the analysis of AEs and SAEs will be based on GSK Core Data Standards.

Separate listings will be produced of all AEs for each treatment and period in Safety analysis set. Summary of death will be summarized and participants profile for death will also be listed using Enrolled participants.

In summary tables, SOCs will be sorted in descending order of the total incidence then alphabetically, PTs will be sorted in descending order of the total incidence then alphabetically within the SOC.

For completely missing or partial missing AE start date or end date, imputation rules will be applied following Appendix 2 Section 6.2.6.

4.5.2.1. Adverse Events of Special Interest

No adverse events of special interest (AESI) are identified for the study therefore no statistical analysis will be perfomed for AESI.

4.5.3. Additional Safety Assessments (if applicable)

4.5.3.1. Laboratory Data

Laboratory evaluations including the analyses of chemistry laboratory tests, hematology laboratory tests and urinalysis will be as per below described Table 6 (refer protocol Appendix 2, Section 10.2).

Table 6 Parameters of laboratory tests assessments

Laboratory Tests	Parameters	
Hematology	• Platelet count	
	• Red blood cell (RBC) count	
	RBC indices	• Mean corpuscular volume (MCV) • Mean corpuscular hemoglobin (MCH) • %Reticulocytes
	Absolute WBC count with differential:	• Neutrophils • Lymphocytes • Monocytes • Eosinophils • Basophils
	• **Hemoglobin**	
	• **Hematocrit**	
Clinical chemistry	• Blood urea nitrogen (BUN)/Urea • Potassium** • Creatinine* • Sodium • Calcium • Glucose fasting** • Creatine phosphokinase(CPK)	• Aspartate aminotransferase (AST)/serum glutamic-oxaloacetic transaminase (SGOT) • Alanine aminotransferase (ALT)/serum glutamic-pyruvic transaminase (SGPT) • Alkaline phosphatase • Total bilirubin • Direct bilirubin • Total protein
Routine urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, [bilirubin, urobilinogen, nitrite, leukocyte esterase] by dipstick • Microscopic examination. Please note, this will only be performed if there is an abnormality in accordance with Clinical Laboratory standard procedures. • Microscopic examination (if blood or protein is abnormal) o Epithelial cells o Red Blood cells o WBC o Casts o Crystals o Culture (if positive: specify pathogen)	

* To assess the kidney function, use eGFR 2021 calculator (CKD-Epi creatinine equation). eGFR (based on CKD-Epi) will be measured at all time points when creatinine is measured.

** Blood sampling for serum potassium and glucose on each dosing day (Day 1, 4, 7 and 10) and at the following time points: predose and 15 and 30 minutes, 1, 1.5, 2 and 4 hours post dose.

Descriptive statistics (n, mean, standard deviation (SD), median, minimum value (min), and maximum value (max)) will be presented for quantitative measurements of absolute value for continuous laboratory parameters (clinical chemistry and hematology) including serum potassium and glucose at baseline and each assessed visit as per SOA of protocol in on-treatment period for Safety analysis set. Counts and percentages will be produced for qualitative measurements measure laboratory parameters for on-treatment period for Safety analysis set.

As per protocol SOA Section 1.3, safety laboratory parameters data are not collected for follow up visit, therefore on-treatment period will be same as overall period.

Summary of liver monitoring/stopping event will be summarized by counts and percentages. Refer to protocol Appendix 5, Section 10.5 Liver safety for more description of liver events.

Participants listing of all clinical laboratory data will be produced for each treatment and period in Safety analysis set.

If a laboratory value which is expected to have a numeric value for summary purposes, has a non-detectable level reported in the database, where the numeric value is missing, but typically a character value starting with '<=' or '=>' (or indicated as less than x or greater than x in the comment field) is present, the number of significant digits in the observed values will be used to determine how much to add or subtract in order to impute the corresponding numeric value.

- Example 1: 2 significant digits = '<= x' becomes x – 0.01
- Example 2: 1 significant digit = '=> x' becomes x + 0.1
- Example 3: 0 significant digits = '<=x' becomes x – 1

4.5.3.2. Vital Signs

The following vital signs measurements will be measured in a supine position after 5 minutes rest at baseline and each assessed visit.

- Systolic and Diastolic blood pressure
- Pulse rate

Descriptive statistics (n, mean, standard deviation (SD), median, minimum value (min), and maximum value (max)) will be presented at baseline, absolute value of vital signs parameters at each assessed visit for on-treatment period for Safety analysis set.

As per protocol SOA Section 1.3, safety vital signs data are not collected for follow up visit, therefore on-treatment period will be same as overall period.

Participants listing for all vital signs data will be produced for each treatment and period in Safety analysis set.

4.5.3.3. ECG

The arithmetic mean of the three recorded 12-lead ECGs measurements will be presented in all data summaries of 12-lead ECGs measurements at predose and single measurement of post dose for days 1, 4, 7 and 10 and discharge. ECG measurements will be recorded, including heart rate (HR), PR interval, QRS duration, QT interval, and RR interval. QT intervals will be based on Fridericia's formula and reported as per captured in eCRF:

Descriptive statistics (n, mean, standard deviation (SD), median, minimum value (min), and maximum value (max)) will be presented at baseline, and absolute and change from baseline for HR, QTc and other ECG parameters at each assessed visit for on-treatment period for Safety analysis set.

As per protocol SOA Section 1.3, safety ECG data are not collected for follow up visit, therefore on-treatment period will be same as overall period.

Participants listings will be provided for all 12 lead ECGs values and findings including abnormal ECGs for each treatment sequence and period in Safety analysis set.

4.6. Other Analyses

No other analysis will be performed for the study.

CCI [redacted]

CCI [redacted]

4.8. Changes to Protocol Defined Analyses

CCI [redacted]

5. SAMPLE SIZE DETERMINATION

Up to 60 healthy participants will be enrolled to either Cohort 1 (200 µg) or Cohort 2 (800 µg) to achieve at least 56 participants in the PK analysis set.

For each cohort, 30 healthy participants will be randomly assigned to a cohort to ensure at least 28 participants are included in the PK analysis set with 15 randomized to each treatment sequence.

