Statistical Analysis Plan

Study ID: 219430

Official Title of Study: A single dose two-way cross-over study in healthy participants to compare the pharmacokinetics (PK) of salbutamol administered via metered dose inhalers containing propellants HFA-152a and HFA-134a

NCT ID: NCT05791565

Date of Document: 15-June-2023

Statistical Analysis Plan

Sponsor:	GlaxoSmithKline Research & Development Limited
Protocol No:	219430
Protocol Title:	A single dose two-way cross-over study in healthy participants to compare the pharmacokinetics (PK) of salbutamol administered via metered dose inhalers containing propellants HFA-152a and HFA 134a
CCI [redacted]	
Version Date:	13-Jun-2023

1.0 Approvals

The undersigned have approved this Statistical Analysis Plan for use in this study.

Name of Sponsor Representative/Title for SAP:	PPD Project Statistician
Signature of Sponsor Representative /Date:	PPD 15-Jun-2023
Name of Sponsor Representative/Title for Shells:	PPD Project Programmer
Signature of Sponsor Representative /Date:	PPD 15-Jun-2023
Name of Author /Title:	PPD, Biostatistician
Signature of Author /Date:	CCI [redacted]

2.0 Table of Contents

3.0 Introduction

This Statistical Analysis Plan (SAP) describes the statistical methods that will be used during the analysis and reporting of data collected under GlaxoSmithKline Research & Development Limited (GSK) Protocol 219430.

This SAP should be read in conjunction with the study protocol and electronic case report form (eCRF). This version of the plan has been developed using the protocol dated 10-Feb-2022 and the final eCRF(s) dated 05-Apr-2023.

An approved and signed SAP is a requirement for database lock. An approved SAP is also required for unblinding of the study treatments.

This SAP only covers the results that will be processed by the CCI [redacted] for pharmacokinetic (PK) parameter calculation.

CCI [redacted] will perform the PK, Pharmacodynamic (PD) and safety and tolerability evaluation.

This SAP supersedes the statistical considerations identified in the protocol; where considerations are substantially different, they will be so identified. Any post-hoc or unplanned analyses, or significant changes from the planned analysis in this SAP performed to provide results for inclusion in the clinical study report (CSR) but not included in this SAP, will be clearly identified in Section 9.8.2 of the CSR. Changes to planned analyses do not require an updated SAP but should be included in the CSR if significant.

4.0 Changes from Previous Version of Approved SAP

This is the second version of the SAP. Changes from the first SAP version:

- Public disclosure tables have been added.
- Additional imputation rules for partial dates have been added for AEs.
- Sections of statistical analysis on PK and PD parameters have been changed slightly to allow for data driven model modifications. In addition, participants with parameter results for only one treatment will no longer be excluded from the statistical analyses.
- Descriptive statistics for routine urinalysis has been added.
- Headline summary PK TFLs as a separate deliverable and dry-run delivery have been removed.

5.0 Study Objectives

5.1 Primary Objectives and Endpoints

Objectives	Endpoints
Primary	
To characterise the PK of single doses of salbutamol in healthy participants delivered via an MDI containing propellant HFA-152a, and to compare to an MDI containing propellant HFA-134a	• AUC(0-30min) • AUC(0-∞) • AUC(0-t) • Cmax

AUC=area under the curve; HFA-134a=1,1,1,2-tetrafluoroethane; HFA-152a=1,1-difluoroethane; MDI=metered dose inhaler.

5.2 Secondary Objectives and Endpoints

Objectives	Endpoints
Pharmacokinetics: To characterise the PK of single doses of salbutamol in healthy participants delivered via an MDI containing propellant HFA-152a, and to compare to an MDI containing propellant HFA-134a	• Tmax • t1/2
Pharmacodynamics: To characterise the PD of single doses of salbutamol in healthy participants delivered via an MDI containing propellant HFA-152a, and to compare to an MDI containing propellant HFA-134a	• Minimum and 0-4h weighted mean serum potassium • Maximum and 0-4h weighted mean heart rate • Maximum and 0-4h weighted mean QTc interval
Safety: To characterise the safety and tolerability of single doses of salbutamol in healthy participants delivered via an MDI containing propellant HFA 152a, and to compare to an MDI containing propellant HFA-134a	• Incidence of AEs and SAEs • Pre- and post-dose 12-lead ECGs recording of HR, PR, QRS, QT and QTc intervals (absolute and change from baseline values) • Clinical laboratory assessment (absolute values) • Vital signs (systolic and diastolic blood pressure and pulse rate) (absolute values)

AE=adverse event; ECG=electrocardiogram; HFA-134a=1,1,1,2-tetrafluoroethane; HFA-152a=1,1-difluoroethane; HR=heart rate; MDI=metered dose inhaler; SAE=serious.

5.3 Primary Estimand

The primary clinical question of interest is: What is the geometric mean ratio (GMR) of the PK parameters of Salbutamol HFA-152a MDI vs Salbutamol HFA-134a MDI after administration of single doses of salbutamol in healthy participants.

The estimand is described by the following attributes:

- **Population:**

  Healthy male or female participants aged 18 to 55 years
- **Endpoints:**

  AUC (0-∞), AUC (0-30min), AUC (0-t) and Cmax
- **Treatment Conditions:**

- Salbutamol will be administered as a single 800 µg dose, given as 8 actuations each separated by a 20-second interval, each delivering 100 µg as the ex-valve dose for the test treatment and a reference treatment.

  The comparison of interest is: The ratio of Salbutamol HFA-152a MDI vs Salbutamol HFA-134a MDI .

- **Intercurrent events:**

  Treatment discontinuation due to any reasons - Hypothetical Strategy
  - Interest lies in the comparisons of ratio of two formulations in a hypothetical scenario where no participant discontinued from the study. The individual PK concentrations affected by occurrence of the intercurrent event would be treated as missing from the occurrence of the intercurrent event until the end of the study and consequently affected individual PK parameters will be missing.

  Occurrence of emesis or coughing on dosing - Hypothetical strategy
  - Interest lies in the comparisons of ratio of two formulations in a hypothetical scenario where no participant experiences an episode of coughing or emesis within a treatment that is judged by the investigator to have impacted inhaled drug delivery to the airways or swallowed drug absorption from the gastrointestinal tract. The individual PK concentrations affected by occurrence of the intercurrent event would be treated as missing from the occurrence of the intercurrent event until the end of the treatment (period) and consequently affected individual PK parameters will be missing for that treatment (period).

  Dosing error: Considered less than or more than prescribed dose - Hypothetical strategy
  - Where the investigator is interested in the treatment effects in a hypothetical scenario where all participants have taken dose correctly as prescribed. The individual PK data affected by occurrence of the intercurrent event would be treated as missing from the occurrence of the intercurrent event until the end of the treatment (period) and consequently affected individual PK parameters will be missing for that treatment (period).

- **Rationale for estimand:** The test formulation is developed to have comparable PK characteristics and treatment effects. Interest lies in the PK values obtained while the participant is exposed to correct dose as prescribed, prior to the discontinuation of the randomized sequence and prior to the occurrence of emesis or coughing on dosing.

- **Population-level summary:** Ratio of geometric mean (for logarithmic transformed values) and 90% CI for the ratio of the geometric means for AUC(0-∞), AUC (0-t), AUC(0-30min), and Cmax.

5.4 Secondary Estimand (1)

The clinical question of interest for the secondary objective is: What is the summarized PK profile using descriptive statistics for tmax and $t_{1/2}$ after administration of single doses of salbutamol in healthy participants.
The estimand is described by the following attributes:

- **Population:**

  Healthy male or female participants aged 18 to 55 years
- **Endpoints:**

  tmax and $t_{1/2}$
- **Treatment conditions:**

  Salbutamol will be administered as a single 800 µg dose, given as 8 actuations each separated by a 20-second interval, each delivering 100 µg as the ex-valve dose for the test treatment and a reference treatment. Descriptive summary by treatment groups are:
  - Salbutamol HFA-152a MDI
  - Salbutamol HFA-134a MDI

- **Intercurrent events:**

  Treatment discontinuation due to any reasons - Hypothetical strategy
  - Interest lies in the descriptive summary by treatment groups in a hypothetical scenario where no participant discontinued from the study. The individual PK concentrations affected by occurrence of the intercurrent event would be treated as missing from the occurrence of the intercurrent event until the end of the study and consequently affected individual PK parameters will be missing.

  Occurrence of emesis or coughing on dosing - Hypothetical strategy
  - Interest lies in the descriptive summary by treatment groups in a hypothetical scenario where no participant experiences an episode of coughing or emesis within a treatment that is judged by the investigator to have impacted inhaled drug delivery to the airways or swallowed drug absorption from the gastrointestinal tract. The individual PK concentrations affected by occurrence of the intercurrent event would be treated as missing from the occurrence of the intercurrent event until the end of the treatment (period) and consequently affected individual PK parameters will be missing for that treatment (period).

  Dosing error: Considered less than or more than prescribed dose - Hypothetical strategy
  - Where the investigator is interested in the treatment effects in a hypothetical scenario where all participants have taken dose correctly as prescribed. The individual PK data affected by occurrence of the intercurrent event would be treated as missing from the occurrence of the intercurrent event until the end of the treatment (period) and consequently affected individual PK parameters will be missing for that treatment (period).

