Protocol

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: 11 February 2023 (This date has been redacted on Page 3)

Clinical Study Protocol

Primary Study Intervention(s)	Salbutamol administered via metered dose inhalers containing propellant HFA-152a (Test)
Other Study Intervention(s)	Salbutamol administered via metered dose inhalers containing propellant HFA-134a (Reference)
Study Identifier	219430
EudraCT Number	2022-003406-77
Approval Date	10 Feb 2023
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
Compound Number/Name	AH3365 (Salbutamol)
Brief Title	Green (Sustainable) Ventolin - PK study in healthy volunteers
Sponsor	GlaxoSmithKline Research & Development Limited 980 Great West Road, Brentford, Middlesex, TW8 9GS, UK
Sponsor Signatory	Jeff Min, MD, MSCE Clinical Development Director Clinical Sciences Respiratory

Medical monitor name and contact information can be found in the Study Team Contact List.

Protocol Amendment 1 Investigator Agreement

I agree:

- **To conduct the study in compliance with this protocol, any future protocol amendments, with the terms of the clinical trial agreement and with any other study conduct procedures and/or study conduct documents provided by GSK.**
- **To assume responsibility for the proper conduct of the study at this site.**
- **That I am aware of and will comply with GCP and all applicable regulatory requirements.**
- **That I will comply with the terms of the site agreement.**
- **To comply with local bio-safety legislation.**
- **To ensure that all persons assisting me with the study are adequately informed about the GSK study intervention and other study-related duties and functions as described in the protocol.**
- **To supervise any individual or party to whom I have delegated study-related duties and functions conducted at the study site.**
- **To ensure that any individual or party to whom I have delegated study-related duties and functions conducted at the study site are qualified to perform those study-related duties and functions.**
- **To acquire the reference ranges for laboratory tests performed locally and, if required by local regulations, obtain the laboratory's current certification or Quality Assurance procedure manual.**
- **To ensure that no clinical samples (including serum samples) are retained on-site or elsewhere without the approval of GSK and the expressphysical or digitalinformed consent of the participant.**
- **To perform no biological assays on the clinical samples other than those described in the protocol or its amendment(s).To co-operate with representative(s) of GSK in the monitoring and data management processes of the study with respect to data entry and resolution of queries about the data.**
- **To have control of all essential documents and records generated under my responsibility before, during, and after the study.**
- **That I have been informed that certain regulatory authorities require the sponsor to obtain and supply, as necessary, details about the investigator(s)' ownership interest in the sponsor or the study intervention(s), and more generally about their financial ties with the sponsor. GSK will use and disclose the information solely for the purpose of complying with regulatory requirements.**

Hence, I:

- **Agree to supply GSK with any necessary information regarding ownership interest and financial ties (including those of my spouse and dependent children).**
- **Agree to promptly update this information if any relevant changes occur during the study and for 1 year following completion of the study.**
- **Agree that GSK may disclose any information about such ownership interests and financial ties to regulatory authorities.**
- **Agree to provide GSK with an updated Curriculum Vitae and all other documents required by regulatory agencies for this study.**

Study identifier	219430
EudraCT number	2022-003406-77
Approval date	10 Feb 2023
Title	Principal Investigator
Investigator name	Salah Hadi, MD
Signature	PPD
Date of signature (DD Month YYYY)	

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date of Issue**
Amendment 1	10 February 2023
Original Protocol	09 December 2022

Amendment 1 (10 Feb 2023)

This amendment is considered substantial based on the criteria defined in EU Clinical Trial Regulation No 536/2014 of the European Parliament and the Council of the European Union because it concerns the Investigational Medicinal Product and therefore impacts the scientific value of the study.

Overall rationale for the current Amendment:

CCI [redacted]. Protocol Amendment 1 addresses the removal of the CCI [redacted] study arm and change in study design from 3-way to 2-way crossover.

CCI [redacted]

Protocol Amendment 1 also addresses clarification required by the Ethics Committee Board.

List of main changes in the protocol and their rationale:

Section # and title	Description of change	Brief rationale
Title page	The title was adapted to a 2-way cross-over study with 1 test formulation.	To reflect the new design of the study.
Section 1, Protocol Summary	The protocol summary has been updated to relflect that the study has a 2-way cross-over design with 1 test reference.	To reflect the new design of the study.
Section 1.2, Schema, Figure 1	The study design overview has been updated to reflect that the study has a 2-way cross-over design with 1 test reference.	To reflect the 2-way cross-over design and the removal of test Formulation 2 from the study design.

Section # and title	Description of change	Brief rationale
Section 1.3, Schedule of activities,Table 1	The schedule of activities has been adapted to reflect that subjects will remain in the clinic for 6 days instead of 9 and will have 2 treatments instead of 3.	To reflect that there will be 2 treatment periods instead of 3.
Section 2.2.2, Background information on the product	Text which describes the CCI formulation has been removed.	To reflect the removal of test Formulation 2 from the study design.
Section 2.3, Benefit/Risk assessment	The text was adapted to reflect that there is 1 test formulation.	To reflect the removal of test Formulation 2 from the study design.
Section 2.3.3, Overall benefit-risk conclusion	The text was adapted to reflect that there is 1 test formulation.	To reflect the removal of test Formulation 2 from the study design.
Section 3, Objectives	The objectives have been rephrased to reflect that there is 1 test reference.	To reflect the removal of test Formulation 2 from the study design.
Section 3.1, Primary Estimand	The text was adapted to reflect the statistics for 1 instead of 2 test formulations.	To reflect the removal of test Formulation 2 from the study design.
Section 3.2, Secondary Estimand (1)	The text was adapted to reflect that there is 1 test formulation.	To reflect the removal of test Formulation 2 from the study design.
Section 3.3, Secondary Estimand (2)	The text was adapted to reflect that there is 1 test formulation.	To reflect the removal of test Formulation 2 from the study design.
Section 3.4, Secondary Estimand (3)	The text was adapted to reflect that there is 1 test formulation.	To reflect the removal of test Formulation 2 from the study design.
Section 4.1, Overall design	The text was adapted to reflect that there will be 2 treatment sequences instead of 6 and clarification to equal assignment of treatment sequence to subjects.	To reflect the removal of test Formulation 2 from the study design.
Section 4.4, End-of-study definition	The text was adapted to reflect that there are 2 treatments instead of 3 treatments in total.	To reflect the removal of test Formulation 2 from the study design.
Section 6.1, Study	Treatment Formulation 2	To reflect the removal of test

Section # and title	Description of change	Brief rationale
intervention(s) administered, Table 4	containing [redacted] has been deleted from Table 4.	Formulation 2 from the study design.
Section 6.3, Assignment to study intervention	Text has been adapted to reflect that there will be 2 treatment sequences instead of 6.	To reflect the removal of test Formulation 2 from the study design.
Section 6.4, Blinding	Text has been adapted to reflect that there will be 2 treatment sequences instead of 6, and 2 treatment periods instead of 3. Also a 2-way cross-over design will be used instead of a Williams squares design.	To reflect the 2-way cross-over design and the removal of test Formulation 2 from the study design.
Section 6.9, Prior and concomitant therapy	Text has been adapted to reflect that day of discharge will be Day 5 instead of Day 8.	To reflect a change in study design.
Section 6.9, Prior and concomitant therapy	Text has been adapted to explain why paracetamol is not allowed during the 24 hours predose or post dose on the dosing days.	To address a comment from the Ethics Committee.
Section 9, Statistical considerations	Text has been adapted to clarify the statistical analysis plan will be finalized prior to database lock.	This information was added as requested by the Independent Ethics Committee.
Section 9.1, Statistical hypotheses	The text was adapted to reflect that there are 2 treatments instead of 3 treatments in total.	To reflect the removal of test Formulation 2 from the study design.
Section 9.3.1, Pharmacokinetic analysis	The text was adapted to reflect that there are 2 treatments instead of 3 treatments in total.	To reflect the removal of test Formulation 2 from the study design.
Section 9.3.2, Safety analysis	The text was adapted to reflect that presentation of the safety data will not be according to GSK's IDSL standards.	Removal of text to reflect that the [redacted] process will be followed, which will be described in the statistical analysis plan.
Section 9.5, Sample size determination	The calculations for the sample size sensitivity were updated.	To reflect the removal of test Formulation 2 from the study design.
Section 10.2, Appendix 2: Clinical laboratory tests,	The footnote in Table 9 was adapted to reflect that there are	To reflect the removal of test Formulation 2 from the study design.