The target number of participants in each cohort is chosen to achieve half width (refer Table 7) of the 90% CI, in the estimate of the geometric mean ratios for the primary endpoints (AUC (0-30 min.), AUC (0-inf) and Cmax).

In the previously conducted 219430 pilot PK study, there was considerable interest in AUC (0-30 min) due to larger than expected observed differences between test and reference product, in addition to observing potentially higher amounts of intra-subject variability that would classify the product as highly variable (~30%). Though, less variability was observed among AUC (0-inf) and Cmax. Due to uncertainty of what the true CV_{WR} may be for both the reference and test products, this current study therefore has considered a more conservative assumption accounting for up to 50% intra subject variability (CV_{WR}) in PK parameters, with a particular interest in AUC (0-30 min).

Therefore, a sample size 28 in each cohort, assuming intra subject variability (CV_{WR}) of 50% in AUC (0-30 min.), the half width of the upper bound of the 90% CI for observed GMR (T/R) is 16.44% (refer Table 7).

For example, if the geometric ratio between test and reference is 1.06 for n=28 and CV_{WR} = 50%, then the upper bound of the 90% CI for observed treatment ratio is 1.06*(1+0.1644) = 1.23 and the lower bound is 1.06/(1+0.1644) = 0.91 (refer Table 8).

Table 7 Sample sizes with varying intra subject variability and associated half-widths of the 90% CI of the observed treatment ratio

CCI

CCI

Table 8 Sensitivity Table

CCI

6. SUPPORTING DOCUMENTATION

6.1. Appendix 1 Study Population Analyses

The study population analyses will be based on the FAS or Enrolled participants, unless otherwise specified. A summary of the number of participants in each of the participant level analysis set will be provided.

Study population analyses will be included in analyses of participant disposition, protocol deviations, demographic and baseline characteristics, prior and concomitant medications etc. based on GSK Core Data Standards. Study population analyses will be performed for each Cohort 1 and Cohort 2 separately.

6.1.1. Participant Disposition

Participant disposition will be tabulated by each treatment sequence, each period (with primary reason for withdrawal including washout period) for all participants combined with the counts and percentages of participants who complete the study, prematurely withdraw, and the reason for study withdrawal for Enrolled participants. Participants disposition will also be summarized for FAS if the difference finds between Enrolled and FAS participants.

Summary of treatment status and reasons for discontinuation of study treatment will be produced for study treatment, with the number of participants who completed study

treatment, or prematurely discontinued treatment, and the primary reasons for treatment discontinuation tabulated for the FAS.

Participant listing of the reasons for study withdrawal will be provided for each treatment sequence and period in enrolled participants.

Summary of screen failure and its reason as per eCRF will be provided for overall (Total) screened participants.

Table will be generated for summarizing the number of participants in each analysis set for all participants who provided informed consent. Listing of participants excluded from any analysis set will also be produced for Enrolled participants. Listing of planned and actual treatment will also be generated.

6.1.2. Demographic and Baseline Characteristics

Demographic characteristics and baseline characteristics such as age, age group, sex, race, ethnicity, childbearing potential, height, weight, and body mass index (BMI) will be summarized and tabulated by treatment sequence and overall (Total) using participants in Enrolled participants. Demographic characteristics and baseline will also be summarized for FAS if the difference finds between Enrolled and FAS participants.

Listing for demographic characteristics will be produced in FAS for each treatment sequence.

Descriptive statistics will be presented for age, height, weight, and BMI. Counts and percentages will be presented for age group (≥18 - ≤55 years), sex, race, ethnicity, childbearing potential.

6.1.3. Protocol Deviations

Important protocol deviations will be summarized using FAS. Listing of important protocol deviation will also be generated for each treatment and period in FAS.

A summary of inclusion and exclusion criteria will be produced for FAS in overall (Total) participants.

Listing for participants with inclusion/exclusion criteria deviations will be generated for each treatment sequence in FAS.

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 treatment details) are captured and categorized 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

Prior and Concomitant medications will be coded using WHO Drug dictionary version on or after Global B3 Sept 2023.

The counts and percentages of participants reporting each concomitant medication will be presented by study treatment sequence for FAS.

A medication will be summarized in each study period (pre/on/post) in which it was taken, so a concomitant medication that was started in the screening and stopped during active treatment will appear in both the pre-treatment and the on-treatment tables.

Concomitant medications include any medication that was taken at some point during the on-treatment period as defined in Section 6.9 of the protocol.

Participants listing of concomitant medication will also be generated for FAS.

6.1.5. Medical History and Current Medical Conditions

Summary (number and percentage) for medical history and current medical conditions will be presented by study treatment sequence for each body system of participants for FAS.

6.1.6. Study Treatment Compliance

The Cohort 1 and Cohort 2 of the study design is **single** dose 2-sequence, 2-treatment, 4-way cross-over so summary statistics will not be produced for study intervention compliance however listing for dose administration will be created along with exposure data (refer Section 4.5.1).

6.2. Appendix 2 Data Derivations Rule

6.2.1. Criteria for Potential Clinical Importance

The potential clinical importance (PCI) criteria will not be applicable for the study.

6.2.2. Study Period

Assessments and events will be classified within each cohort according to the time of occurrence relative to the study treatment period (days).

Pre-Treatment: For the presentation of serious adverse events (SAEs), concomitant medications, and other assessments in pre-treatment is defined as -

Date of assessment < Study treatment start date of period 1 (day 1).

On-Treatment: For the presentation of adverse events (AEs), serious adverse events (SAEs), concomitant medications, 12-lead ECG, vital signs, and other assessments in on-treatment is defined as -

Study treatment start date of period 1 (day 1) <= Date of assessment <=Study treatment stop date of period 4 (Day 10) or early withdrawal + 1 day

Worsening in AE (change in AE severity from lower severity to higher severity category) relative to the pre-study treatment state will also be considerd as on-treatment AE.

If time of assessment or study treatment is not collected (missed), the following assessment on the first dose date will be assumed to be taken prior to the first dose and therefore considered pre-treatment.