- **Rationale for estimand:**

  The test formulation is developed to have comparable PK characteristics and treatment effects. Interest lies in the PK values obtained while the participant is exposed to correct dose as prescribed, prior to the discontinuation of the randomized sequence and prior to the occurrence of emesis or coughing on dosing.
- **Population-level summary:**

  PK data of tmax and $t_{1/2}$ will be summarized using descriptive statistics (arithmetic mean, geometric mean, median, 95% CI [arithmetic and geometric], standard deviation [arithmetic and on ln-scale], minimum, maximum, and geometric CV), and will be listed and summarized in tabular and/or graphical form.

5.5 Secondary Estimand (2)

The clinical question of interest is for the secondary objective: What is the geometric mean ratio (GMR) of the PD parameters of Salbutamol HFA-152a MDI vs Salbutamol HFA-134a MDI after administration of single doses of salbutamol in healthy participants.

- **Population:**

  Healthy male or female participants aged 18 to 55 years
- **Endpoints:**

  - Minimum and 0-4h weighted mean serum potassium
  - Maximum and 0-4h weighted mean heart rate
  - Maximum and 0-4h weighted mean QTc interval

- **Treatment conditions:**

Salbutamol will be administered as a single 800 µg dose, given as 8 actuations each separated by a 20-second interval, each delivering 100 µg as the ex-valve dose for the test treatment and a reference treatment.
The comparison of interest is: The ratio of Salbutamol HFA-152a MDI vs Salbutamol HFA-134a MDI .

- **Intercurrent events:**

  Treatment discontinuation due to any reasons - hypothetical strategy
  - Interest lies in the comparisons of ratio of formulations in a hypothetical scenario where no participant discontinued from the study. The individual PD concentrations affected by occurrence of the intercurrent event would be treated as missing from the occurrence of the intercurrent event until the end of the study and consequently affected individual PD parameters will be missing.

  Occurrence of emesis or coughing on dosing - Hypothetical strategy
  - Interest lies in the comparisons of the ratio of formulations in a hypothetical scenario where no participant experiences an episode of coughing or emesis within a treatment that is judged by the investigator to have impacted inhaled drug delivery to the airways or swallowed drug absorption from the gastrointestinal tract. The individual PD concentrations affected by occurrence of the intercurrent event would be treated as missing from the occurrence of the intercurrent event until the end of the treatment (period) and consequently affected individual PD parameters will be missing for that treatment (period).

  Dosing error: Considered less than or more than prescribed dose - Hypothetical strategy
  - Where the investigator is interested in the treatment effects in a hypothetical scenario where all participants have taken dose correctly as prescribed. The individual PD data affected by occurrence of the intercurrent event would be treated as missing from the occurrence of the intercurrent event until the end of the treatment (period) and consequently affected individual PD parameters will be missing for that treatment (period).

- **Rationale for estimand:**

  Interest lies in the PD values obtained while the participant is exposed to correct dose as prescribed, prior to the discontinuation of the randomized sequence and prior to the occurrence of emesis or coughing on dosing.
- **Population-level summary:**

  Ratio of geometric mean (for logarithmic transformed values) and 90% CI for the ratio of the geometric means for serum potassium, heart rate and QTc interval (weighted means and minimum or maximum).

5.6 Secondary Estimand (3)

The clinical question of interest is for the secondary objective: What is the safety and tolerability profile of single doses of salbutamol in healthy participants delivered via MDIs.

- **Population:**

  Healthy male or female participants aged 18 to 55 years
- **Endpoints:**

  - Incidence of AEs and SAEs
  - Pre- and post-dose 12-lead ECGs recording of HR, PR, QRS, QT and QTc intervals (absolute and change from baseline values).
  - Clinical laboratory (absolute values)
  - Vital signs (systolic and diastolic blood pressure and pulse rate) (absolute values)

- **Treatment conditions:**

  Salbutamol will be administered as a single 800 µg dose, given as 8 actuations each separated by a 20-second interval, each delivering 100 µg as the ex-valve dose for the test treatment and a reference treatment.
  - Salbutamol HFA-152a MDI
  - Salbutamol HFA-134 a MDI

- **Remaining intercurrent events:**

  Treatment discontinuation due to any reason - Treatment policy strategy.
- **Rationale for estimand:**

  Safety data will be monitored throughout the study after the start of treatment. There is interest in evaluating and reporting safety events regardless of whether participants discontinued treatment.
- **Population-level summary:**

  Frequency and percentages for incidence of AEs and SAEs. Absolute and changes from baseline values for pre-dose and post-dose 12-lead ECG recording of HR, PR, QRS, QT and QTc intervals, absolute values for clinical laboratory values, and vital signs (systolic and diastolic blood pressure and pulse rate) parameters will be listed and will be summarized descriptively (arithmetic mean, SD, median, minimum, and maximum).

6.0 Study Design

This is a randomized, double-blind, single dose, 2-way cross-over study in healthy male and female participants with salbutamol. Salbutamol will be administered as a single 800 µg dose, given as 8 actuations at 20-second intervals, each delivering 100 µg as the ex-valve dose for a test treatment and a reference treatment. There will be a minimum washout period of 72 hours between treatment (dosing) periods.

Following a screening period of up to 28 days, eligible participants will be confined to the clinical research unit (CRU) from Day -1 until Day 5, (24 hours after the last dose on Day 4), when all study assessments are completed.

Thirty participants will be randomly assigned to one of 2 treatment sequences in 2 treatment interventions using a cross-over design:

Table 1: Treatment Sequences

Sequence
AB (n=15)
BA (n=15)

The following treatments will be administered as single 800 µg inhalation doses, given as 8 x 100 µg (ex-valve) at 20-second intervals:

- Treatment A: Salbutamol HFA-152a MDI (Test formulation).
- Treatment B: Salbutamol HFA-134a MDI (Reference formulation, currently approved Ventolin).

For the first dose of the treatment sequence, the first 2 participants will be randomized to one of the following: currently approved Ventolin, or Salbutamol HFA-152a MDI.

Remaining participants will be randomized only after review of at least 24 hours safety and tolerability data (i.e. adverse events (AEs) / serious AEs (SAEs), clinical laboratory values, vital signs and 12-lead ECGs)

from the sentinel participants by the Investigator or appropriately qualified delegate, in consultation with the Medical Monitor or delegate if unavailable, and it has been deemed safe to do so.

The remaining 28 participants will be dosed in various groups in accordance with CRO bed space and clinical resourcing CCI [redacted] The participant population will be assigned equally to the total number of treatment sequences.

6.1 Sample Size Considerations

No formal sample size calculation has been performed.

The target number of participants is chosen to achieve sufficient half width of the 90% CI, in the estimate of the geometric mean ratios for the primary endpoints. Assuming a within-participant CVw of 25.4% for Cmax and 22% for AUC parameters (from previously conducted studies (Study 200921, Study SALB1003)), the sample size of 30 participants is expected to result in a half-width of the 90% CI for Test/Reference ratio of 11.61% for Cmax and 10.02% for the AUC parameters.

Presented in Table 2 are the half width of the 90% CI for observed treatment ratios, based on varying sample size and by fixing CVw% of 25.4% for Cmax and 22% for AUC.

Table 2: Sample size sensitivity table

Parameter		Sample size	Within Subject SD	Half width of the 90% CI for Observed Treatment Ratio
AUC(0-inf)		18	0.22 (CVw=22%)	13.49%
		24	0.22 (CVw=22%)	11.38%
Cmax		18	0.25 (CVw=25.4%)	15.66%
		24	0.25 (CVw=25.4%)	13.20%

CI=confidence interval; CVw=coefficient of variation within

It is assumed that all AUC parameters will follow a similar level of variability as AUC(0-inf).

Note: A sample size of 18, and a CVw of 22%, the half width of the 90% CI for observed treatment ratio of AUC between two treatment arms is estimated to be within 13.49% of the point estimate. (As an example, if the observed treatment ratio is 0.95, the upper bound of the 90% CI for observed treatment ratio will be 0.95*(1+0.1349) = 1.08 and the lower bound will be 0.95/(1+0.1349) = 0.84).

Participants who drop out during the study will not be replaced.

6.2 Randomization and Unblinding

After obtaining informed consent, participants will receive a screening number and will be screened according to the inclusion and exclusion criteria.

The GSK Randomization Officer will use the Randall NG system to generate randomization codes.

With central randomization, knowledge of the randomized treatment group for previous participants does not predict which treatment group will be assigned to the next randomized participant.

Randomization and study intervention assignment will be facilitated by the interactive response technology (IRT) through the central Randomization and Medication Ordering System Next Generation (RAMOS NG).

Following confirmation of fulfilment of study entry criteria, study site personnel will be required to register participants using RAMOS NG for assignment of a unique identifier which comprises of 4 digits (randomization numbers PPD) (designating the participant's randomization code and treatment sequence assignment) for each participant in the study. Participant numbers will be within PPD range.

At study Day 1 participants will be assigned a unique randomization number in ascending numerical order. The randomization number encodes the participant's assignment to one of the 2 treatment sequences of

the study, according to the randomization schedule generated prior to the study by the statistics department at GSK.

The randomization code will be kept at GSK (by the randomization officer and is not accessible for blinded study team members. The CCI [redacted] and GSK study team are blinded throughout the study and will receive the actual randomization code from GSK randomization officer only after database lock and after approval from GSK.