Section # and title	Description of change	Brief rationale
Table 9	2 dosing days instead of 3.	
Section 10.4.2, Contraception guidance	The contraceptive period for male participants has been changed from 90 days after last study interventions to 48 hours after last study intervention.	To address a comment from the Ethics Comittee
Section 10.8, Appendix 8: Protocol amendment history	A reference to the protocol amendment summary of changes was added to this section.	To reflect that a protocol amendment has been prepared for this study.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ADE	Adverse device effect
AE	Adverse event
ALT	Alanine transaminase
AST	Aspartate transaminase
ATC	Anatomical Therapeutic Chemical code
AUC	Area under the curve
AxMP	Auxiliary medicinal product
BMI	Body mass index
CA	Competent authority
CCMO	Centrale Commissie Mensgebonden Onderzoek
CFC	Chlorofluorocarbon
CFR	Code of Federal Regulations
CI	Confidence intervals
CIOMS	Council for International Organizations of Medical Sciences
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	Coronavirus disease 2019
CPK	Creatine phosphokinase
CRF	Case report form
CRO	Clinical Research Organization
CSR	Clinical study report
ECG	Electrocardiogram
eCRF	Electronic case report form
FDA	Food and Drug Administration, United States of America

Abbreviation	Definition
FEV1	Forced expiratory volume in 1 second
FSFV	First subject first visit
FSH	Follicle stimulating hormone
GC	Gas chromatography
GCP	Good Clinical Practice
GINA	Global Initiative for Asthma
GMR	Geometric mean ratio
GSK	GlaxoSmithKline
GWP	Global warming potential
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HFA	Hydrofluoroalkane
HFA-134a	1,1,1,2-tetrafluoroethane
HFA-152a	1,1-difluoroethane
HIV	Human immunodeficiency virus
HR	Heart rate
HRT	Hormonal replacement therapy
ICF	Informed consent form
ICH	International Council for Harmonisation
ICMJE	International Committee of Medical Journal Editors
ICSR	Individual case safety reports
IDSL	Integrated Data Standards Library
IEC	Independent ethics committee
IFU	Instructions for use

Abbreviation	Definition
IgG	Immunoglobulin G
IMP	Investigational medicinal product
INR	International normalized ratio
IRB	Institutional review board
IRT	Interactive response technology
LC-MS-MS	Liquid chromatography tandem mass spectrometry
LDH	Lactate dehydrogenase
LLOQ	Lower limit of quantification
MDI	Metered dose inhaler
MedDRA	Medical Dictionary for Regulatory Activities
MRT	Mean residence time
MSDS	Material Safety Data Sheet
NIMP	Noninvestigational medicinal product
PCR	Polymerase chain reaction
PD	Pharmacodynamic(s)
PFT	Pulmonary function testing
PK	Pharmacokinetic(s)
QTc	Corrected QT interval
QTcF	QT interval corrected using Fridericia's formula
QTL	Quality tolerance limit
RAMOS NG	Randomization and Medication Ordering System Next Generation
RR	Respiratory rate
SADE	Serious adverse device effect

Abbreviation	Definition
SAE	Serious adverse event
SARS-CoV-2	Severe acute respiratory syndrome-corona virus type 2
SMG	Safety and medical governance
SmPC	Summary of product characteristics
SoA	Schedule of activities
SPO2	Saturation of peripheral oxygen
TEAE	Treatment-emergent adverse event
THC	Tetrahydrocannabinol
ULN	Upper limit of normal
USADE	Unanticipated serious adverse device effect
WOCBP	Woman of childbearing potential
WONCBP	Woman of nonchildbearing potential

1. PROTOCOL SUMMARY

1.1. Synopsis

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

Brief Title:

Green (Sustainable) Ventolin - PK study in healthy volunteers

Rationale:

In a metered dose inhaler (MDI), micronized particles of salbutamol are suspended in a propellant, currently hydrofluoroalkane 1,1,1,2-tetrafluoroethane (HFA-134a). However, this propellant has significant global warming potential and hence its use in medicine and other applications is being phased out under mounting environmental pressure to replace it with a low carbon footprint alternative such as hydrofluoroalkane 1,1-difluoroethane (HFA-152a).

GSK is seeking to develop a sustainable version of Ventolin Evohaler (salbutamol sulfate suspension in propellant hydrofluoroalkane, HFA-134a) to address global climate change.

Objectives, Endpoints, and Estimands:

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
Secondary	
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 • $t_{1/2}$
Pharmacodynamics (PD): 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)

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 and wrong treatment - 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.

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 and wrong treatment - 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.

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 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 and wrong treatment - 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 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).

- **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).

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 MDI.

- **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. Descriptive summary by treatment groups are:

  - Salbutamol HFA-152a MDI
  - Salbutamol HFA-134a 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 ECGs 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).

Overall Design:

This is a randomized, double-blind, single dose, 2-way cross-over study in healthy male and female participants with salbutamol. On each dosing day, 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. There will be a minimum washout period of 72 hours between each treatment period.

Number of Participants:

Thirty (30) participants will be included in the trial.

Intervention Groups and Duration:

While HFA-152a alone has been well-tolerated in humans, this is the first administration of salbutamol + HFA-152a. Therefore, a sentinel dosing approach will be utilized, so that any emergent safety signals from the combination can be identified prior to dosing of the broader cohort.

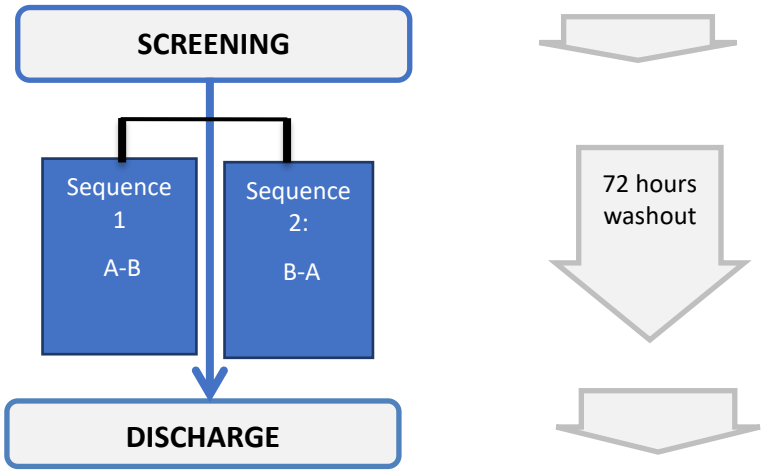
For the first dose of the treatment sequence, sentinel dosing will be implemented in the first 2 participants. Two participants will be dosed (one to currently approved Ventolin Evohaler [HFA-134a] and one to Salbutamol HFA-152a MDI). Following review of a minimum of 24 hours safety data, all remaining 28 participants will be dosed.

Remaining participants will be randomized only after review of at least 24 hours safety and tolerability data (i.e. AE/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 (e.g., 4 groups of seven or 2 groups of fourteen etc). The participant population will be assigned equally to the total number of treatment sequences. The site will have no visibility of the order in which the treatment arms are to be assigned as this will be managed by the RAMOS IRT system.

1.2. Schema

Figure 1 Study design overview



Treatment A: Salbutamol HFA-152a MDI

Treatment B: Salbutamol HFA-134a MDI

HFA-152a=hydrofluoroalkane 1,1-difluoroethane; HFA-134a=hydrofluoroalkane 1,1,1,2-tetrafluoroethane; MDI=metered dose inhaler

1.3. Schedule of activities (SoA)

The Schedule of Activities (SoA) can be found in Table 1 on the next page.

Table 1 Schedule of Activities

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 device on Day -1 and prior to each dosing on Days 1 and 4. Additional training instructions are provided using the CCI device which provides auditory feedback when the participant generates an adequate breath in:
   Day -1: using the CCI 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 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 (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.