As per study design, Four Treatment Periods of the study are defined below.

Treatment Period 1 (Day1):

Treatment Period 1 dose start time<= Treatment Period 1< Treatment Period 2 dose start time

Treatment Period 2 (Day4):

Treatment Period 2 dose start time<= Treatment Period 2< Treatment Period 3 dose start time

Treatment Period 3 (Day7):

Treatment Period 3 dose start time<= Treatment Period 3< Treatment Period 4 dose start time

Treatment Period 4 (Day10):

Treatment Period 4 dose start time<= Treatment Period 4< Treatment Period 4 dose start time +1 day

Post-Treatment: For the presentation of adverse events (AEs), serious adverse events (SAEs), concomitant medications,12-lead ECG, vital signs and laboratory assessments in post-treatment is defined as

> Date of assessment > Study treatment stop date of period 4 (Day 10) or early withdrawal + 1 day.

Please refer Section 6.2.6 for handling of missing and partial dates of assessments.

6.2.3. Study Day and Reference Dates

CCI [redacted]

CCI

[redacted]

6.2.4. Assessment Window

Protocol assessment window as defined in protocol Section 1.3 will be followed for the statistical analysis.

6.2.5. Multiple measurements at One Analysis Time Point

When triplicate 12-lead ECG assessments are taken, the mean of the 3 measurements will be calculated first and summary statistics will be based on the calculated mean.

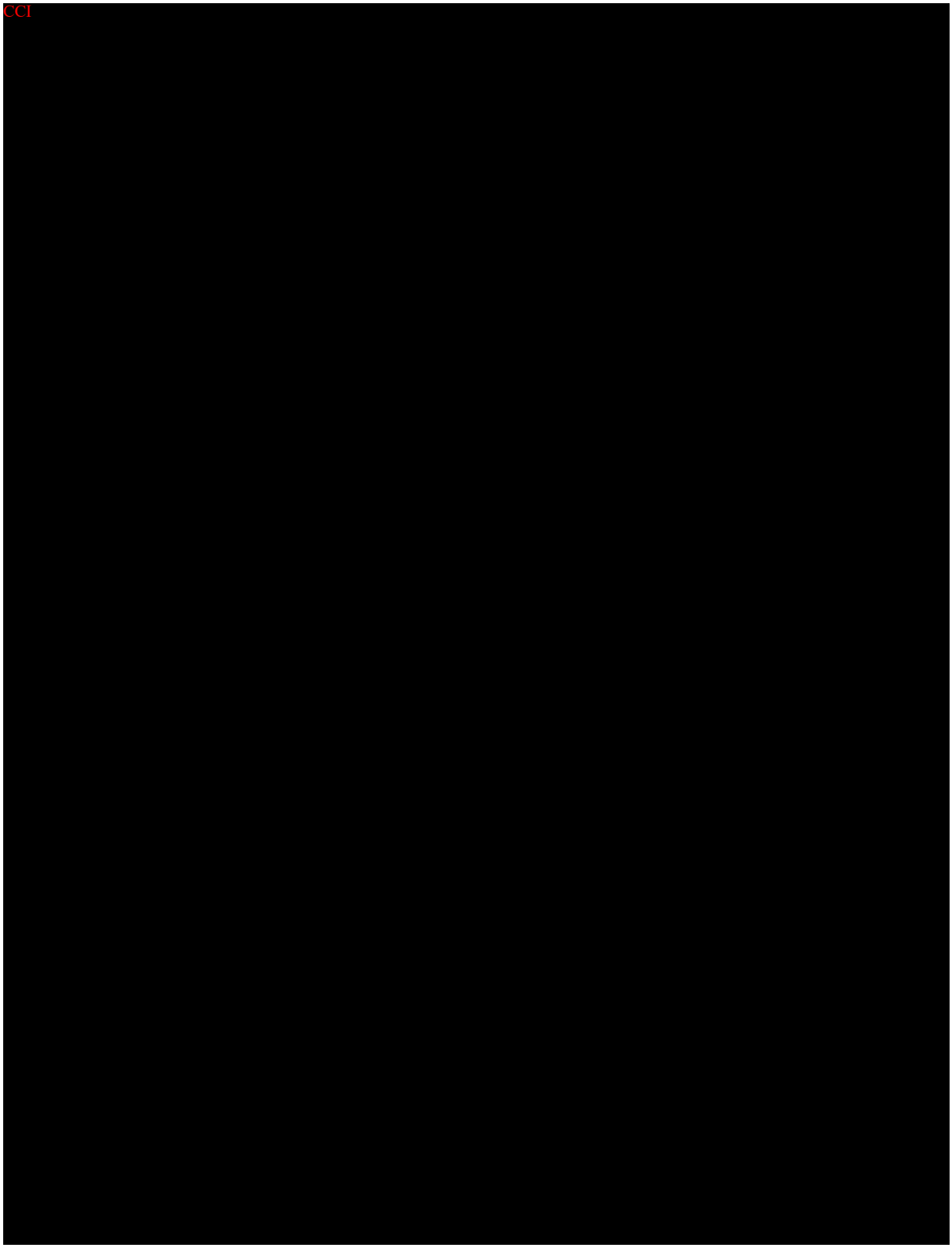
If multiple assessments are taken from the same type for lab parameter or other assessments, the worst case will be used.