The RAMOS NG will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator may, at the investigator's discretion, contact GSK to discuss the situation prior to unblinding a participant's intervention assignment unless this could delay emergency treatment for the participant. If a participant's intervention assignment is unblinded, GSK must be notified within 24 hours of this occurrence. The date and reason for the unblinding must be recorded.

7.0 Overview of Planned Analysis

7.1 Changes from Protocol

PD evaluation is not only related to serum potassium results, but also related to heart rate and QTcF results. Therefore, the PD set has been changed from "The PD set consists of all participants who received at least one dose of study intervention and have at least 1 non-missing potassium concentration result" to "The PD set consists of all participants who received at least one dose of study intervention and have at least 1 non-missing potassium concentration result, or having at least 1 non –missing heart rate or QTc result.

Modified an intercurrent event since "wrong treatment scenario in the dosing error event" is not applicable.

7.2 Key Results and Final Analysis

Draft TFLs will be provided after database lock.

The finalization of TFLs will be done after the incorporation of sponsor comments, and before GSK's Statistical Analysis Complete (SAC), which will be included in the first draft CSR.

8.0 Data Review

8.1 Data Management

Data handling and transfer will take place under the CCI [redacted] Data Management Plan for the study.

8.2 Acceptance of Data for Summarization

Programming of analysis datasets and TFLs may be ongoing during the data management of the study. However, programming of analysis datasets and TFLs will be completed and quality controlled (QC'd) after database lock

Analysis datasets and TFLs will be QC'd for each deliverable per the CCI [redacted] QC plan.

Only quality assured (QA'd) results released by the Safety Laboratory, Bioanalytical Laboratory, or other external data source will be used for the programming of analysis datasets and TFLs for the final report. Any data values requiring investigation or corrections that are identified while programming the analysis datasets and TFLs will be sent to the project Data Manager. If the issue affects the TFLs the Programmer or Statistician who identified the issue will follow it to resolution.

9.0 Definitions and General Analysis Methods

9.1 Analysis Data Presentation

9.1.1 Rounding

In listings, data will be presented with the same precision as the original data. Derived data will be rounded for presentation purposes, derived data will be unrounded in the dataset.

Values of PK parameters, except tmax, will generally be presented with 3 significant figures. Values greater than 999 will be presented as integers.

Tmax will be rounded to 2 decimals. Coefficient of variation (CV%) will be presented with one decimal.

Percentages will be presented with 1 decimal, except for 0 and 100%, these are rounded to integers.

For all summaries, descriptive statistics for mean and median will be presented with 1 additional decimal, Standard deviation will be presented with 2 additional decimals. Minimum and maximum will be presented with the same precision (number of decimals) as the data they are calculated from. Median Tmax will be presented with 2 decimals.

P-values will be reported to four decimal places; p-value less than 0.0001 will be reported as p <0.0001.

9.1.2 Imputation

Data will not be imputed, except for the following data:

- PK concentrations below the quantifiable limit (BQL) (see Section 16.2.1).
- If the actual time or dose time is missing, the scheduled time may be substituted in order to calculate the PK parameters (see Section 16.2.2).
- Missing start or end date/times of AEs for the calculation of onset and duration (see Section 18.1.1). Partial dates will be displayed as captured in the participant listing displays.
- Missing AE severity, relationship and seriousness of AEs see Section 18.1.1).
- Safety laboratory data that are <x or >x (e.g. “<1.03”, “>1000”): the analysis value or normal limit value will be the value of the detection limit itself plus or minus one precision unit for the parameter concerned (respectively 1.02 and 1001 in the example). The values before imputation (“<1.03”, “>1000”) will only be shown in listings. Listings will present the values before imputation.

9.1.3 Descriptive Statistics

Unless otherwise indicated, continuous variables will be summarized with the following descriptive statistics: n (number of observations), (arithmetic) mean, standard deviation (SD), minimum (min) value, median, and maximum (max) value. For PK data, n, arithmetic mean. SD, min, median, max, CV%, 95% CI, geometric mean, geometric SD, CV% of the geometric mean (geoCV%), and geometric 95% CI, will be presented. For PD data, n, (arithmetic) mean, SD, min, median, max, CV% and geometric mean will be presented.

Categorical data will be summarized with frequencies and percentages. Percentages by categories will be based on the number of participants exposed within a treatment.

For categorical data the categories will be presented in the tables exactly as they appear in the eCRF / Database.

9.1.4 Pooling

For summaries on demographic data (data summarized in tables of Appendix 4: List of End of Text Outputs, *Section 15.1 – Disposition and Demographic Data*), an overall summary (i.e. on all participants) will be provided for table 15.1.1. Summary of Participant Disposition, and table 15.1.3 Summary of Demographics.

Table 15.1.2 Summary of Participant Treatment Status and Reasons for Discontinuation of Study Treatment will be summarized by treatment, and table 15.1.4 Summary of Major Protocol Deviations will be summarized by treatment sequence and overall. TEAE summaries will be provided by treatment and overall. Other summary statistics (data summarized in tables of Appendix 4: List of End of Text Outputs, *Section 15.2 – Pharmacokinetic Data, Section 15.3– Pharmacodynamic Data*, Section *15.4.3 Laboratory Data* , and *Section 15.4.4 Other Safety Parameters)* will be displayed by treatment (and time point, if applicable).

The treatments used for summaries are presented in Section 9.2.2.

9.1.5 Unscheduled Measurements

Unscheduled measurements will be included in the listings. With the exception of unscheduled measurements used for baseline, unscheduled measurements will be excluded from the descriptive statistics and statistical analysis. In case an unscheduled measurement was performed immediately after the scheduled measurement because of a previous measurement error (e.g. equipment failure), this repeated measurement will be used, and the original erroneous measurement will be excluded from the analysis. Listings will provide any scheduled and unscheduled measurements, and measurements used as baseline.

9.2 Analysis Data Definitions

9.2.1 Baseline Definition

Unless otherwise stated, baseline for post-dose evaluations within each (dosing) period is defined as the last observation recorded before the first study drug administration in each dosing period. The last observation can be an unscheduled / repeated measurement. If a pre-treatment observation is missing in a given period then the screening value may be used.

For electrocardiogram (ECG) measurements, the average of the triplicate measurements taken at pre-dose on Days 1 and 4 for heart rate and QTcF (as provided in the database) are taken as baseline. For other triplicate ECG measurements taken at pre-dose on Days 1 and 4, but not provide as an average in the database (PRS duration, QRS duration, QT interval), the triplicate measurements will be averaged and taken as baseline.

If no triplicate is available before the first study drug administration, the mean of the last recorded duplicate closest to the first study drug administration will be considered as baseline. If no duplicate is available, the last single ECG recorded before the first study drug administration will be considered as baseline.

9.2.2 Treatment/Participant Grouping

Label	Grouping
Study Drug	Salbutamol
Treatment	Treatment A: Salbutamol HFA-152a MDI (Test formulation) Treatment B: Salbutamol HFA-134a MDI (Reference formulation, currently approved Ventolin). Overall
Treatment Labels for TFLs	HFA-152a MDI HFA-134a MDI Overall A footnote will provide details on the treatments: HFA-152a MDI: 800 ug Salbutamol HFA-152a MDI (Test formulation) HFA-134a MDI: 800 ug Salbutamol HFA-134a MDI (Reference formulation)

9.2.3 Common Variable Derivations

Variable	Data Type	Definition/Calculation
Change from Baseline	All	Post-dose Observation minus Baseline Observation in each dosing period If either the baseline or post-randomization value is missing, the change from baseline is set to missing as well.
Analysis Study Day (Prior to First Dose)	All	Date of Measurement minus Dose Date
Analysis Study Day (Post Dose)	All	For intervention period: Date of Measurement minus Dose Date +1 in each dosing period (timepoint 0-24h all set to 1)
Actual Dose	Exposure	Value given after 8 actuations at 20-second intervals, each delivering 100 µg as the ex-valve dose (800 ug)

9.2.4 QC

Clinical Data Interchange Standard Consortium (CDISC) compliant analysis datasets and TFLs will be QC'd according to the CCI [redacted] QC plan.

All datasets will be double programmed per the CCI [redacted] QC plan.

9.2.5 ADaM Datasets and Metadata

The analysis datasets will be generated in accordance with CDISC Analysis Data Model (ADaM) Version 2.1, and CDISC ADaM Implementation Guide 1.2. The following ADaM datasets will be prepared:

ADaM Dataset Name	Description
ADSL	Subject-Level Analysis Dataset
ADAE	Adverse Events Analysis Dataset

ADEG	ECG Analysis Dataset
ADLB	Laboratory Test Results Analysis Dataset
ADPC	Pharmacokinetic Concentrations Analysis Dataset
ADPDP	Pharmacodynamic Parameters Analysis Dataset
ADPP	Pharmacokinetic Parameters Analysis Dataset
ADVS	Vital Signs Analysis Dataset

ADaM compliant datasets will be delivered to the Sponsor. A define.xml file Version 2 with the corresponding metadata will be included. Analysis results (analysis displays or program details) metadata are excluded.

9.3 Software

The statistical analysis and reporting will be done using SAS® for Windows™ version 9.4 or higher (SAS Institute, Inc.).

PK parameter calculations will primarily be done using Phoenix® WinNonlin® version 8.3 or higher (Certara USA Inc.). Additional PK computations may be performed in SAS®.

9.4 Statistical Methods

9.4.1 Statistical Outlier Determination

No statistical outlier analysis is planned.