2. INTRODUCTION

2.1. Study rationale

In the currently marketed Ventolin MDI, micronized particles of salbutamol are suspended in a propellant, currently HFA-134a. However, this propellant has significant GWP and hence its use in medicine and other applications is being phased out under mounting environmental pressure to replace it with a low carbon footprint alternative such as HFA-152a.

GSK is seeking to develop a sustainable version of Ventolin Evohaler (salbutamol sulfate suspension in propellant hydrofluoroalkane, HFA-134a) to address global climate change.

Salbutamol sulfate is a selective β2–adrenergic receptor agonist that acts on bronchial smooth muscle providing short acting (4 to 6 hour) bronchodilation with a fast onset (within 5 minutes) and is suitable for the relief and prevention of asthma symptoms and reversible airway obstruction.

Inhaled salbutamol has been approved for human use since 1968 initially as an MDI containing CFC propellants. These were later replaced with propellant HFA-134a due to international treaties phasing out CFC production arising from environmental concern. The current product, Ventolin Evohaler, is approved in over 130 countries.

The change in propellant from HFA-134a to HFA-152a is supported by a nonclinical toxicology program for HFA-152a conducted by the propellant manufacturer in accordance with ICH guidelines.

In human exposure studies, HFA-152a was well tolerated, had minimal impact on taste, and was rapidly cleared from the blood. HFA-152a has similar PK properties to the current HFA-134a propellant and has also been shown to have no toxic effect at vapor concentrations far in excess of those likely to be experienced by patients.

The maximum recommended total daily dose of salbutamol for chronic use delivered via the Ventolin MDI is 800 µg. This dose requires 8 inhalations (800 µg salbutamol). The exposure to HFA-152a (8 x 63 µL) is estimated to be 454 µg/day (6.87 µmol/day). This is well below the exposures of HFA-152 shown to have no adverse effects in humans (Section 2.2.5.1).

2.2. Background

The current propellant used in Ventolin Evohaler MDI is a potent greenhouse gas, which urgently needs to be addressed to reduce our climate impact. GSK is developing a sustainable version of its Ventolin Evohaler product using an alternative new propellant (HFA-152a) with a much lower GWP compared to the current propellant HFA-134a. CCI [redacted]

2.2.1. Background information on the disease to be treated

Salbutamol sulfate is used in the management of bronchospasm and reversible airway obstruction. These symptoms arise in patients with a variety of airway diseases including asthma, chronic bronchitis, and emphysema. The predominant use of salbutamol is in asthma, which is a heterogeneous disease usually characterized by chronic airway inflammation. It is defined by a history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation [GINA, 2022].

Asthma is also usually associated with airway hyperresponsiveness to direct or indirect stimuli and with chronic airway inflammation. These features usually persist, even when symptoms are absent or lung function is normal but may normalize with treatment [GINA, 2022].

Approximately 339 million people currently suffer from asthma, and it is the most common noncommunicable disease among children [WHO, 2020]. Asthma requires medical assessment and care when it occurs on either a persistent, or intermittent but frequently recurring basis. Exacerbations of asthma are episodes characterized by a progressive increase in symptoms of shortness of breath, cough, wheezing, or chest tightness and a progressive decrease in lung function, such that they represent a change from the patient's usual status that is sufficient to require a change in treatment [GINA, 2022]. Severe exacerbations are potentially life threatening and their treatment requires close medical supervision [GINA, 2022].

Pharmacotherapy for asthma follows a stepwise process determined by symptoms and disease severity. The most common treatment options are short- and long-acting bronchodilators, corticosteroid anti-inflammatory agents, and combination products containing both bronchodilators and corticosteroids. Biological agents are also available for more severe disease in patients with eosinophilic asthma. Short-acting reliever medications such as salbutamol sulfate are a cornerstone of asthma therapy for as-needed relief of breakthrough symptoms, including worsening asthma or exacerbations [GINA, 2022].

2.2.2. Background information on the product

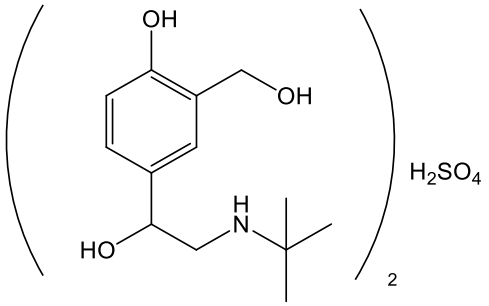
Salbutamol sulfate, the active ingredient in Ventolin Evohaler (HFA-134a), is approved in over 130 countries globally.

Salbutamol sulfate is available in a variety of formulations suitable for inhalation by adults and children including solutions for nebulization, dry powder inhalers, and MDIs with or without spacers. Salbutamol sulfate is widely used in all severities of asthma to relieve and/or prevent symptoms. Salbutamol sulfate is a selective β2-adrenoceptor agonist that acts on the β2-adrenoceptors in bronchial smooth muscle providing short acting (4 to 6 hour) bronchodilation with a fast onset (within 5 minutes if salbutamol is inhaled) and is suitable for the relief and prevention of asthma symptoms and reversible airway obstruction. It is used to relieve symptoms when they occur and to prevent them

in those circumstances recognized by the patient to precipitate an asthma attack (e.g., before exercise or unavoidable allergen exposure).

Information on the chemical structure of salbutamol sulfate is provided in Table 2.

Table 2 Structural information for salbutamol sulfate

Structural formula:	
Molecular formula:	$(C_{13}H_{21}NO_3)_2 \times H_2SO_4$

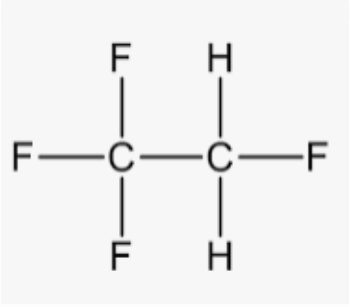
ATC=Anatomical Therapeutic Chemical code
Pharmacotherapeutic group: adrenergic, inhalants. Selective β2-adrenoreceptor agonists. ATC code: R03AC02

The sustainable new version of Ventolin will use propellant HFA-152a which is being investigated to replace propellant HFA-134a. The chemical structures of these 2 propellants are presented in Figure 2.

Figure 2 Chemical structures of HFA-134a and HFA-152a

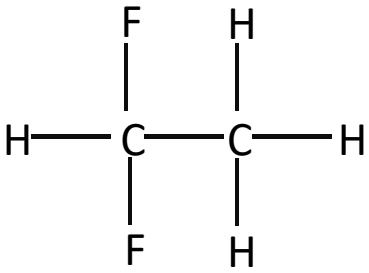
Propellant HFA-134a

1,1,1,2–tetrafluoroethane



Propellant HFA-152a

1,1–difluoroethane



Ventolin HFA-152a will be developed as a replacement product for the current Ventolin Evohaler (HFA-134a) with the same indications and posology. Ventolin HFA-152a is an MDI delivering 100 µg of salbutamol (as salbutamol sulfate) per dose; 200 doses per device. Salbutamol has a duration of action of 4 to 6 hours with administration of up to 2 inhalations (200 µg total) not exceeding 4 times daily.

In this study, one formulation of salbutamol HFA-152a MDI will be compared to the current Ventolin Evohaler (HFA-134a).

2.2.3. Quality development

GSK's Ventolin brand of salbutamol sulfate or salbutamol has existed as an MDI medicinal product and has been available to patients for over 50 years. The Ventolin MDI product was originally introduced containing CFC-based propellants (P11 and P12) with the drug substance salbutamol and oleic acid as a surfactant-type excipient. The product was later reformulated to remove CFC propellants and switched to a 2-component formulation comprising HFA propellant (HFA-134a), with the drug substance salbutamol sulfate, to address concerns about depletion of the ozone in the stratosphere over 20 years ago. This product is referred to as Ventolin Evohaler (HFA-134a).