6.2.6. Handling of Partial Dates

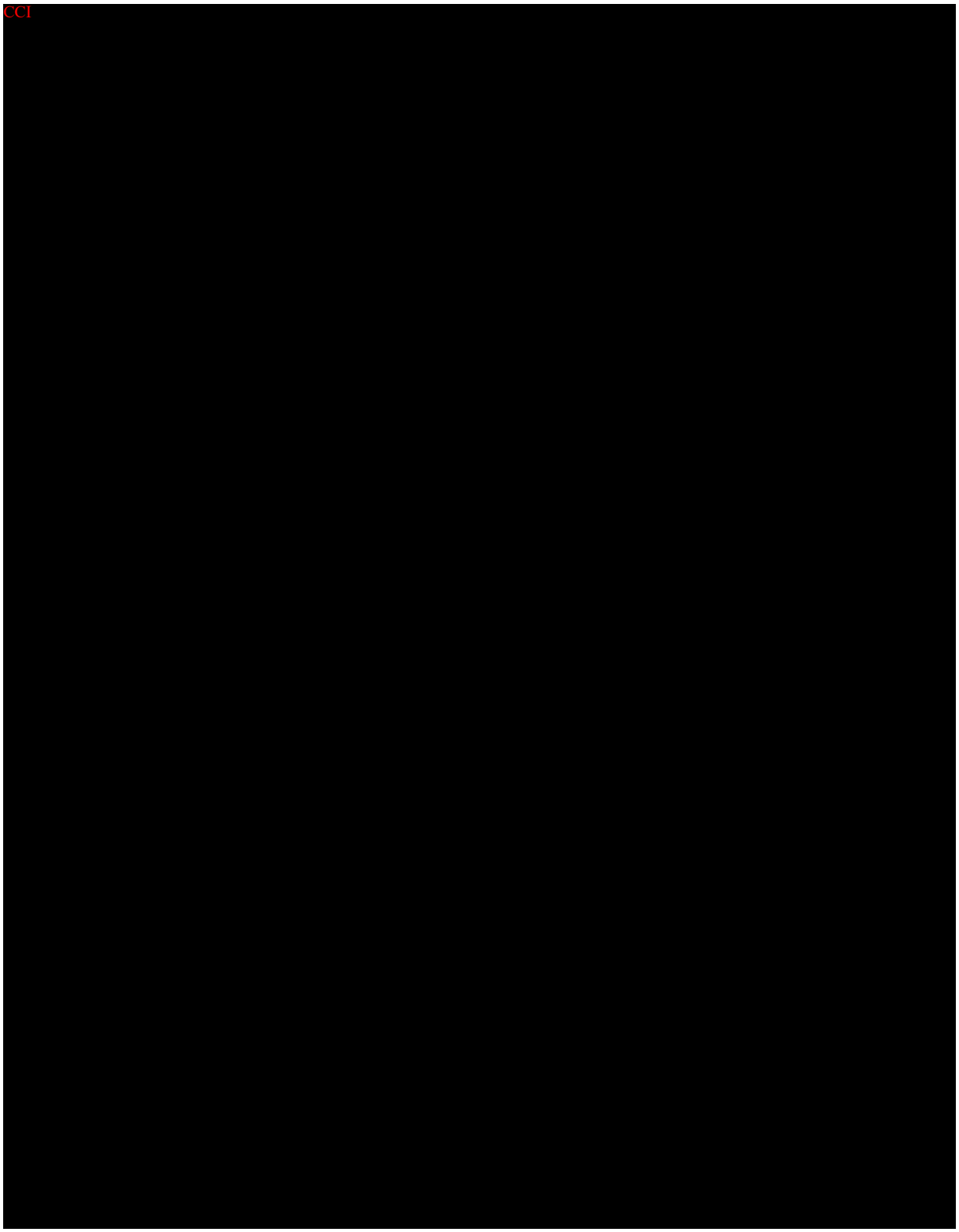
CCI

[redacted]

CCI



CCI



6.2.7. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
METEOR

Trademarks not owned by the GlaxoSmithKline Group of Companies
MedDRA
SAS
WinNonlin

6.3. Appendix 3 List of Abbreviations and Definitions of Terms

Abbreviation	Definition
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine transaminase
AM	Arithmetic mean
AST	Aspartate aminotransferase
AUC (0-∞)	Area under the curve (from zero to infinity)
AUC(0-last)	Area under the curve (from zero to last)
BMI	Body mass index
CI	Confidence intervals
Cmax	Maximum plasma concentration
COVID-19	Coronavirus disease 2019
CPK	Creatine phosphokinase
CRF	Case report form
CSR	Clinical study report
CVb	Between subject coefficient of variation
CVw	Within subject coefficient of variation
ECG	Electrocardiogram
eCRF	Electronic case report form
eGFR	Estimated Glomerular Filtration Rate
EMA	European Medicines Agency
FAS	Full analysis set
FDA	Food and Drug Administration, United States of America