9.4.2 Predetermined Covariates and Prognostic Factors

There are no predetermined covariates or prognostic factors.

9.4.3 Hypothesis Testing

No formal hypothesis testing will be done.

No formal hypothesis will be tested. For each primary PK endpoint, point estimates and corresponding 90% CIs will be constructed for the ratio of the geometric mean of the test treatment to the geometric mean of the reference treatment, μ(test)/μ(reference)

9.5 TFL Layout

Report layout will be according to the CCI [redacted] – ICH E3 compliant – CSR Template. The layout TFLs will be according to the CCI [redacted] standards.

Table shells will be provided as separate document to this SAP. The TFLs will be provided in Adobe PDF format (in A4 format), one for the Participant Data Listings, and one for the Table and Figures, referred to, but not included in text. Separate files will be created for in-text tables (RTF) and in-text figures (PNG) planned for this study.

In addition, tables shells will be provided for the public disclosure tables.

Format:

- Page size: A4
- Data in listings will be sorted by participant number, and time point (if applicable).
- Data in tables will be sorted by analyte/parameter, treatment and time point (if applicable). Laboratory data will be sorted by laboratory category, parameter, treatment and time point.

AE tables will be sorted by SOC and PT, by descending (total) number of participants per system organ class and within the system organ class per preferred term.

- Column titles will be in title case letters.
- All end-of-text tables and listings and participant data listings will be in landscape format. In-text tables will be in portrait format. Layout can be adapted to landscape at the discretion of the medical writer to enhance overview and readability.
- The treatment labels will be as outlined in Section 9.2.2.

10.0 Analysis Sets

Analyses	Screened Set	Enrolled Set	Safety Set	PK Set	PD Set
Disposition Summaries	✓	✓			
Safety Assessments			✓		
Baseline Characteristics			✓		
Primary Analysis				✓	
PK Concentrations				✓	
PK Parameters				✓	
PD Concentrations					✓
PD Parameters					✓

10.1 Screened Set

The screened set will consist of all participants who were screened for eligibility.

In this study, a limited amount of information of screen failures will be included in study data tabulation model (SDTM), like information on demographics, results on eligibility criteria, screen failure details, and any SAEs.

All participants who have a signed informed consent whether screen failure or met eligibility criteria will be summarized in the disposition table.

10.2 Enrolled Set

The enrolled set will consist of all participants who entered the study (who were randomized or received study intervention or underwent a post screening study procedure).

This set will be used for disposition summaries.

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.

10.3 Safety Set

The safety set will consist of all participants who received at least one dose of study intervention. This set will be used for the safety data summaries and baseline characteristic summaries.

10.4 PK Set

The PK set will consist of all participants in the safety analysis set who had at least 1 non-missing PK assessment (non-quantifiable values will be considered as non-missing values). The PK set will be determined by a blinded data review meeting of the data prior to database lock, based on collected protocol deviations and available data at DB freeze.

This set will be used for PK concentration and PK parameter summaries.

10.5 PD Set

The PD set consists of all participants who received at least one dose of study intervention and have at least 1 non-missing potassium concentration result, or having at least 1 non –missing heart rate or QTc result.

This set will be used for PD value summaries and PD parameter summaries.

11.0 Participant Disposition

The number of participants enrolled, and the number and percentage of participants randomized, dosed, members of each analysis set will be presented by treatment sequence and overall. The number and percentage of participants who withdrew from the study after dosing prematurely and a breakdown of the corresponding reasons for withdrawal will also be presented. The number of screen failures and reason for screen failure will be presented for overall (all subjects).

A listing information on early study intervention/treatment unblinding will be provided.

12.0 Protocol Deviations

Protocol deviations will be listed, based on the available information of the SDTM.PD dataset. Any major deviations will be summarized by treatment sequence.

13.0 Demographic and Baseline Characteristics

All demographic data as collected during the screenings visit will be listed by participant.

Only year of birth is collected on eCRF. Age (in years) is derived using the year of the screening visit. Birth date will be presented in listings as ‘YYYY’.

Participant demographics will be summarized for the enrolled set. Participant demographics will be summarized descriptively for all participants (overall). The summary will include the participants’ age (in years), sex, race, ethnicity, weight (in kg), height (in cm), and body mass index (BMI) [in kg/m^2].

13.1 Medical History

Medical history will be listed. Medical history will be coded according to Medical Dictionary for Regulatory Activities (MedDRA), version 25.0 or higher.

13.2 Other Baseline Characteristics

Substance use will be listed.

The results of drug and alcohol screen will be listed.

The results of serology at screening will be listed.

The results of pregnancy tests (beta-human chorionic gonadotropin [β-HCG]) and follicle stimulating hormone (FSH) test results will be listed.

The results of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) tests will be listed.

Non-compliance to inclusion- or exclusion criteria (if any) will be listed.

14.0 Concomitant Medications

Concomitant medications, categorized by medication group and subgroup according to World Health Organization (WHO) Drug Dictionary (Version WHO Drug Global B3 September 2022 or later), will be listed by participant. The reported name of the drug and standardized medication name will be reported.

Medications with an end date prior to the first dose of study drug will be considered prior medications and will be noted as 'prior' in the listing. Concomitant medications are defined as those taken by the participant at any time between the date of first study drug administration and study completion/discontinuation.

Any ongoing medications with a start date before study drug administration will be reported as concomitant medication.

15.0 Treatment Compliance and Exposure

Exposure data (date, time, dose form, fasting and other requirements met, etc.) will be listed by participant.

A listing of study dates (Date of informed consent signature, date of medication, and follow-up) will be provided.

16.0 Pharmacokinetic Analyses

The concentrations of salbutamol in plasma will be determined using a validated liquid chromatography tandem mass spectrometry assay by GSK. LLOQ is 50 pg/mL.

16.1 Pharmacokinetic Variables

PK concentrations will be measured in plasma.

16.1.1 Plasma Variables

16.1.1.1 Concentrations

Plasma concentration of salbutamol.

16.1.1.2 Parameters

PK Parameters for salbutamol will be calculated as defined in Table 3, as data permit.

Table 3 PK Parameters for Salbutamol in Plasma

Parameter	Description	SAS Programming Notes
Primary PK parameters		
AUC(0-30)	Area under the plasma concentration-time curve calculated from time 0 (pre-dose measurement) to 30 minutes post-dose	AUC0_30 from WNL The partial AUC is calculated according to the WinNonlin rules for partial areas.
AUC(0-t)	Area under the plasma concentration-time curve calculated from time 0 (pre-dose measurement) to time t of last quantifiable concentration	AUClast from WNL
AUC(0-inf)	Area under the plasma concentration-time curve from time 0 (pre-dose measurement) to extrapolated to infinity, calculated as AUC(0-inf) =AUC(0-t) + Clast/kel Where Clast is the observed concentration at the last timepoint with a quantifiable concentration and kel is the terminal elimination rate constant.	AUCINF_obs from WNL If AUC_%Extrap_obs>20% and/or Rsq_adjusted ≤ 0.80 then parameter is flagged, and maybe excluded.
Cmax	Maximum observed plasma concentration. Observed peak analyte concentration obtained directly from the concentration-time data without interpolation, expressed in concentration units. If multiple maxima occur at equal concentrations, the first temporal value will be taken.	CMAX from WNL
PK parameters related to secondary endpoints:		
tmax	Time to reach Cmax, expressed in time units.	TMAX from WNL
t1/2	Terminal elimination half-life expressed in time units. $t1/2=\frac{\ln(2)}{\lambda_z}$	HL_Lambda_z from WNL If Rsq_adjusted ≤ 0.80 then parameter is flagged, and maybe excluded.
Other PK parameters (listed only):		
kel (λ_z) Reported as kel	Terminal elimination rate constant calculated by linear regression of the terminal log-linear portion of the concentration vs. time curve. Linear regression of at least three datapoints, excluding Cmax are required to obtain a reliable k_{el}.	Lambda_z from WNL If Rsq_adjusted ≤ 0.80 then parameter is flagged, and maybe excluded.
AUCextra	Percentage of AUC0-inf obtained by extrapolation, calculated as:	AUC_%Extrap_obs from WNL

	$\frac{AUC(t-inf)}{AUC(0-inf)}\ x\ 100\%$	
Adj r^2	Goodness of fit statistic for the log-linear terminal elimination phase of the concentration time profile identified by least squares linear regression and adjusted for the number of points (minimum of 3, not including Cmax) used in the estimation of K_{el}	Rsq_adjusted from WNL. If adjusted Rsq ≤ .80 then a flag will be added Listed only
kel_Start	The start time used in the regression for the determination of k_{el}	Lambda_z_lower from WNL Listed only
kel_End	The end time used in the regression for the determination of k_{el}	Lambda_z_upper from WNL Listed only
kel_N	The number of points used in the regression for the determination of k_{el}	No_points_lambda_z from WNL Listed only
tlast	Time of last measurable observed concentration.	Tlast from WNL Listed only

Note: AUCs will be calculated using linear up / log down trapezoidal rule, expressed in units of concentration x time.

16.2 Pharmacokinetic Summaries

16.2.1 Pharmacokinetic Concentrations

Individual plasma concentrations for salbutamol before the first quantifiable concentration will be set to zero. If a single value below the lower limit of quantification (LLOQ) occurs between measurable concentrations in a profile, the LLOQ will be set to missing. If two or more LLOQ values occur in succession between measurable concentrations, the LLOQ will be set to zero, and the profile will be deemed to have terminated at the last measurable concentration prior to these LLOQs; for the purpose of individual plots, these non quantifiable results (NQ) will be set to O and the subsequent measurable concentrations will be retained. The LLOQ value which are after the last measurable concentration will be set to missing in the individual subject plots.