2.2.4. Nonclinical development

The change in propellant from HFA-134a to HFA-152a is supported by a nonclinical toxicology program for HFA-152a conducted by the propellant manufacturer in accordance with current ICH guidelines for the technical requirements of nonclinical testing of pharmaceuticals for human use. CCI [redacted]

[redacted]

2.2.5. Clinical development

Inhaled salbutamol sulfate marketed as Ventolin has been approved for human use since 1968 initially as an MDI containing CFC propellants and later replaced with propellant HFA-134a with continued positive risk-benefit profile. GSK is now planning to replace the HFA-134a propellant with the HFA-152a propellant to reduce its global warming potential as stated above.

2.2.5.1. Background information on propellant HFA-152a

In humans, a study was performed to determine the uptake, distribution, and elimination of HFA-152a during and after short-term inhalation exposure [Ernstgård, 2012]. Healthy participants were exposed to 0 ppm, 200 ppm or 1000 ppm HFA-152a for 2 hours at light

exercise in an exposure chamber. Capillary blood, urine, and exhaled air were sampled up to 22 hours post-exposure and analyzed for HFA-152a. Fluoride and other potential metabolites were analyzed in urine. Symptoms of irritation and central nervous system effects were rated, and inflammatory markers were analyzed in blood. Within a few minutes of exposure to 200 and 1000 ppm, HFA-152a increased rapidly in blood and reached average levels of 7.4 and 34.3 µM, respectively. The post-exposure decreases in blood were fast and parallel to those in exhaled air. The estimated net uptake during exposure to 1000 ppm of 6.6 mmol (6.7%) equates to the amount exhaled post-exposure. About 20 µmol excess fluoride (0.013% of inhaled HFA-152a on a molar basis) was excreted in urine after exposure to 1000 ppm, compared to control. No fluorine-containing metabolites were detected in urine. Symptom ratings and changes in inflammatory markers revealed no exposure-related effects.

CCI

2.2.5.2. Salbutamol sulfate and propellant HFA-152a MDI

At the maximum recommended daily dose of 8 inhalations of salbutamol sulfate, the exposure to HFA-152a (8 x 63 µL) is estimated to be 454 µg/day (6.87 µmol/day). This is well below the exposures shown to have no adverse effects in humans. The human peak blood exposure (Cmax) of HFA-152a from the salbutamol HFA-152a propellant MDI for 8 actuations of 63 µL (delivering a total dose of 800 µg of salbutamol) is estimated to be 1.739 mg/L (26.2 µmol/L). This represents acute and transient exposure to HFA-152a, whereas, following extended exposure 1000 ppm of HFA-152a for 2 hours in an exposure chamber resulted in average concentrations of 34.3 µmol/L, which was well tolerated, had minimal impact on taste, and was rapidly cleared from the blood.

Therefore, HFA-152a is expected to have similar characteristics to the HFA-134a propellant used in the currently marketed Ventolin Evohaler (HFA-134a), in that it has been shown to have no toxic effect at vapor concentrations in excess of those likely to be experienced by patients.

2.3. Benefit/risk assessment

This study will be conducted to assess the PK and safety of salbutamol delivered via MDI containing propellant HFA-152a, and to compare to MDI containing propellant HFA-134a. There is no added benefit expected for the healthy participants. A risk assessment has been presented in Section 2.3.1.

2.3.1. Risk assessment

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
Study interventions		
Based on nonclinical and clinical studies conducted with HFA-152a, and information from the 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 arrythmias).	Hypokalemia: β-adrenergic agonist medicines may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects. The decrease in serum potassium is usually transient, not requiring supplementation. Hyperglycemia: β-adrenergic agonist medicines may produce a transient rise in serum glucose which is not expected to be clinically significant with inhalational administration. However, large doses of intravenous salbuterol have been reported to aggravate preexisting diabetes mellitus and ketoacidosis. Cardiovascular effects: β-adrenergic agonist medicines may produce clinically significant cardiovascular effects in some patients such as changes in pulse rate or blood pressure. In addition, β-agonists have been reported to produce ECG changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression. The clinical relevance of these findings is unknown.	Healthy participants are included who will be carefully screened against the defined inclusion and exclusion criteria (including overall cardiac health, vital signs, ECG interval values, and lab safety values [including serum potassium and glucose levels) and by ECG monitoring and lab PD/safety assessments (including serum potassium and glucose levels) as per the SoA. A sentinel dosing approach will be implemented for the first dosing period such that post-dose safety data in a limited number of participants will be reviewed prior to further dosing.
Study procedures		
There are no specific risks associated with the study design.		

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
Other		
COVID-19 infection	The risk-benefit assessment for the participants receiving the study intervention remains unchanged in relation to the COVID-19 pandemic as available clinical data do not suggest that administration of salbutamol will lead to suppression or modulation of the immune system. In addition, the mode of action does not appear to have any clinically significant adverse effects on the respiratory or cardiovascular system, which are the systems most affected by a SARS-CoV-2 infection.	As the participants to be included in this study are in general young to middle aged without major comorbidities, the study population is not considered to be a high-risk population for serious COVID-19. Only persons with a negative SARS-CoV-2 test at admission to the clinical research centre will be allowed to participate in the study. In addition, all appropriate measures to prevent SARS-CoV-2 infection during the study will be taken as detailed in Section 4.2.2.

COVID-19=coronavirus disease 2019; ECG=electrocardiogram; HFA-134a=1,1,1,2-tetrafluoroethane ; HFA-152a=1,1-difluoroethane; SARS-CoV-2=severe acute respiratory syndrome-corona virus type 2; SmPC=summary of product characteristics; SoA=schedule of activities

2.3.2. Benefit assessment

The study data will provide generally applicable information to support understanding of the PK and PD for all MDI-based therapies with salbutamol and based on HFA-152a as a propellant.

2.3.3. Overall benefit-risk conclusion

Taking into account the measures taken to minimize risk to participants in this study, the potential risks identified in association with salbutamol sulfate suspension in propellant HFA-152a (Test) or HFA-134a (Reference) are justified by the anticipated benefits to all ongoing and future programs with HFA-152a as a propellant.

3. OBJECTIVES, ENDPOINTS, AND ESTIMANDS

Table 3 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
Secondary	
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 • $t_{1/2}$
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)

AUC=area under the curve; ECG=electrocardiogram; HFA-134a=1,1,1,2-tetrafluoroethane ; HFA-152a=1,1-difluoroethane ; HR=heart rate; MDI=metered dose inhaler; PD=pharmacodynamic(s); PK=pharmacokinetic(s)

3.1. 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 and wrong treatment - 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.

3.2. 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 and wrong treatment - 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.

3.3. 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 and wrong treatment - 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).

3.4. 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-134a 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).

4. STUDY DESIGN

4.1. Overall 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 the test treatment and a reference treatment. There will be a minimum washout period of 72 hours between each treatment period.

Participants will be randomly assigned to one of 2 treatment sequences in 2 treatment periods using a cross-over design. The following treatment sequences will be tested:

Treatment Sequence 1: AB

Treatment Sequence 2: BA

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. AE/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 [redacted]. The participant population will be assigned equally to the total number of treatment sequences. The site will have no visibility of the order in which the treatment arms are to be assigned as this will be managed by the RAMOS IRT system.

4.2. Scientific rationale for study design

Healthy participants have been chosen as the study population due to the study design and the low risk of clinically significant toxicity at anticipated exposure levels. Additionally, the duration of exposure is sufficiently short to not be able to provide clear therapeutic benefit and justify patients discontinuing current therapies. Moreover, use of healthy participants as opposed to patients will allow a clearer interpretation of the study results, as there will be no confounding factors resulting from changes in disease state and/or concomitant medications.

A cross-over design to compare the different treatments was chosen to reduce the influence of confounding covariates as each participant serves as their own control. The cross-over design requires a small number of participants compared to a parallel group design. Carryover effects are expected to be eliminated by introducing a washout phase of a minimum of 72 hours between study drug administrations (expected to be equivalent to at least 5 half-lives of salbutamol).

4.2.1. Participant input into design

Not applicable.

4.2.2. COVID-19 risk mitigation

This study will be conducted in accordance with guidance from the Central Committee on Research Involving Human Subjects CCMO Dutch CA on conducting Phase 1 trials in clinical research centres in the Netherlands during the COVID-19 pandemic.