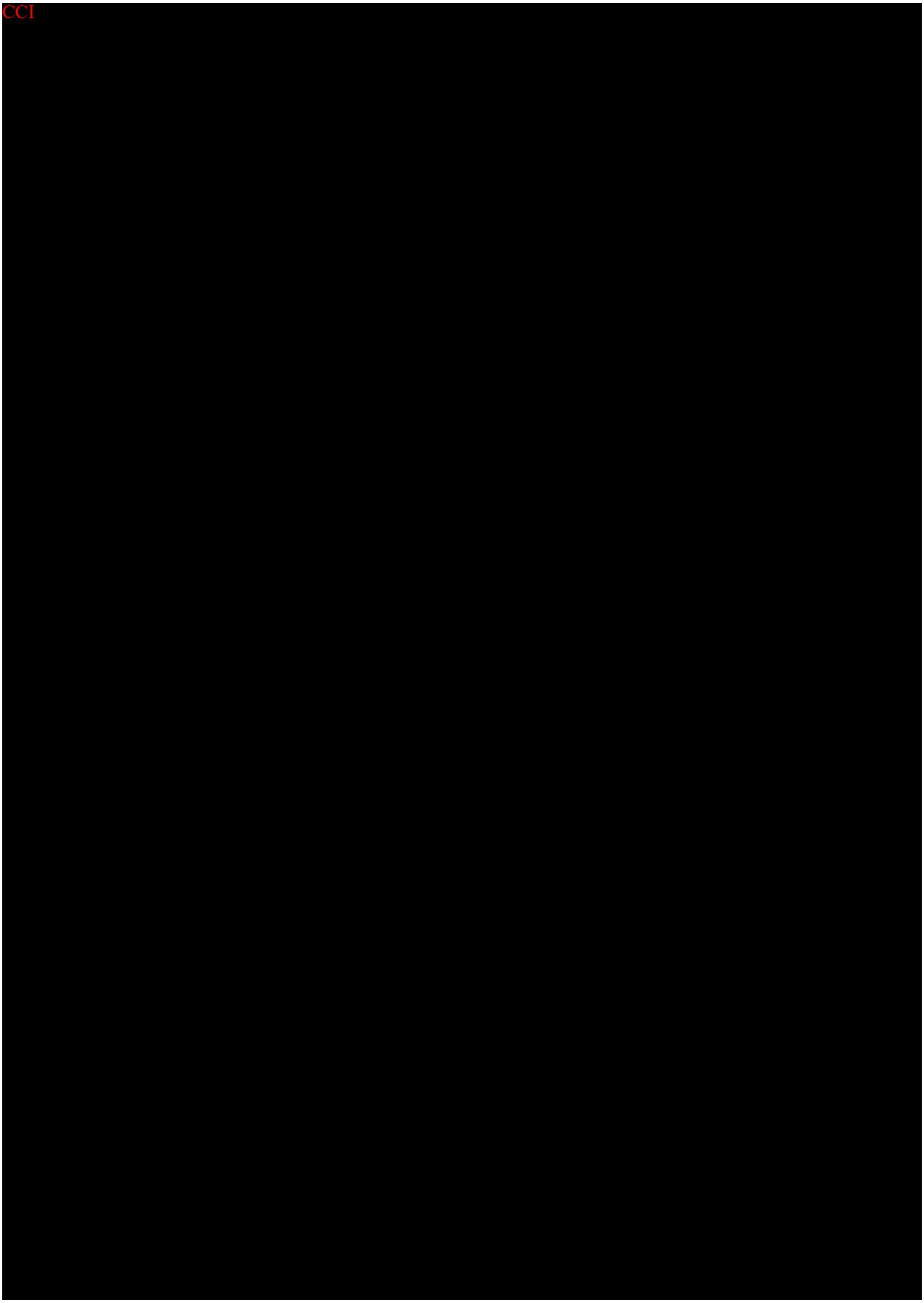
Abbreviation	Definition
FSFV	First subject first visit
GCP	Good Clinical Practice
GM	Geometric mean
GMR	Geometric mean ratio
HBsAg	Hepatitis B surface antigen
HFA	Hydrofluoroalkane
HFA-134a	1,1,1,2-tetrafluoroethane
HFA-152a	1,1-difluoroethane
HIV	Human immunodeficiency virus
HR	Heart rate
ICE	Intercurrent event
ICF	Informed consent form
ICH	International Council for Harmonisation
IDSL	Integrated Data Standards Library
LLOQ	Lower Limit of Quantification
LSLV	Last Subject Last Visit
MDI	Metered Dose Inhaler
MedDRA	Medical Dictionary for Regulatory Activities
MHR	Maximum Heart Rate
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PR	Pulse Rate
QTc	Corrected QT interval

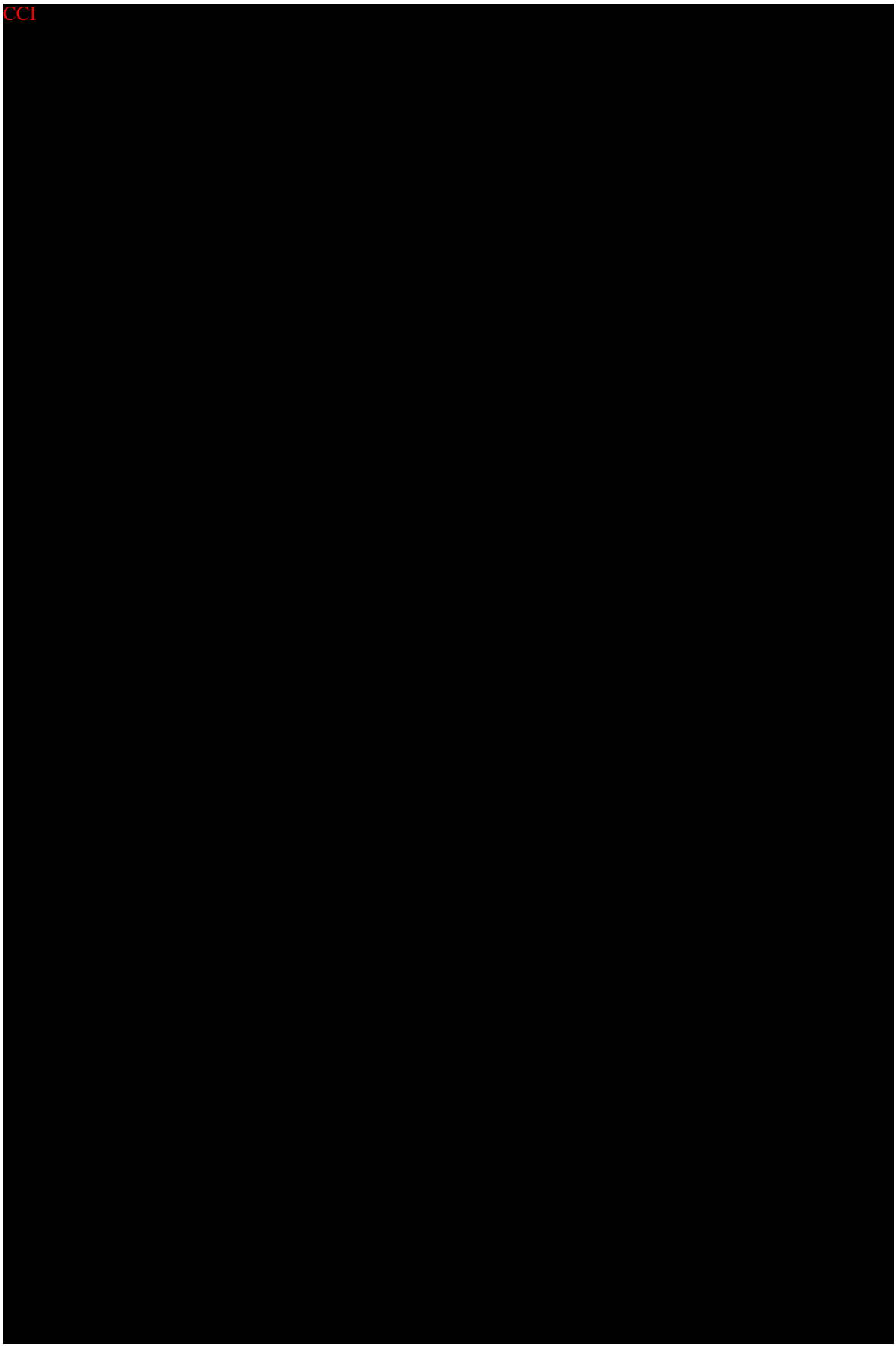
Abbreviation	Definition
QTcF	QT interval corrected using Fridericia's formula
RR	Respiratory Rate
RSABE	Reference-scaled average bioequivalence
SADE	Serious adverse device effect
SAE	Serious adverse event
SD	Standard Deviation
SE	Standard Error
SmPC	Summary of product characteristics
SoA	Schedule of activities
TEAE	Treatment-emergent adverse event
Tmax	Time to reach maximum plasma concentration
ULN	Upper limit of normal
WHO	World Health Organization