If there is physiological or operational plausibility for erratic absorption - NQ in the middle of a concentration profile may be set to missing while subsequent valid concentrations are retained.

Descriptive statistics (n, arithmetic mean, SD, CV, 95% CI of arithmetic mean, median, min, and max) will be used to summarize the plasma concentrations by treatment at each scheduled time point. In the calculation of descriptive statistics, all LLOQ values will be set to zero except when an individual LLOQ falls between two quantifiable values in which case it will be omitted (set to missing) from the calculation. Descriptive statistics at a time point where one or more samples have LLOQ values will be reported (as per listings), irrespective of the number of LLOQ results.

Participants excluded from the PK analysis set will be flagged in the listing and excluded from descriptive statistics.

All individual participant PK concentrations, time deviations and comments will be listed.

Linear and semi-logarithmic plots of the arithmetic mean plasma concentration by scheduled sampling time will be provided for each treatment (treatments in one plot). Linear plots will show the zero concentrations before the first measurable concentration. These plots will show nominal (scheduled) time in hours. The plots will match the summary table results.

Linear and semi-logarithmic plots of the median plasma concentration by scheduled sampling time will be provided for each treatment (treatments in one plot). Linear plots will show the zero concentrations before the first measurable concentration. These plots will show nominal (scheduled) time in hours. The plots will match the summary table results.

Linear and semi-logarithmic plots of the individual plasma concentration by actual sampling time will be provided by participant (two PK profiles per participant in one plot). These plots will show actual time in hours. Linear plots will show the zero concentrations before the first measurable concentration. Individual plots will match the individual PK concentration results (and imputations).

Linear and semi-logarithmic spaghetti plots of the (combined) individual plasma concentrations by actual sampling times will be provided by treatment. These plots will show actual time in hours. Spaghetti plots will match the individual PK concentration results (and imputations) for each participant.

16.2.2 Pharmacokinetic Parameters

PK parameters for salbutamol will be estimated using non-compartmental methods with WinNonlin® (WNL).

The plasma PK parameters will be estimated from the concentration-time profiles. In estimating the PK parameters, below LLOQ (BQL) values prior to the first quantifiable concentration will be set to zero. BQL values that occur after the first quantifiable point will be considered missing. Values that are embedded between BQLs, or quantifiable values occurring after two or more BQLs, will be set to missing at the discretion of the pharmacokineticist. LLOQ value which are after the last measurable concentration will be set to missing. Actual sampling times, rather than scheduled sample collection times, will be used in all computations involving sample collection times. If the actual sample collection time or dose time is missing, the scheduled time will be substituted in order to calculate the PK parameter.

Descriptive statistics (n, arithmetic mean, geometric mean, SD, CV, geoSD, geoCV%, 95% CI of geometric and arithmetic mean, median, min, and max) will be used to summarize the calculated PK parameters by treatment. For tmax only median, min, max and 95% CI will be presented.

Participants excluded from the PK analysis set will be flagged in the listing and excluded from descriptive statistics.

All individual participant PK parameters will be listed.

The points to be included in the λz range will be determined after inspection of the semi-log concentration-time profiles. At least 3 points will be required to be used, the Cmax data point will not be included. Parameters based on adjusted r2 equal or below 0.85 will be flagged but not excluded from descriptive statistics.

If AUCextra value is above 20%, it will be flagged but not excluded from descriptive statistics if the proportion of AUC extrapolated that exceed 20% does not exceed 20% of the values. If more than 20% of the values exceed 20% or if an individual value is >40% then this will be discussed with the Sponsor.

The individual values and geometric mean of salbutamol AUCs and Cmax will be presented graphically versus treatment with a line connecting the geometric means of the treatments.

16.2.2.1 Statistical Analyses

Analysis will be performed to compare the PK profile of salbutamol HFA-152a MDI and salbutamol HFA-134a MDI (currently marketed Ventolin product). Analysis will be performed on the natural logarithm of AUC(0-30), AUC(0-t), AUC(0-inf) and Cmax using a linear mixed model with the treatment and period (dosing day) as fixed effects and subjects as random effects. A one model will be used, grouped by parameter.

Point estimates and 90% CIs for treatment differences on the log scale derived from the model will be exponentiated to obtain estimates for geometric mean (GM) ratios and CIs on the original scale. The within-subject coefficients of variation (CVw) for AUC and Cmax will be calculated based on the loge-normal distribution. The within-subject coefficients of variation (CVw) for AUC and Cmax will be calculated based on the loge-normal distribution.

Model Checking & Diagnostics:

- Model assumptions will be checked before analysis.
- The underlying distributional assumptions involved in the statistical analyses will be assessed by visual inspection of residual plots. Normality will be examined by normal probability plots while homogeneity of variance will be assessed by plotting the residuals against the predicted values for the model.
- If the assumptions are seriously violated, then alternative data transformations will be explored. If no suitable transformation can be found, equivalent nonparametric analyses (ex. Wilcoxon signed-rank test) will be performed.

The following kernel code of SAS PROC MIXED will be used:

```
proc mixed;
by parameter;
class subject treatment period;
model log(value)= treatment period / ddfm=kenwardroger cl;
random subject type=un;
lsmeans treatment period /alpha=0.1;
/*estimates for treatment order Test1-Ref*/
estimate "T vs R" treatment 1  -1 /alpha=0.1;
run;
```

SAS code might be updated depending on the data. An unstructured type of the covariance matrices R (accounting for the within subject variability) and G (accounting for the between subject variability) will be used. If this model fails to converge, alternative covariance structures may be considered based on a lower AIC values (for example variance component, etc.). For the described linear mixed model analyses, 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. Statistical analysis model table will present N, n, least squares GM values and associated 90% CI, GM ratios and associated 90% confidence intervals and within-subject CV.

Intercurrent events and handling of missing data:

- Participant level missing PK concentration considered as missing at random, will not be imputed.
- The PK concentration will be affected by occurrence of the intercurrent event (Treatment discontinuation of the study) would be treated as missing at random from the occurrence of the intercurrent event until the end of the study and only reliable available data will be used in the primary analysis and summary descriptive.

17.0 Pharmacodynamic Analysis

Based on nonclinical and clinical studies conducted with HFA-152a, and information from the Summary of product characteristics (SmPC) of Ventolin Evohaler (salbutamol sulfate containing propellant HFA-134a), the safety concerns following salbutamol dosing at the levels employed in this study include hypokalemia, hyperglycemia, and cardiovascular effects (including tachycardia and, in rare cases, cardiac arrhythmias).

The analysis of potassium in serum samples will be performed at CCI [redacted]

Heart rate and QTcF data used for PD parameters will result from the 12-Lead ECG measurements as part of the safety measurements.

17.1 Pharmacodynamic Variables

17.1.1 Variables

17.1.1.1 Serum Potassium, Heart Rate and QTcF

- Serum potassium.

Heart rate and QTcF results will be reported as safety assessments, see Section 18.1.5. Additional parameters will be part of the PD assessments, see section 17.1.1.2.

17.1.1.2 Parameters

PD parameters for serum potassium, heart rate and QTcF will be calculated as defined in Table 4, as data permit.

Table 4 PD Parameters for Serum Potassium, Heart Rate and QTcF

Parameter	Description	SAS Programming Notes
Emin, K	Minimum observed serum potassium	Minimum observed concentration after dose (pre-dose not included)
AUEC, K	Weighted mean serum potassium (0-4 hr).	Summation of each interval, each interval calculated as: (C2-C1)/2 * (t2-t1), where C2 and t2 are concentration and timepoint at the end of each interval, and C1 and t1 are concentration and timepoint at the start of each interval.
Emax, HR	Maximum observed heart rate	Maximum observed heart rate after dose (pre-dose not included)
AUEC, HR	Weighted mean heart rate (0-4 hr).	Summation of each interval, each interval calculated as: (C2-C1)/2 * (t2-t1), where C2 and t2 are heart rate and timepoint at the end of each interval, and C1 and t1 are heart rate and timepoint at the start of each interval.
Emax, QTcF	Maximum observed QTcF	Maximum observed QTcF after dose (pre-dose not included)
AUEC, QTcF	Weighted mean QTcF (0-4 hr).	Summation of each interval, each interval calculated as: (C2-C1)/2 * (t2-t1), where C2 and t2 are QTcF and timepoint at the end of each interval, and C1 and t1 are QTcF and timepoint at the start of each interval.

17.2 Pharmacodynamic Summaries

17.2.1 Pharmacodynamic Levels

Serum Potassium

BLQ serum potassium concentrations will be set to ½ lower limit of quantification (LLOQ) in the computation of mean concentration values. Descriptive statistics (n, arithmetic mean, SD, CV%, median, min, and max,) will be used to summarize serum potassium concentrations and changes from baseline by treatment at each scheduled time point.

Participants excluded from the PD analysis set will be flagged in the listing and excluded from descriptive statistics.

All individual participant serum potassium concentrations, time deviations and comments will be listed.

Linear plots of the arithmetic mean serum potassium concentrations by scheduled sampling time will be provided by treatment (2 treatments in one plot). These plots will show time in hours. The plots will match the summary table results.