During the entire study, the clinical research centre will implement all recommendations issued by the Dutch government, including specific guidelines related to clinical research executed in clinical research centres with respect to minimizing the risk of disease spreading (e.g., social distancing, disinfection, hygiene, and wearing of personal protection equipment by study staff). Details on specific procedures are described in the site-specific manual.

In cases where participants are not able to attend study visits due to an infection with SARS-CoV-2, the investigator will discuss with the sponsor potential mitigation approaches (including, but not limited to, extending the visit window, conducting evaluations via video link or phone call, allowing for safety procedures to be conducted at a local facility). The rationale (e.g., the specific limitation imposed by the SARS-CoV-2 infection that led to the inability to perform the protocol specified assessment) and outcome of the discussion will be documented in the eCRF.

In addition, the following containment measures will be taken during the study:

- PCR testing for SARS-CoV-2 will be performed at the time points indicated in the SoA.
- A participant should not be admitted if there was any close contact with a person who tested positive for SARS-CoV-2 or a COVID-19 patient within the last 2 weeks prior to admission to the clinical research centre.
- If a participant is tested to be SARS-CoV-2 positive on Day -1, the participant will be excluded from participation with reference to Exclusion Criterion 26, and referred for treatment.
- Physical examinations will be limited.
- If a participant becomes ill and/or is tested to be SARS-CoV-2 positive after the first administration of study intervention, dosing will be stopped.

Furthermore, it is not anticipated that there will be any interaction between the study intervention and any of the currently approved vaccines against SARS-CoV-2 that would lead to increased risk to the participant above that of receiving such a vaccination without participating in this study. Therefore, both vaccinated and unvaccinated participants are allowed. However, to mitigate against any interruptions to study-related procedures and assessments, vaccination against SARS-CoV-2 is not allowed from 2 weeks prior to admission until discharge (i.e., up to Day 11) (see Exclusion Criterion 8).

These COVID-19 risk mitigation measures will be kept in place for as long as the pandemic is ongoing, as defined by country and site-specific regulations. Once the pandemic has ended, SARS-CoV-2 testing may be omitted at the discretion of the investigator.

4.3. Justification for dose

The dose of 800 µg was chosen to ensure adequate plasma concentration-time profile to estimate the AUC(0-∞) with minimal extrapolation (assuming a LLOQ of 50 pg/mL) and minimize within- and between-participant variability in inhaled drug dosing. In addition, the 800 µg dose (8 inhalations) is the maximum recommended daily dose for salbutamol which has been approved in the EU. Any differences in systemic exposure between the (2) test and (single) reference formulations at this dose level are not expected to increase the risk of known safety concerns with salbutamol, which (as per Section 2.3.1) are being mitigated in any case via careful participant screening and safety assessments.

Three previous studies (Study 200921 SALB1002 and SALB1003) used a single dose of 600, 1200 and 1200 µg. Study 200921 only collected PK samples for 12 hours, SALB1002 and SALB1003 collected PK samples for 24 hours. Based on these data, 800 µg would give lowest quantifiable concentrations of 100 pg/mL assuming the HFA-152a MDI produces similar concentrations. Where reported in these studies, treatments were generally well tolerated with no clinically significant laboratory safety

abnormalities and no serious adverse events. Adverse events were those expected with high dose beta2- agonists but reported in low numbers, these included: tremor, palpitations, tachycardia, flushing and headache which was usually the most frequently reported event.

At the proposed dose of 8 inhalations of salbutamol sulfate, the exposure to HFA-152a (8 x 63 µL) is estimated to be 454 µg/day (6.87 µmol/day). This is well below the exposures shown to have no adverse effects in humans (see Section 2.2.5.2).

4.4. End-of-study definition

A participant is considered to have completed the study if the participant has completed the 2 treatments of the study including the last visit or the last scheduled procedure shown in the SoA.

The end of the study is defined as the date of the last visit of the last participant in the study or last scheduled procedure shown in the SoA for the last participant in the study.

5. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted.

It is aimed to enrol up to 30 healthy male and female participants.

5.1. Inclusion criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

1. Sex : male or female; females may be of childbearing potential, of nonchildbearing potential, or postmenopausal
2. Age : 18 to 55 years, inclusive, at screening
3. BMI : 18.0 to 30.0 kg/m^2, inclusive, at screening
4. Weight : ≥50 kg
5. Status : healthy participants
6. At screening, females must not be pregnant or lactating, or of nonchildbearing potential (see for definition Section 10.4.1.2).
7. Female participants of childbearing potential (see for definition Section 10.4.1.1) who have a fertile male sexual partner must agree to use adequate contraception as described in Section 10.4.2.
8. Male participants, if not surgically sterilized, must agree to use adequate contraception as described in Section 10.4.2.

9. All prescribed medication must have been stopped at least 30 days prior to admission to the clinical research centre based on investigator judgment. An exception is made for hormonal contraceptives, which may be used throughout the study.
10. All over-the-counter medication, vitamin preparations and other food supplements, or herbal medications (e.g., St. John's wort) must have been stopped at least 14 days prior to admission to the clinical research centre based on investigator judgment. An exception is made for acetaminophen, which is allowed up to admission to the clinical research centre.
11. Ability and willingness to abstain from alcohol from 48 hours (2 days) prior to screening, and from 48 hours (2 days) prior to admission until discharge from the clinical research centre.
12. Ability and willingness to abstain from methylxanthine-containing beverages or food (coffee, tea, cola, chocolate, energy drinks) from 48 hours (2 days) prior to admission to the clinical research centre.
13. Good physical and mental health on the basis of medical history, physical examination, clinical laboratory, ECG, and vital signs, as judged by the investigator.
14. Serum potassium and serum glucose levels within reference ranges of the clinical research centre.
15. Willing and able to sign the ICF.

5.2. Exclusion criteria

Participants are excluded from the study if any of the following criteria apply:

1. History or presence of cardiovascular, respiratory, hepatic, renal, gastrointestinal, endocrine, hematologic, or neurological disorders capable of significantly altering the absorption, metabolism, or elimination of drugs; constituting a risk when taking the study intervention or interfering with the interpretation of data.
2. History or presence of any form of asthma, including childhood asthma and exercise induced asthma.
3. Systolic blood pressure <90 mmHg or >140 mmHg, or diastolic blood pressure <50 mmHg or >90 mmHg.
4. History of pathological tachycardia, or a pulse rate > 85 bpm at screening or Day -1.
5. Lymphoma, leukemia, or any malignancy within the past 5 years except for basal cell or squamous epithelial carcinomas of the skin that have been resected with no evidence of metastatic disease for 3 years.
6. Breast cancer within the past 10 years.
7. A QTcF value of >450 msec at screening based on a single measurement.
8. Vaccine(s) within 2 weeks prior to admission, or plans to receive such vaccines during the study.
9. Donation or loss of more than 450 mL of blood within 60 days prior to (the first) drug administration. Donation or loss of more than 1.5 L of blood (for male participants) or

more than 1.0 L of blood (for female participants) in the 10 months prior to (the first) drug administration in the current study.

10. Participation in a drug study within 30 days prior to (the first) drug administration in the current study. Participation in 4 or more other drug studies in the 12 months prior to (the first) drug administration in the current study.
11. Current enrollment or past participation in this clinical study.
12. ALT >1.5x ULN.
13. Total bilirubin >1.5xULN (isolated total bilirubin >1.5xULN is acceptable if total bilirubin is fractionated and direct bilirubin <35%).
14. Current or chronic history of liver disease or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones).
15. Presence of HBsAg at screening or within 3 months prior to first dose of study intervention.
16. Positive hepatitis C antibody test result at screening or within 3 months prior to first dose of study intervention. NOTE: Participants with positive hepatitis C antibody test result due to prior resolved disease can be enrolled if a confirmatory negative hepatitis C RNA test is obtained.
17. Positive pre-study drug/alcohol screen, including THC.
18. Positive HIV antibody test.
19. Cotinine levels indicative of smoking or history or use of tobacco- or nicotine-containing products within 6 months prior to screening
20. Average intake of more than 24 units of alcohol per week (clinical site standard: 1 unit of alcohol equals approximately 250 mL of beer, 100 mL of wine, or 35 mL of spirits).
21. Regular use of known drugs of abuse, including tetrahydrocannabinol.
22. Use of combustible tobacco products, and non-combustible nicotine delivery systems, inclusive of cigarettes, cigars, pipes, and materials used to “vape” within 6 months prior to screening.
23. Hypersensitivity to heparin or heparin-induced thrombocytopenia.
24. Hypersensitivity to any of the study interventions, or components thereof, or drug or other allergy that, in the opinion of the investigator, contraindicates participation in the study.
25. Use of any products intended to treat medical conditions that are not approved by the governing health authority in a given country or region (for example, herbal medicine, health supplements, traditional medicine, homeopathic remedies, etc.).
26. Positive nasopharyngeal PCR test for SARS-CoV-2 on Day -1 or any known close contact with a person who tested positive for SARS-CoV-2 or with a COVID-19 patient within 2 weeks prior to admission.