6.4. Appendix 4 Standard Error (SE) Calculation for 2x2x4 Full Replicate Design

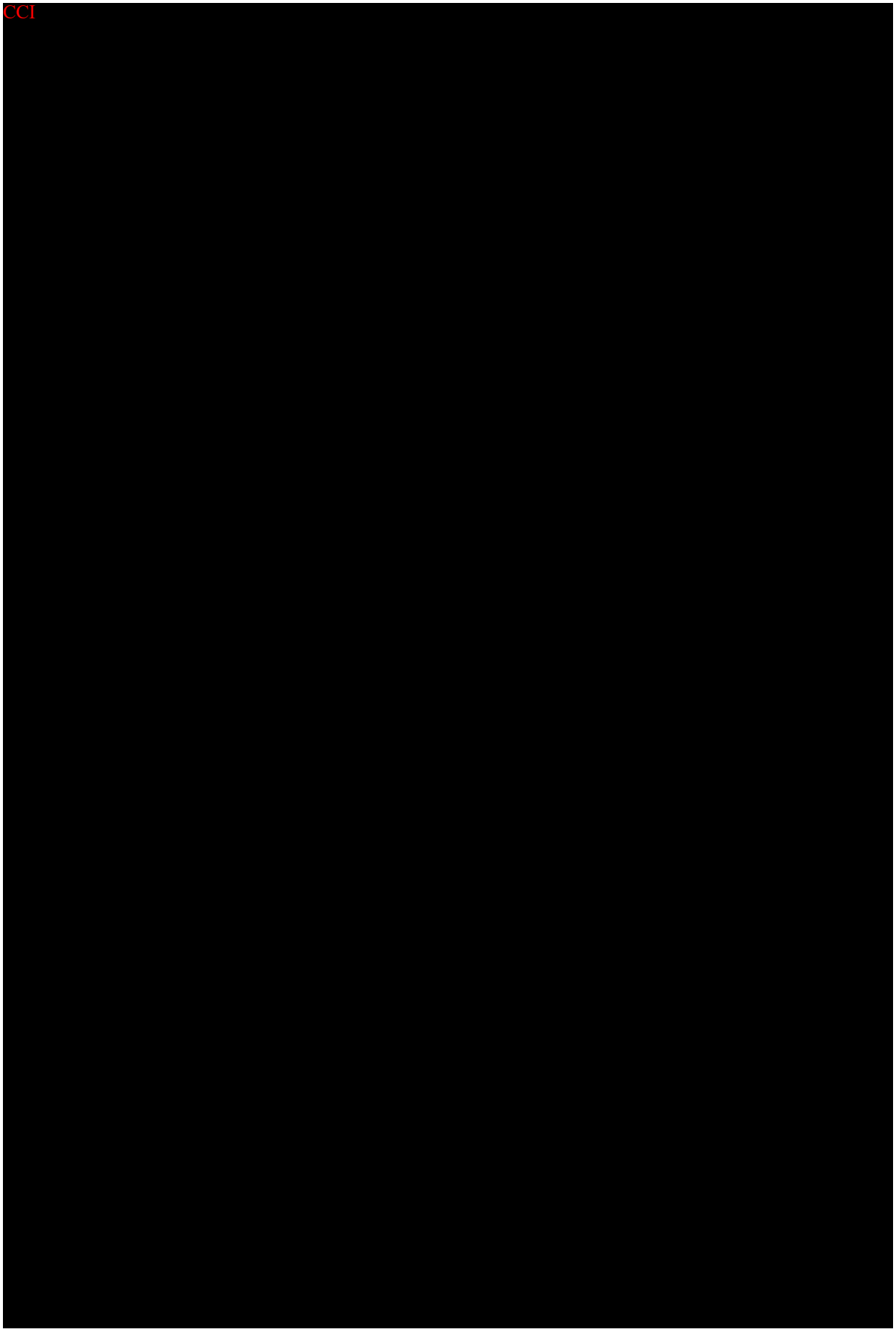
CCI

CCI

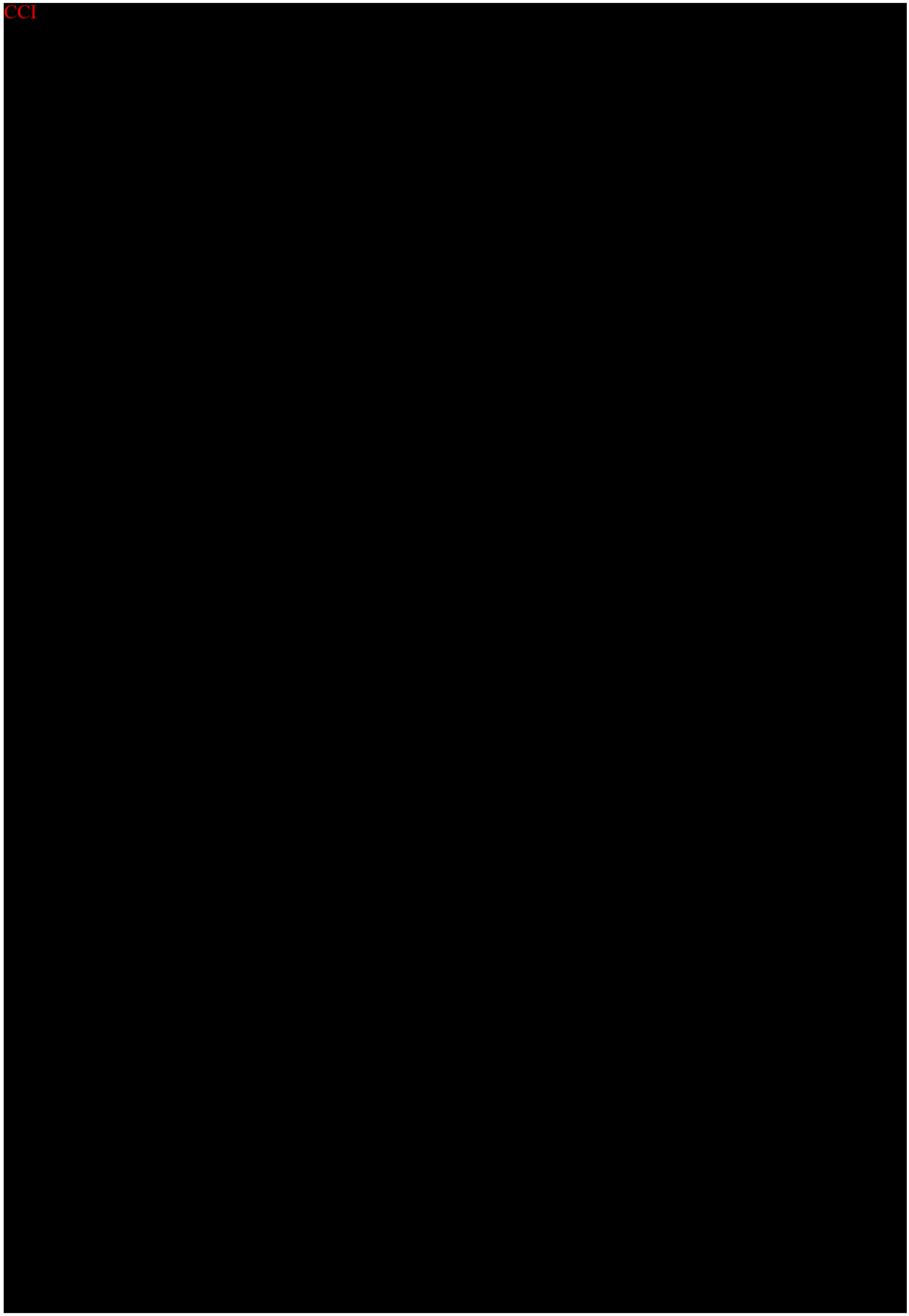



CCI

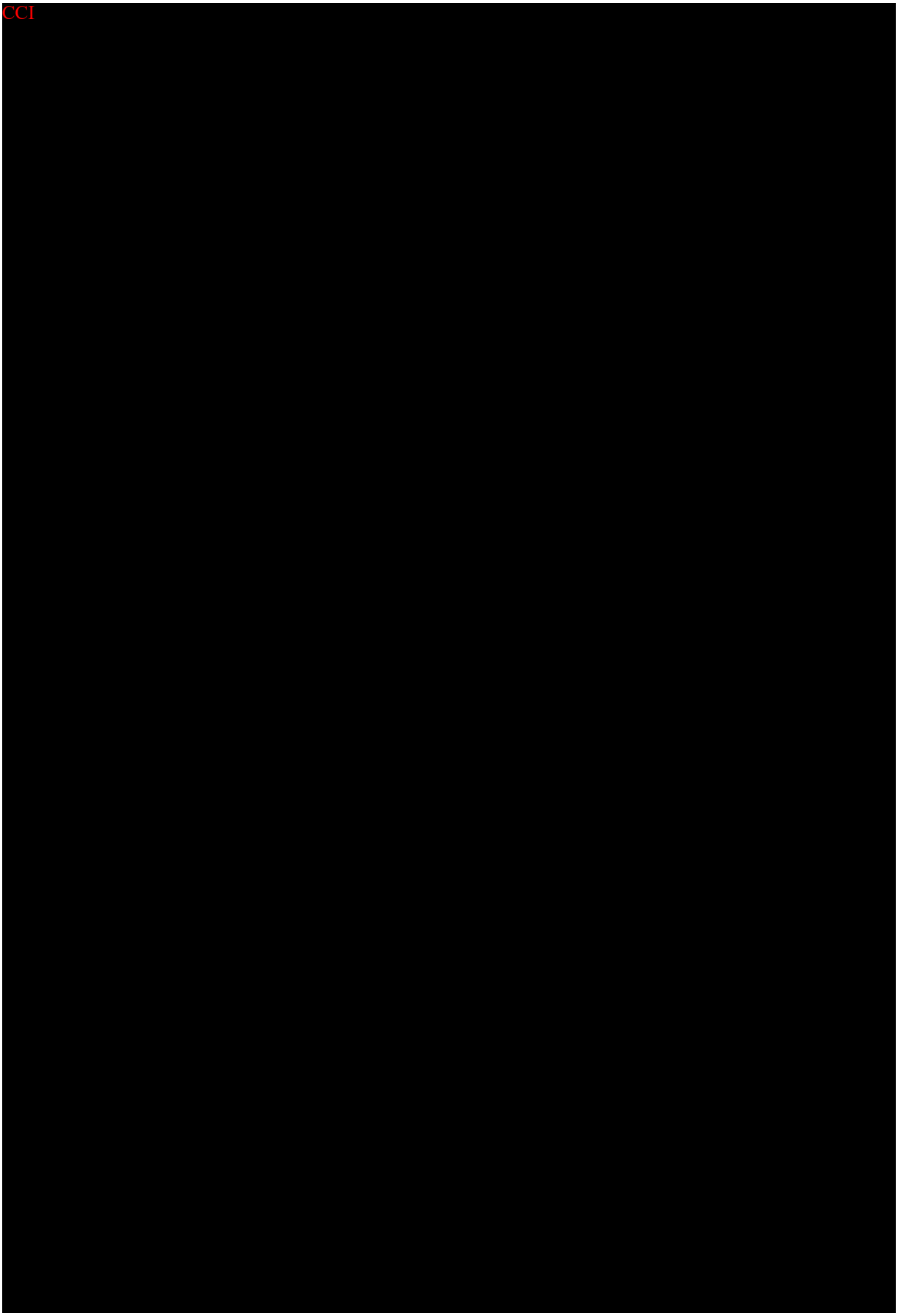
CCI



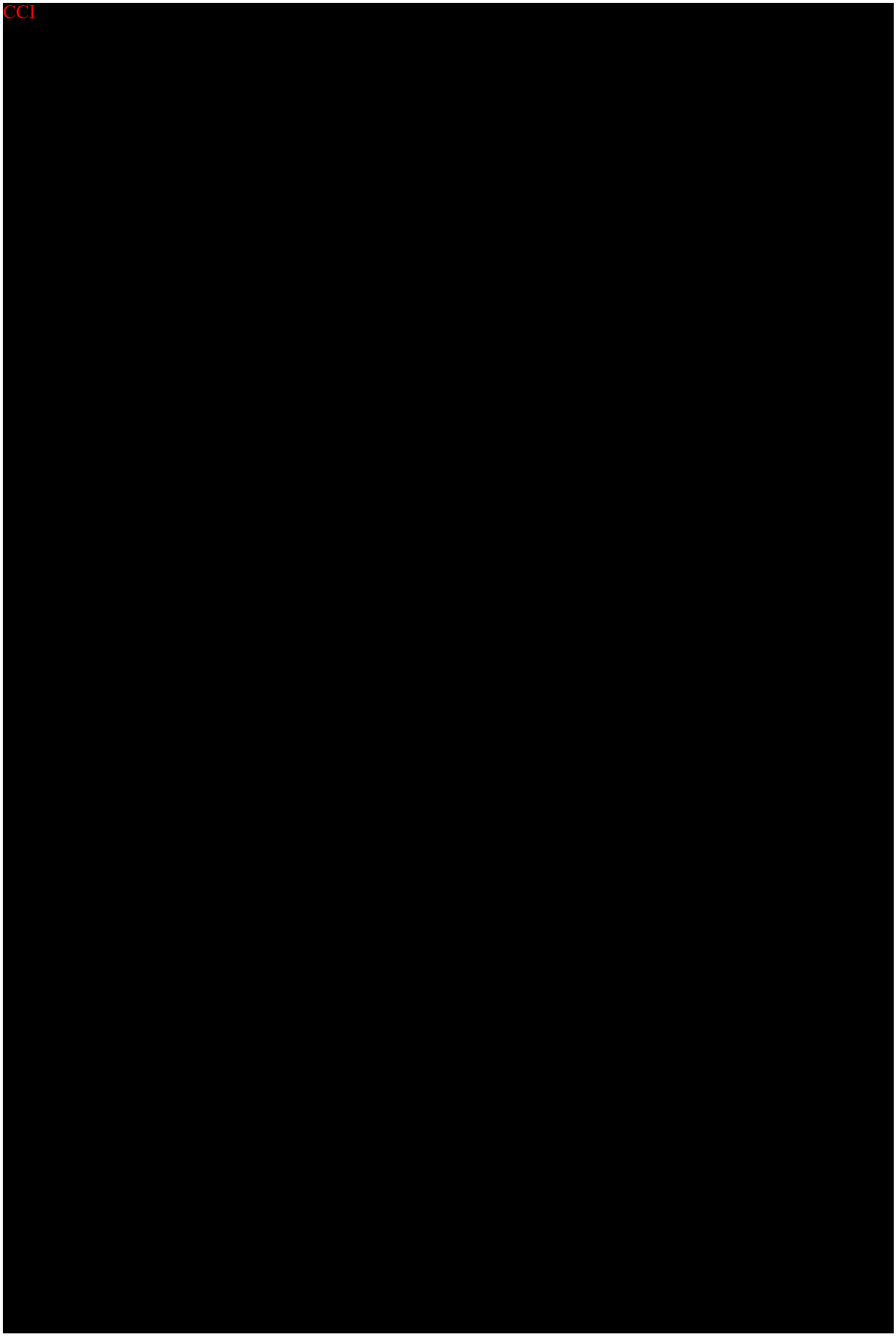
CCI



CCI



CCI



CCI

[redacted]

6.6. Appendix 5 Maintaining Integrity of Accumulating Data

Table 10 Maintaining Integrity of Accumulating Data in the Randomized Open-Label Double-Arm Study

Objective/ deliverable	Milestone	Responsible	Outputs Reviewer's
Dry run	Dry run will be perfomed as per GSK SOP		Clinical Development Lead Clinical Science Lead Medical Monitor CPMS Team Medical Writer Team SERM Team Regulatory Team "Safety team and Medical Monitor will review aggregate safety data and individual cases prior to SRT. Summary and safety conclusion and benefit/risk will be presented at SRT". Statistical and Programming team.
Interim Analysis (IA) SAC	Once Cohort 1 participants completed the study	Statistical and Programming team	
Final Analysis SAC	2 weeks after the DBL of study		Outputs of SAC will be shared by S&P team with cross functional team

Study data will be shared with only core study team members for their review during the study trial phase as mentioned in outputs reviewer's column of the Table 10.

7. REFERENCES

Barbara Myers Davit, Mei-Ling Chen, Dale P Conner, Sam H Haidar. Implementation of a Reference-Scaled Average Bioequivalence Approach for Highly Variable Generic Drug Products by the US Food and Drug Administration. The AAPS Journal, 2012. 14(4):915-24

Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA Guidance for Industry

EMA guideline: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-investigation-bioequivalence-rev1_en.pdf

FDA guideline: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/submission-summary-bioequivalence-data-abbreviated-new-drug-applications

ICH E9: Statistical Principles for Clinical Trials