Linear spaghetti plots of serum potassium concentrations by actual sampling times will be provided by treatment.

Heart rate and QTcF

Refer to Section 18.1.5 for reporting of the heart rate and QTcF values.

17.2.2 Pharmacodynamic Parameters

PD parameters will be calculated in SAS.

Actual times, rather than scheduled sampling times, will be used in all computations involving timepoints, except for pre-dose timepoint. Pre-dose timepoints will be set to zero.

Descriptive statistics (number of participants, arithmetic mean, SD, CV, geometric mean, median, min, and max) will be used to summarize the calculated PD parameters by treatment. For Emax and Emin, only median, min and max will be presented.

Participants excluded from the PD analysis set will be flagged in the listing and excluded from descriptive statistics.

All individual participant serum potassium parameters, heart rate and QTcF parameters will be listed.

17.2.2.1 Statistical Analysis of Pharmacodynamic Parameters

Analysis will be performed to compare the PD parameters after dosing of salbutamol HFA-152a MDI and salbutamol HFA-134a MDI (currently marketed Ventolin product). Analysis will be performed on the natural logarithm of Emin and AUEC of serum potassium, and EMax and AUEC of heart rate and QTcF, using a linear mixed model with the treatment and period (dosing day) as fixed effects and subjects as random effects. A one model will be used, grouped by parameter.

Point estimates and 90% CIs for treatment differences on the log scale derived from the model will be exponentiated to obtain estimates for geometric mean (GM) ratios and CIs on the original scale. The within-subject coefficients of variation (CVw) for AUEC, Emin and Emax will be calculated based on the loge-normal distribution.

Model Checking & Diagnostics:

- Model assumptions will be checked before analysis.
- The underlying distributional assumptions involved in the statistical analyses will be assessed by visual inspection of residual plots. Normality will be examined by normal probability plots while homogeneity of variance will be assessed by plotting the residuals against the predicted values for the model.
- If the assumptions are seriously violated, then alternative data transformations will be explored. If no suitable transformation can be found, equivalent nonparametric analyses (ex. Wilcoxon signed-rank test) will be performed.

The following kernel code of SAS PROC MIXED will be used:

```
proc mixed;
by parameter;
class subject treatment period;
model log(value)= treatment period / ddfm=kenwardroger cl;
random subject /type=un;
lsmeans treatment period /alpha=0.1;
/*estimates for treatment order Test1-Ref*/
estimate "T vs R" treatment 1  -1 /alpha=0.1;
run;
```

SAS code might be updated depending on the data. An unstructured type of the covariance matrices R (accounting for the within subject variability) and G (accounting for the between subject variability) will be used. If this model fails to converge, alternative covariance structures may be considered based on a lower AIC values (for example variance component, etc.). For the described linear mixed model analyses, 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.

Statistical analysis model table will present N, n, least squares GM values and associated 90% CI, GM ratios and associated 90% confidence intervals and within-subject CV.

Intercurrent events and handling of missing data:

- Participant level missing PD measurements considered as missing at random, will not be imputed.
- The PD measurements will be affected by occurrence of the intercurrent event (Treatment discontinuation of the study) would be treated as missing at random from the occurrence of the intercurrent event until the end of the study and only reliable available data will be used in the primary analysis and summary descriptive.

18.0 Safety Analyses

18.1 Safety Variables

The following safety variables will be summarized:

• Adverse Events (AEs)

• Vital Signs

- Supine Blood Pressure
  - Systolic Blood Pressure (SBP)
  - Diastolic Blood Pressure (DBP)
- Pulse rate

• Electrocardiograms (ECG)

- Heart Rate
- PR Interval
- QRS-Duration
- QT Interval
- QTc (Fridericia's) Interval

• Clinical Laboratory Evaluations

- Clinical Chemistry (including glucose measurements)
- Hematology
- Urinalysis

Impact of COVID-19 Pandemic on Safety Results

Available safety results of participants with COVID-19 will not be excluded from any safety analysis.

No specific analyses on safety endpoints will be performed on subjects without and with COVID-19.

18.1.1 Adverse Events

All AE summaries will include only treatment emergent adverse events (TEAEs). TEAE are those which occur (or worsen) after the first dose of study drug.

TEAEs 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.

A summary overview of the number of events, and number and percentage of participants reporting TEAEs, TEAEs by severity, TEAEs by relationship, SAEs, and participants who discontinued study drug due to an AE will be provided.

A breakdown of the number of TEAEs, number and percentage of participants reporting each TEAE, categorized by body system and preferred term coded according to MedDRA (Version 25.0 or higher), will be presented by treatment and overall. One such table will be presented for all TEAEs and one such table will be presented for TEAEs considered to be related to the study medication.

Participants will only be counted once within each body system or preferred term.

The system organ class and preferred terms in these tables will be ordered by descending (total) number of participants per system organ class and within the system organ class per preferred term.

A summary of events reported, categorized by relationship not related vs related, will be provided by treatment and overall.

A summary of events reported, categorized by severity (categories as recorded in the eCRF: mild, moderate, severe) will be provided by treatment and overall. If AEs are judged as severe, the additional indication life-threatening or results in death will be combined in the summary, resulting in the following severities:

mild

moderate

severe (no indication of life-threatening or fatal AE)

life-threatening (severe AE with indication life-threatening)

fatal (severe AE with indication results in death).

These tables will present the number of events, and number and percentage of participants per given category.

A listing of adverse events (AEs) leading to study discontinuation will be provided.

All AEs (including non-treatment-emergent events in a separate listing) recorded on the eCRF will be listed.

The following missing data will be imputed as defined (for calculations only / will not be presented):

- Missing AE start and / or end times for the calculation of onset and duration will be assumed to be at 00:01 for a start time and 23:59 for end times
- Missing AE severity or relationship will be assumed to be severe or related, respectively
- Missing AE start times for the determination of treatment emergence will be assumed to occur after treatment unless partial date documents the AE as happening prior to treatment
- Missing AE start times for the determination of treatment assignment will be assumed to occur after treatment on the recorded date one minute after dosing
- Missing AE start date: First of the month will be used unless this is before the date of first study treatment of the cohort (i.e. clinic group); in this case the date of first study treatment date will be used.
- Missing AE end date: Last day of the month will be used, unless this is after the date of last visit of the cohort (i.e. clinic group); in this case the last visit date of the cohort will be used.
- Completely missing start or end dates will remain missing, with no imputation applied. Consequently, time to onset and duration of such events will be missing.

Onset of AEs related to treatment and duration of AEs will be calculated as follows:

Onset (time since last dosing in days, hours, minutes [dd hh:mm])	AE start date/time - treatment start date/time.
Duration (in dd hh:mm)	AE end date/time – AE start date/time.

18.1.2 Deaths and Serious Adverse Events

A listing of deaths and other SAEs will be provided by participant.

If applicable, narratives of deaths, other SAEs, and other significant AEs will be described in the CSR.

18.1.3 Laboratory Data

Clinical laboratory data will be presented using units from the study data tabulation model (SDTM) Controlled Terminology.

All laboratory data will be listed, including laboratory variables not listed in the protocol. A separate listing, of out-of-normal-range values will also be provided. Normal ranges will be used directly from the clinical laboratory. An overview of clinical laboratory normal ranges is provided in separate document RefSet21001_21Jun21_4.pdf.

Clinical laboratory results outside the reference normal range will be flagged. In case the out of reference normal range values were considered clinically significant by the investigator, this will also be indicated in the listings. Comments with regard to the laboratory test results will be shown in a separate listing, and will cover reasons for not done measurements, specimen conditions, any comment available in the database related to laboratory measurements.

Descriptive statistics summarizing continuous laboratory results of clinical chemistry, hematology and routine urine analysis (observed values) by treatment and scheduled time will be provided.

Glucose

Linear plots of the arithmetic mean glucose concentrations by scheduled sampling time will be provided by treatment (2 treatments in one plot). These plots will show time in hours. The plots will match the summary table results.

Linear spaghetti plots of glucose concentrations by actual sampling times will be provided by treatment.

18.1.4 Vital Signs

Vital signs data (observed values) will be listed by participants and summarized descriptively by treatment per scheduled time point.

If SBP, DBP and/or pulse rate is out of the normal range, the physician's evaluation for that vital signs measurement will be listed. Normal ranges are as follows:

- SBP: 90 – 140 mmHg
- DBP: 50 – 90 mmHg
- Pulse Rate: 50 – 100 beats/min

If pulse rate is >85 beats/min at screening or day -1, the participant is not eligible for the study.

18.1.5 Electrocardiograms

The observed measurements for all ECG parameters (HR, PR, QRS, QT and QTc) and the corresponding abnormalities and physicians' conclusions will be listed by participant. The means of triplicate measurements for continuous parameters and the change from baseline of the mean triplicate measurements at each scheduled timepoint will be listed by participant.

Descriptive statistics will be provided to summarize mean ECG parameters (observed and changes from baseline) by treatment and scheduled time.

For heart rate and QTcF, linear plots of the arithmetic mean values (absolute values) by scheduled time will be provided by treatment (2 treatments in one plot). These plots will show time in hours. The plots will match the summary table results.

Linear spaghetti plots of the heart rate and QTcF values by actual times will be provided by treatment.

18.1.6 Other Observations Related to Safety

Bodyweight results will be listed.