27. Impairment which would prevent the correct and consistent use of an MDI, as determined by the investigator.

5.3. Lifestyle considerations

5.3.1. Meals and dietary restrictions

- A fasting period of at least 4 hours is required before obtaining clinical laboratory blood samples at all time points.
- Participants will be advised not to consume any foods containing poppy seeds within 48 hours (2 days) prior to admission to the clinical research centre as this could cause a false positive drug screen result.
- Meals and snacks (such as decaffeinated coffee, herbal tea, fruit, biscuits) will be provided according to the standard operating procedures of the clinical research centre. A light supper will be provided on the evening before dosing days.
- Study drug will be administered to participants after a light breakfast. Participants will fast for a period of 4 hours after drug administration on all dosing days, i.e., until scheduled lunch. During fasting, no fluids other than water are allowed; water is allowed ad libitum throughout.

5.3.2. Caffeine, alcohol, and tobacco

- During the study, participants will abstain from ingesting caffeine- or xanthine-containing products (e.g., coffee, tea, cola drinks, and chocolate) from 48 hours prior to admission until after collection of the final PK sample.
- During the study, participants will abstain from alcohol from 48 hours prior to admission until after collection of the final PK sample.
- Use of tobacco products will not be allowed from 6 months prior to screening until after discharge.

5.3.3. Activity

- Participants will abstain from strenuous exercise for 96 hours before each blood collection for clinical laboratory tests. Participants may participate in light recreational activities during the clinical study (e.g., watching television, reading).

5.3.4. Other restrictions

- Participants must not donate blood during the study until discharge (other than the blood sampling planned for this study).

5.4. Screen failures

A screen failure occurs when a participant who has consented to participate in the clinical study is not subsequently randomized. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the

CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes (but not limited to) demography, screen failure details, eligibility criteria, and any SAEs.

Screen failure data will be included in the datasets. For all participants (including screen failures) a source data review will be performed.

5.5. Criteria for temporarily delaying administration of study intervention

Not applicable for this study.

6. STUDY INTERVENTIONS AND CONCOMITANT THERAPY

The definition of study intervention is defined as a set of investigational product(s) or marketed products or placebo intended to be administered to a participant.

Note: "Study intervention" and "study treatment" are used interchangeably unless otherwise specified.

6.1. Study intervention(s) administered

Table 4 Study Intervention(s) Administered

Intervention Label	Treatment A	Treatment B
Intervention Name	Salbutamol HFA-152a MDI	Salbutamol HFA-134a MDI
Intervention Description	A single 800 µg dose, given as 8 x 100 µg (ex-valve) at 20-second intervals	A single 800 µg dose, given as 8 x 100 µg (ex-valve) at 20-second intervals
Type	Test	Reference
Dose Formulation	Salbutamol sulfate HFA-152a suspension	Salbutamol sulfate HFA-134a suspension
Unit Dose Strength(s)	100 µg (ex-valve)	100 µg (ex-valve)
Dosage Level(s)	800 µg	800 µg
Route of Administration	Inhalation	Inhalation
Use	Experimental	Active comparator
IMP and NIMP/AxMP.	IMP	IMP
Sourcing	GSK	GSK
Packaging and Labeling	Study intervention will be provided in a canister fitted with a metering valve within an actuator. Each canister will be labeled as required per country requirement.	Study intervention will be provided in a canister fitted with a metering valve within an actuator. Each canister will be labeled as required per country requirement.

The study intervention will be administered with the participant in the upright, seated position. Dosing for each individual participant will be at around the same time (± 1 hour) on each dosing day.

The start and end-time of the dosing will be recorded (clock time and as precise as in seconds).

6.1.1. Medical devices

- The GSK manufactured medical devices (or devices manufactured for GSK by a third party, if applicable) provided for use in this study are MDI.
- Instructions for medical device use are provided in a separate manual.
- All device deficiencies (including malfunction, use error, and inadequate labeling) shall be documented and reported by the investigator throughout the clinical investigation (see Section 8.4.6 and 10.6) and appropriately managed by GSK.

Of note, MDIs need to be primed before use. The priming of the MDIs should not be done in the vicinity of the participants, as unintended inhalation of micronized particles of salbutamol may affect the salbutamol plasma concentrations of the participants.

6.2. Preparation, handling, storage, and accountability

- The investigator or designee must confirm appropriate conditions (e.g., temperature) have been maintained during transit for all study intervention received, and any discrepancies are reported and resolved before use of the study intervention.
- Only participants enrolled in the study may receive study intervention, and only authorized site staff may supply, prepare, or administer study intervention.
- All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
- The investigator, or authorized site staff is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
- Further guidance and information for the final disposition of unused study interventions are provided in the pharmacy manual.
- Under normal conditions of handling and administration, study intervention is not expected to pose significant safety risks to site staff. Take adequate precautions to avoid direct eye or skin contact and the generation of aerosols or mists. In the case of unintentional occupational exposure notify the monitor, medical monitor and/or GSK study contact.

- A MSDS or equivalent document describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or is available upon request from GSK.

6.3. Assignment to study intervention

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 IRT through the central 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 (e.g., 1001 and increasing) (designating the participant's randomization code and treatment sequence assignment) for each participant in the study.

On Day 1, participants will be assigned a unique number (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.

6.4. Blinding

Participants will be randomly assigned to 1 of 2 treatment sequences in 2 treatment periods using a cross-over design as indicated in Section 4.1 (Overall design).

Investigators will remain blinded to each participant's assigned study intervention throughout the course of the study. Each participant will be dispensed blinded study intervention, labelled with the participant's unique randomization number, throughout the study.

Participants will be instructed to avoid discussing the taste, dosing frequency, or packaging of the study intervention with the investigator.

In the event of a quality assurance audit, the auditor(s) will be allowed access to unblinded study intervention records at the site to verify that randomization/dispensing has been conducted accurately.

A participant will be withdrawn if the participant's intervention code is unblinded by the investigator or treating physician. The primary reason for discontinuation (the event or condition which led to the unblinding) will be recorded in the eCRF.

GSK's Global Safety staff may unblind the intervention assignment for any participant with an SAE. If the SAE requires that an expedited regulatory report be sent to one or

more regulatory agencies, a copy of the report, identifying the participant's intervention assignment, may be sent to investigators in accordance with local regulations and/or GSK policy.

This is a double-blind study in which participants and investigators are blinded to study intervention. 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.

If the investigator is unable to access RAMOS NG, they can contact the GSK helpdesk (available 24/24 hours and 7/7 days) based on the information provided in the study specific manuals.

6.5. Study intervention compliance

When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents.

In order to adhere to study intervention, participants will be required to perform pre-dose MDI training as described in the SoA and in study specific training manual. The study will adopt MDI training systems CCI [redacted] which provide flow and co-ordination coaching.

6.6. Dose modification

In this study a fixed dose level will be administered. Dose modifications will not be applicable.

6.7. Continued access to study intervention after the end of the study

Participants will not receive any additional treatment from GSK after completion of the study because only healthy participants are eligible for study participation.

6.8. Treatment of overdose

An overdose is any dose of study intervention given to a participant that exceeds the planned, randomized dose for an individual within a given dose group.

GSK does not recommend specific treatment for an overdose.

6.9. Prior and concomitant therapy

The use of all prescribed medication is not allowed from 30 days prior to admission to the clinical research centre until discharge (i.e., up to Day 5 or early discontinuation). An exception is made for hormonal contraceptives, which are allowed throughout the study.

The use of all over-the-counter medication, vitamin preparations and other food supplements, or herbal medications (e.g., St. John's wort) is not allowed from 14 days prior to admission to the clinical research centre until discharge.

Vaccination (including vaccination against SARS-CoV-2) is not allowed from 2 weeks prior to admission until discharge.

Acetaminophen (paracetamol), at doses of 2 grams/day, is permitted for use any time during the study, except during the 24 hours pre-dose or post-dose on each dosing day. The reason is that acetaminophen may decrease the excretion rate of salbutamol, which could result in a higher serum level (drugbank online). Other concomitant medications may be considered on a case-by-case basis by the investigator in consultation with the GSK Medical Monitor.

Other medication to treat AEs may only be prescribed if deemed necessary by the investigator. If medication is used, the name of the drug, the dose, and dosage regimen will be recorded in the eCRF.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of study intervention

'Discontinuation' of study intervention refers to any participant who has not received all planned sequences of the study intervention. In rare instances, it may be necessary for a participant to permanently discontinue study intervention. If study intervention is permanently discontinued in a particular period, all reasonable attempts will be made to ensure the collection of endpoints and safety information (e.g., telephone contact) in that period and follow-up.

See the SoA for data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed.

The primary reason for premature discontinuation of the study intervention will be documented in the eCRF based on the list below:

Reasons	Additional items/Sub-reasons
AE	Unsolicited AE Solicited AE

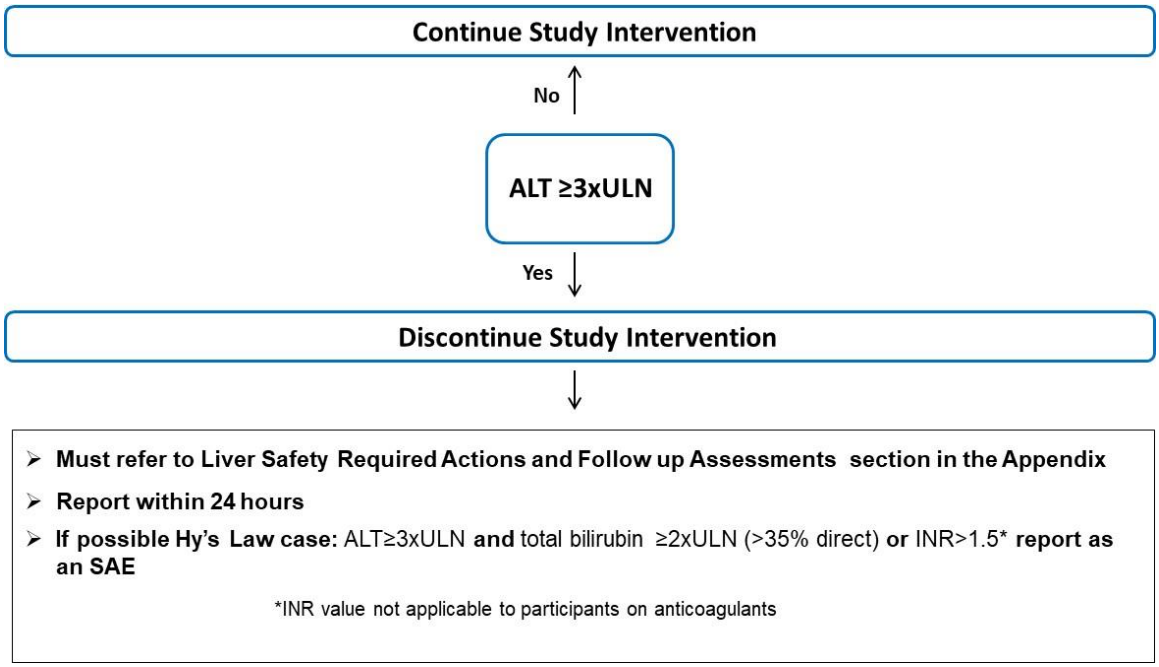
Reasons	Additional items/Sub-reasons
Lost to follow-up	Subject Relocated Subject was Incarcerated Other, specify Unknown
Participant Reached Protocol-Defined Stopping Criteria	Liver chemistry stopping criteria QTc Stopping criteria
Physician Decision	Specify
Pregnancy	
Protocol Deviation	Specify
Site Terminated by Sponsor	
Study Terminated by Sponsor	
Withdrawal by Participant	Burden of Procedure Participant Relocated COVID-19 Pandemic Other
Other	Specify
Death	

AE=adverse event; COVID-19=coronavirus disease-19; QTc=corrected QT interval

7.1.1. Liver chemistry stopping criteria

Discontinuation of study intervention and any further treatments for abnormal liver tests is required by the investigator when a participant meets one of the conditions outlined in Figure 3 or in the presence of abnormal liver chemistries not meeting protocol-specified stopping rules if the investigator believes that it is in best interest of the participant.

Figure 3 Phase 1 Liver Chemistry Stopping Criteria – Liver Stopping Event Algorithm



Abbreviations: ALT = alanine transaminase; INR = international normalized ratio; SAE = serious adverse event; ULN = upper limit of normal

Refer to Section 10.5 (Appendix 5) for required liver safety actions and follow-up Assessments.

7.1.2. QTc stopping criteria

If a clinically significant finding is identified (including, but not limited to, changes from baseline [screening value] in QTcF after enrolment, and based on rounded values), the investigator or qualified designee will determine if the participant can continue the study intervention and if any change in participant management is needed. This review of the ECG printed at the time of collection must be documented. Any new clinically relevant finding should be reported as an AE.

If an ECG meets any of the below potential stopping criteria, then the ECG measurement should be repeated in triplicate, with the averaged QT and QTcF values used to determine stopping.

- QTcF > 500 msec
- QT uncorrected > 600 msec
- Change from baseline: QTcF > 60 msec

7.2. Participant discontinuation/withdrawal from the study

A participant may withdraw from the study at any time at the participant's own request for any reason (or without providing any reason).

A participant may be withdrawn at any time at the discretion of the investigator for safety, behavioural, or compliance reasons.

If during the study a participant becomes ill and/or tests positive for SARS-CoV-2, dosing will be stopped. The participant will be isolated from other study participants and referred for treatment. The participant will be followed up in quarantine in the clinical research centre until complete elimination of the study compound or will be asked to quarantine at home according to guidelines of the Dutch government.

Investigators will attempt to contact participants who do not return for scheduled visits or follow-up (if applicable).

At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA. See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

The participant will be permanently discontinued from the study intervention and the study at that time.

All data and samples collected up to and including the date of withdrawal of/last contact with the participant will be included in the study analyses. If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a participant withdraws from the study, the participant may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

The primary reason for participant discontinuation/withdrawal from the study will be documented in the eCRF based on the list below:

Reasons	Additional items/Sub-reasons
AE	Unsolicited AE Solicited AE

Reasons	Additional items/Sub-reasons
Lost to follow-up	Subject Relocated Subject was Incarcerated Other, specify Unknown
Participant Reached Protocol-Defined Stopping Criteria	Liver chemistry stopping criteria QTc Stopping criteria
Physician Decision	Specify
Pregnancy	
Protocol Deviation	Specify
Site Terminated by Sponsor	
Study Terminated by Sponsor	
Withdrawal by Participant	Burden of Procedure Participant Relocated COVID-19 Pandemic Other
Other	Specify
Death	

AE=adverse event; COVID-19=coronavirus disease-19

Participants who are withdrawn from the study because of AEs/SAEs must be clearly distinguished from participants who are withdrawn for other reasons. Investigator will follow participants who are withdrawn from the study due to an AE/SAE until the event is resolved (see Section 10.3.6.5).

7.3. Lost to follow-up

A participant will be considered lost to follow-up if the participant repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls, and if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.