19.0 Result Summary Public Disclosure Information

The following public study disclosure information will be provided:

- Summary of Subject Disposition at Each Study Period
- Summary Demographics
- Summary of Site Related Information
- Summary of Adverse Events Overview – Any AEs
- Summary of Adverse Events Overview – Any SAEs
- Summary of Adverse Events Overview – Any Drug Related SAEs
- Summary of Adverse Events Overview – Any Fatal SAEs
- Summary of Adverse Events Overview – Any Drug Related Fatal SAEs
- Summary of Common Non-serious AEs (>=5%) by System Organ Class and Preferred Term
- Summary of All-cause Mortality - Occurrence of Death Due to Any Cause
- Summary of Urinary Dipstick Results

The complete list of result summary public disclosure tables will be provided in Appendix 5: List of Public Disclosure Tables.

20.0 References

SAS Institute, Inc., SAS® Version 9.4 software, Cary, NC.

Clinical Study Protocol. A single dose two-way cross-over study in healthy participants to compare the pharmacokinetics (PK) of salbutamol administered via metered dose inhalers containing propellants HFA-152a and HFA 134a. Version 2.0, Final, 10 Feb 2022.

Appendix 1: Glossary of Abbreviations

Glossary of Abbreviations:	
ADAE	Adverse event analysis dataset
ADaM	Analysis data model
ADEG	ECG analysis dataset
ADLB	Laboratory analysis dataset
ADPC	Pharmacokinetic concentrations analysis dataset
ADPP	Pharmacokinetic parameters analysis dataset
ADSL	Subject-level analysis dataset
ADVS	Vital signs analysis dataset
AE	Adverse event
β-HCG	Beta-human chorionic gonadotropin
BMI	Body mass index
BQL	Below the quantifiable limit
CDISC	Clinical data interchange standard consortium
CI	Confidence interval
CRU	Clinical research unit
CSP	Clinical study protocol
CSR	Clinical study report
CV%	Coefficient of variation
CVw	Within participant coefficient of variation
DBP	Diastolic blood pressure
ECG	Electrocardiogram
eCRF	Electronic case report form
EDS	Early development services
FSH	Follicle stimulating hormone
geoCV%	CV% of the geometric mean
GSK	GlaxoSmithKline Research & Development Limited
ICH	The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IRT	Interactive response technology
LLOQ	Lower Limit of Quantification
LSM	Least Square Means
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities

MDI	Metered dose inhaler
Min	Minimum
PD	Pharmacodynamic
PK	Pharmacokinetic
RAMOS NG	Randomization and Medication Ordering System Next Generation
QA'd	Quality assured
QC'd	Quality controlled
SAP	Statistical analysis plan
SAE	Serious adverse event
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SBP	Systolic blood pressure
SD	Standard deviation
SDTM	Study data tabulation model
SmPC	Summary of product characteristics
TEAE	Treatment-emergent adverse event
TFL(s)	Tables, Figures and Listings
ULOQ	Upper Limit of Quantification
WHO	World Health Organization
WNL	WinNonlin
For PK and PD parameters please refer to Section 16 and 17	

Appendix 2: Schedule of Assessments

Procedure	Screening	Intervention period[a]						Discharge or early discontinuation
Study day	-28 to -1	-1	1 (pre-dose)	1	2	3	4	5
Confinement		X	X	X	X	X	X	X
Admission		X						
Discharge								X
Informed consent	X							
Inclusion and exclusion criteria	X	X	X					
Demography	X							
Physical examination[b]	X							X[b]
Body weight	X	X						
Height and BMI calculation	X							
Medical history (includes substance usage)	X							
Serum pregnancy test (females only)	X	X						X
FSH (females only)	X							
Serology (HBsAg, anti-HCV, anti-HIV 1 and 2)	X							
SARS-CoV-2 PCR test[c]		X			X			
Drug and alcohol screen	X	X						
Clinical laboratory assessments[d]	X	X						X
Blood sampling for serum potassium (PD) and glucose (safety)[e]			X[e]	X[e]			X[e]	
Vital signs[f]	X	X	X	X			X	X
12-lead ECG[g]	X	X	X	X			X	X
MDI teaching[h]		X	X				X	
Randomization			X					
Administration of study intervention[i]				X			X	
Blood sampling for PK[j]			X	X	X		X	X
AE review[k]				X[i]	X	X	X	X
SAE review[k]	X	X	X	X	X	X	X	X
Concomitant medication review	X	X	X	X	X	X	X	X

AE=adverse event; HCV=hepatitis C virus; HIV=human immunodeficiency virus; BMI=body mass index; ECG=electrocardiogram; FSH=follicle stimulating hormone; HBsAg=hepatitis B surface antigen; HR=heart rate; IMP=investigational medicinal product; MDI=metered dose inhaler; PCR= polymerase chain reaction; PD=pharmacodynamic(s); PK=pharmacokinetic(s); QTcF=QT interval corrected using Fridericia's formula; SARS-CoV-2= severe acute respiratory syndrome-corona virus type 2; SAE=serious adverse event;

a. Participants will be in the clinic for 1 period, from Day -1 until Day 5 (24 hours after the last dose on Day 4).
b. Complete physical examinations will be conducted at screening. Symptom driven physical examinations may be conducted at discharge or any other time, per the investigator's discretion.
c. Sampling of nasal and throat mucosal cells for PCR testing for SARS-CoV-2. If deemed necessary, additional tests may be conducted during the study per site specific requirements.
d. Clinical laboratory assessments (including clinical chemistry [includes liver chemistries], hematology, and urinalysis): at screening, on Day -1 (admission), and at discharge;
e. Blood sampling for serum potassium (PD) and glucose (safety): on each dosing day (Day 1 and 4), blood samples will be taken pre-dose and at the following time points post-dose: 15 and 30 minutes and 1, 1.5, 2 and 4 hours post-dose.
f. Vital signs (systolic and diastolic blood pressure, and pulse rate): vital signs will be recorded at screening, admission, on each dosing day (Day 1 and 4) at pre-dose and at the following time points post-dose: 15 and 30 minutes and 1, 1.5, 2 and 4 hours post-dose, and at discharge.
g. 12-lead ECG: 12-lead ECG will be recorded at screening, admission, on each dosing day (Day 1 and 4) at pre-dose and at the following time points post-dose: 15 and 30 minutes and 1, 1.5, 2 and 4 hours post-dose, and at discharge. As the ECG parameters QTc and HR will be PD parameters, ECG will be measured in triplicate at pre-dose on Days 1 and 4. The 3 pre-dose measures will be averaged for QTc interval and HR to derive one baseline value. Each individual capture of the triplicate 12-lead ECG set will be separated by 1 to 5 minutes between the first and the third ECG. Post-dose 12-lead ECG measurements will be single measurements on both dosing days. Note: if an ECG meets potential stopping criteria, then the ECG measurement should be repeated in triplicate, with the averaged QT and QTcF used to determine stopping.
h. Participants will be trained by using the CCI [redacted] device on Day -1 and prior to each dosing on Days 1 and 4. Additional training instructions are provided using the CCI [redacted] device which provides auditory feedback when the participant generates an adequate breath in:
   Day -1: using the CCI [redacted] device, review the instructions, with particular focus on Steps 4-7. Once the participant is comfortable with using the training device, practice completing a sequence of 8 puffs.
   Dosing days: using the CCI [redacted] device, review the instructions, and observe the patient performing a single puff using the training device. Provide feedback as necessary until proper technique is observed before conducting the full dose using the investigational inhaler.
   Additional training using the CCI [redacted] (eg, on Day 3) may be performed at the discretion of the clinic.
i. Administration of study intervention: start of the 8 inhalations study intervention, with the inhalations administered at 20-second intervals. Note: All post-dose time points will be from start of dosing (first inhalation).
j. PK blood sampling: on each dosing day (Day 1 and 4), PK blood samples will be taken at pre-dose, at 3, 5, 10, 15, 20, 30, and 45 minutes post-dose; and at 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16 and 24 hours post-dose for plasma salbutamol determination. PK collection will be from start of study intervention (i.e. first inhalation). When assessments are scheduled at the same time, ECG and vital signs will be taken first followed by the blood samples, with PK blood sampling on time.
k. All SAEs will be collected from the signing of the ICF until discharge.
   All AEs will be collected from the start of study intervention until discharge.

Appendix 3: List of In-Text Outputs

List of CSR In-Text Tables and Figures:		
Output	**Title**	**Analysis Set**
Table	Summary of Participant Disposition	Screened (all participants), and enrolled
Table	Summary of Demographics for Safety Set	Enrolled
Figure	Geometric Mean Plasma Salbutamol Concentrations versus Time Profile (Linear and Semi-Logarithmic Scale)	PK
Table	Summary Statistics of Salbutamol Plasma PK Parameters	PK
Figure	Scatterplot of Individual Values and Geometric Mean Salbutamol Plasma PK Parameters	PK
Table	Statistical Analysis on PK Parameters	PK
Figure	Arithmetic Mean PD Potassium versus Time Profile (Linear and Semi-Logarithmic Scale)	PD
Table	Summary Statistics of PD Potassium Parameters	PD
Table	Statistical Analysis on PD Potassium Parameters	PD
Figure	Arithmetic Mean Heart Rate and QTcF Values versus Time Profile by Parameter (Linear and Semi-Logarithmic Scale)	PD
Table	Summary Statistics of PD Heart Rate and QTcF Parameters	PD
Table	Statistical Analysis on PD Heart Rate and QTcF Parameters	PD
Table	Summary of all TEAEs by System Organ Class and Preferred Term	Safety
Table	Summary of Related TEAEs by System Organ Class and Preferred Term	Safety
Table	Summary of all TEAEs by Treatment by Relationship to Study Drug	Safety
Table	Summary of all TEAEs by Treatment by Severity	Safety

Appendix 4: List of End of Text Outputs

List of End of Text Tables and Figures:		
Output	**Title**	**Analysis Set**
Section 15.1 – Disposition and Demographic Data		
Table 15.1.1	Summary of Participant Disposition	Screened (all participants), and enrolled

Table 15.1.2	Summary of Participant Treatment Status and Reasons for Discontinuation of Study Treatment	Enrolled
Table 15.1.3	Summary of Demographics	Enrolled
Table 15.1.4	Summary of Major Protocol Deviations	Safety
Section 15.2 – Pharmacokinetic Data		
Table 15.2.1	Descriptive Statistics of Salbutamol Plasma Concentrations by Treatment	PK
Table 15.2.2	Descriptive Statistics of Salbutamol Plasma PK Parameters by Treatment	PK
Table 15.2.3	Statistical Analysis on Salbutamol PK Parameters	PK
Figure 15.2.4	Plot of Arithmetic Mean Salbutamol Plasma Concentrations versus Time (Linear and Semi-Logarithmic Scale)	PK
Figure 15.2.5	Plot of Median Salbutamol Plasma Concentrations versus Time (Linear and Semi-Logarithmic Scale)	PK
Figure 15.2.6	Combined Individual Salbutamol Plasma Concentrations versus Time Profile Linear and Semi-Logarithmic Scale)	PK
Figure 15.2.7	Individual Salbutamol Plasma Concentrations versus Time Profile (Linear and Semi-Logarithmic Scale)	PK
Figure 15.2.8	Individual Salbutamol PK parameters and Geometric Mean versus Treatment	PK
Section 15.3 – Pharmacodynamic Data		
Table 15.3.1	Descriptive Statistics of Serum Potassium Concentrations by Treatment	PD
Table 15.3.2	Descriptive Statistics of PD Serum Potassium Parameters by Treatment	PD
Table 15.3.3	Statistical Analysis on PD Serum Potassium Parameters by Treatment	PD
Figure 15.3.4	Plot of Arithmetic Mean PD Serum Potassium Concentrations versus Time (Linear Scale)	PD
Figure 15.3.5	Combined Individual PD Serum Potassium Concentrations versus Time Profile (Linear Scale)	PD
Table 15.3.6	Descriptive Statistics of PD Heart Rate and QTcF Parameters by Treatment	PD
Table 15.3.7	Statistical Analysis on PD Heart Rate and QTcF Parameters	PD
Figure 15.3.8	Plot of Arithmetic Mean PD Heart Rate and QTcF Values versus Time by Parameter (Linear Scale)	PD
Figure 15.3.9	Combined Individual PD Heart Rate and QTcF Values versus Time Profile by Parameter (Linear Scale)	PD
Section 15.4 Safety Data		
15.4.1 Adverse Events		

Table 15.4.1.1	Overview of Treatment-emergent Adverse Events	Safety
Table 15.4.1.2	Summary of Treatment emergent Adverse Events by System Organ Class and Preferred Term	Safety
Table 15.4.1.3	Summary of Treatment-emergent Adverse Events by Severity and by System Organ Class and Preferred Term	Safety
Table 15.4.1.4	Summary of Treatment-emergent Adverse Events Leading to Study Discontinuation by System Organ Class and Preferred Term	Safety
Table 15.4.1.5	Summary of Related Treatment-emergent Adverse Events by System Organ Class and Preferred Term	Safety
Table 15.4.1.6	Summary of Treatment-emergent Serious Adverse Events by System Organ Class and Preferred Term	Safety
Table 15.4.1.7	Summary of Related Treatment-emergent Serious Adverse Events by System Organ Class and Preferred Term	Safety
Table 15.4.1.8	Summary of Treatment-emergent Serious Adverse Events Leading to Discontinuation from the Study by System Organ Class and Preferred Term	Safety
15.4.2 Lists of Deaths, Other Serious and Significant Adverse Events		
Table 15.4.2.1	Listing of Deaths and Other Serious Adverse Events	Screened
15.4.3 Laboratory Data		
Table 15.4.3.1	Listing of Abnormal Laboratory Values	Safety
Table 15.4.3.2	Summary of Hematology Parameters	Safety
Table 15.4.3.3	Summary of Blood Chemistry Parameters	Safety
Table 15.4.3.4	Summary of Routine Urinalysis Parameters	Safety
Figure 15.4.3.5	Plot of Arithmetic Mean Glucose Concentrations versus Time (Linear Scale)	Safety
Figure 15.4.3.6	Combined Individual Glucose Concentrations versus Time Profile (Linear Scale)	Safety
Section 15.4.4 Other Safety Parameters		
Table 15.4.4.1	Summary of Vital Signs (Absolute Values)	Safety
Table 15.4.4.2	Summary of 12-Lead Electrocardiogram (Absolute Values and Changes from Baseline)	Safety

List of Subject Data Listings:	
Output	**Title**
Section 16.2.1 – Disposition	
Listing 16.2.1	Participant Disposition
Section 16.2.2 – Protocol Deviations	
Listing 16.2.2	Protocol Deviations

Section 16.2.3 – Excluded Participants	
Listing 16.2.3	Analysis Sets
Section 16.2.4 – Demographics and Baseline Characteristics	
Listing 16.2.4.1	Participant Demographics
Listing 16.2.4.2	Medical History
Listing 16.2.4.3	Drug and Alcohol Screen Results
Listing 16.2.4.4	Serology Test Results
Listing 16.2.4.5	Pregnancy Test and FSH Test Results
Listing 16.2.4.6	SARS-CoV-2 Results
Listing 16.2.4.7	Substance Use
Listing 16.2.4.8	Non-compliance to Inclusion or Exclusion Criteria
Listing 16.2.4.9	Early Study Intervention /Treatment Unblinding
Section 16.2.5 - Compliance	
Listing 16.2.5.1	Study Dates
Listing 16.2.5.2	Study Drug Administration
Section 16.2.6 – Response Data PK and PD	
Listing 16.2.6.1	Salbutamol Plasma Concentrations, Sampling Time Deviations and Comments
Listing 16.2.6.2	Salbutamol Plasma PK Parameters
Listing 16.2.6.3	Serum Potassium Concentrations, Sampling Time Deviations and Comments
Listing 16.2.6.4	Serum Potassium Parameters
Listing 16.2.6.5	Heart Rate and QTcF Parameters
Section 16.2.7 – Adverse Events Data	
Listing 16.2.7.1	Adverse Events
Listing 16.2.7.2	Adverse Events Leading to Study Discontinuation
Listing 16.2.7.3	Prior and Concomitant Medications
Section 16.2.8 – Laboratory Data	
Listing 16.2.8.1	Clinical Laboratory Results – Hematology
Listing 16.2.8.2	Clinical Laboratory Results – Chemistry
Listing 16.2.8.3	Clinical Laboratory Results – Urinalysis
Listing 16.2.8.4	Clinical Laboratory Results – Comments
Section 16.2.9 – Other Safety Data	
Listing 16.2.9.1	Vital Signs
Listing 16.2.9.2	12-Lead Electrocardiogram Results
Listing 16.2.9.3	Body Weight

Other Appendix Outputs:	
Output	**Title**
Appendix 16.1.9.2	Statistical Appendices

Appendix 5: List of Public Disclosure Tables

All outputs related to primary and secondary endpoints will be taken from the main list of outputs in Appendix 4: List of End of Text Outputs.

Public Disclosure Tables:	
Table 1	Summary of Subject Disposition at Each Study Period
Table 2	Summary Demographics
Table 3	Summary of Site Related Information
Table 4	Summary of Adverse Events Overview – Any AEs
Table 5	Summary of Adverse Events Overview – Any SAEs
Table 6	Summary of Adverse Events Overview – Any Drug Related SAEs
Table 7	Summary of Adverse Events Overview – Any Fatal SAEs
Table 8	Summary of Adverse Events Overview – Any Drug Related Fatal SAEs
Table 9	Summary of Common Non-serious AEs (>=5%) by System Organ Class and Preferred Term
Table 10	Summary of All-cause Mortality - Occurrence of Death Due to Any Cause
Table 11	Summary of Urinary Dipstick Results

19.0 Document History

Version Date	Modified/Reviewed By	Brief Summary of Changes (if created from a template, include template code)
17-Jan-2023	PPD	Internal review version
24-Jan-2023		First draft version – CSP version 1.0 (09Dec22)
13-Feb-2023		Second draft version – CSP version 2.0 (10Feb23)- internal review version
17-Feb-2023		Second draft version – CSP version 2.0 (10Feb23)
21-Mar-2023		Third draft version – CSP version 2.0 (10Feb23)
04-Apr-2023		Fourth draft version – CSP version 2.0 (10Feb23)
13-Apr-2023		Prefinal – CSP version 2.0 (10Feb23)
18-Apr-2023		Final – CSP version 2.0 (10Feb23)
20-Apr-2023		Final – CSP version 2.0 (10Feb23)
02-Jun-2023		Draft v2.0 (see SAP version 4.0 for an overview of the updates).
13-Jun-2023		Final version for signatures