- Should the participant continue to be unreachable, the participant will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the Schedule of activities (SoA). Protocol waivers or exemptions are not allowed.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. Participants who have signed informed consent but are not eligible to proceed should be recorded in the eCRF with a status of 'screen failure'.
- In the event of a significant study-continuity issue (e.g., caused by a pandemic), alternate strategies for participant visits, assessments, study intervention distribution and monitoring may be implemented by the sponsor or the investigator, as per local health authority/ethics requirements.

The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed 500 mL.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1. Administrative procedures

8.1.1. Collection of demographic data

Record demographic data such as year of birth, sex, race, and ethnicity in the participant's eCRF.

Collection of sex, race and ethnicity data is necessary to assess and monitor the diversity of the trial participants, and to determine if the trial participants are truly representative of the impacted population.

8.1.2. Medical and vaccination history

Obtain the participant's medical and vaccination history by interviewing the participants and/or review of the participant's medical records. Record any pre-existing conditions, signs and/or symptoms present prior to the first dose of study intervention in the eCRF.

8.2. Efficacy and/or immunogenicity assessments

Efficacy and/or immunogenicity will not be evaluated in this study.

8.3. Safety assessments

Planned timepoints for all safety assessments are provided in the SoA (see Section 1.3).

8.3.1. Physical examination

- A complete physical examination will include, at a minimum, assessments of the (cardiovascular, respiratory, gastrointestinal, and neurological) systems. Height and weight will also be measured and recorded.

8.3.2. Vital signs

- Pulse rate and blood pressure will be recorded.
- Blood pressure and pulse measurements will be assessed with a completely automated device after the participant has been resting for at least 5 minutes in the supine position. Manual techniques will be used only if an automated device is not available.

8.3.3. Electrocardiograms

- A standard 12-lead ECG will be obtained as outlined in the SoA (see Section 1.3) using an ECG machine that automatically calculates the HR and measures PR, QRS, QT, and QTcF intervals. The ECG will be obtained after the participant has been resting for at least 5 minutes in the supine position. Refer to Section 7.1.2 for QTc withdrawal criteria and any additional QTc readings that may be necessary.
- Pre-dose 12-lead ECG will be measured in triplicate. 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. Screening and post-dose 12-lead ECG measurements will be single measurements.

8.3.4. Clinical safety laboratory tests

- See Section 10.2 for the list of clinical laboratory tests to be performed in accordance with CCI and the SoA (Section 1.3).
- The investigator must review the laboratory results, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory results must be retained with source documents.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 1 day after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.
    - In the absence of a diagnosis, abnormal laboratory findings assessments or other abnormal results the investigator considers clinically significant will be recorded as an AE or SAE, if they meet the definition of an AE or SAE (refer to Sections 10.3.1 and 10.3.2).

- If clinically significant values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified, and the sponsor notified.
- If laboratory values from non-protocol-specified laboratory tests performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (e.g, SAE or AE), then the results must be recorded.

The addresses of clinical laboratories performing the laboratory assessments are documented in the Protocol Supporting Documentation.

8.3.5. Pregnancy testing

- Female participants of childbearing potential must perform a blood pregnancy test before the administration of any dose of study intervention. Pregnancy testing must be done even if the participant is menstruating at the time of the study visit. The study intervention may only be administered if the pregnancy test is negative.
- Refer to Section 8.4.5 for the information on study continuation for participants who become pregnant during the study.

8.4. Adverse Events (AEs), serious adverse events (SAEs), and other safety reporting

For definitions relating to safety information see Section 10.3

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and other safety information and remain responsible for following up all AEs (see Section 7). This includes events reported by the participant.

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 10.3.

8.4.1. Time period and frequency for collecting AE, SAE, and other safety information

All SAEs will be collected from the signing of the ICF until discharge at the time points specified in the SoA.

All AEs will be collected from the start of study intervention until discharge at the timepoints specified in the SoA.

Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded as medical history, not as AEs.

All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Section 10.3. The

investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and the investigator considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.4.2. Method of detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.4.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Section 10.3.6.5.

8.4.4. Regulatory reporting requirements for SAEs

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a study intervention under clinical investigation are met. See Section 8.4.1 for reporting timeframes.

For SAEs, the investigator must always provide an assessment of causality at the time of the initial report, as defined in the Section 10.3.6.3.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file it along with the IB, IFU, or package insert (as applicable) and will notify the IRB/IEC, if appropriate according to local requirements.

Table 5 Timeframes for submitting SAE and pregnancy reports to GSK

Type of event	Initial reports		Follow-up of relevant information on a previous report	
	Timeframe	Documents	Timeframe	Documents
SAEs	24 hours* ‡	paper Adverse Events Report	24 hours*	paper Adverse Events Report
Pregnancies	24 hours*	paper pregnancy notification report	24 hours *	paper pregnancy follow-up report

SAE(s)=serious adverse events

* Timeframe allowed after receipt or awareness of the information by the investigator/site staff.

‡ Paper Adverse Events Report will be dated and signed by the investigator (or designee). For each SAE, the investigator(s) must document in the medical notes that they have reviewed the SAE and have provided an assessment of causality.

8.4.5. Pregnancy

Female participants who become pregnant after the first study intervention dose must not receive subsequent doses of the study intervention but may continue other study procedures at the discretion of the investigator.

- Details of all pregnancies in female participants and, if indicated, female partners of male participants will be collected after the start of study intervention and 90 days after the last study intervention.
- If a pregnancy is reported, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the female participant or female partner of male participant (after obtaining the necessary signed informed consent from the female partner) pregnancy.
- Any pregnancy or pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, foetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.
- The participant/pregnant female partner will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant/pregnant female partner and the neonate and the information will be forwarded to the sponsor. See Table 5 for reporting timeframes.
- Any poststudy pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.4.4. While the investigator is not obligated to actively seek this information in former study participants/pregnant female partners, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study intervention or be withdrawn from the study.

8.4.6. Contact information for reporting SAEs and pregnancies

Table 6 Contact information for reporting SAEs and pregnancies

Study contact for questions regarding SAEs and pregnancies	**Study contact for reporting of stopping rules**
Contact GSK's local and/or medical contacts	If a stopping rule is met, the investigator must immediately inform GSKs Local and/or Medical contacts.
Contacts for reporting SAEs and pregnancies	**Back-up study contact for escalation of stopping rules**
Available 24/24 hours and 7/7 days OAX37649@gsk.com	OAX37649@gsk.com OR facsimile number +44-20-8754 7822.

8.4.7. Medical device Deficiencies

Medical devices are being provided for use in this study as the study intervention. To fulfil regulatory reporting obligations worldwide, the investigator is responsible for the detection and documentation of events meeting the definitions of device deficiency that occur during the study with such devices.

The definition of a medical device deficiency can be found in Section 10.6.

NOTE: Deficiencies fulfilling the definition of an AE/SAE will follow the processes outlined in Section 10.6 of the protocol.

8.4.11.1. Time Period for Detecting Medical Device Deficiencies

- Medical device deficiencies that result in an incident will be detected, documented, and reported during all periods of the study in which the medical device is used.
- If the investigator learns of any device deficiency at any time after a participant has been discharged from the study, and such a deficiency is considered reasonably related to a medical device provided for the study, the investigator will promptly notify the sponsor.

The method of documenting medical device deficiencies is provided in Section 10.6.

8.4.11.2. Follow-up of Medical Device Deficiencies

- Follow-up applies to all participants, including those who discontinue study intervention.
- The investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality of the deficiency.
- New or updated information will be recorded on the originally completed form with all changes signed and dated by the investigator.

8.4.11.3. Prompt Reporting of Device Deficiencies to the Sponsor

- Device deficiencies will be reported to the sponsor within 24 hours after the investigator determines that the event meets the protocol definition of a medical device deficiency.
- The medical device deficiency report form will be sent to the sponsor via email/facsimile equipment. If email/facsimile equipment is unavailable, then notification by telephone is acceptable with a copy of the data collection tool sent by overnight mail or courier service.
- The sponsor will be the contact for the receipt of device deficiency reports.

8.4.11.4. Regulatory Reporting Requirements for Device Deficiencies

- The investigator will promptly report all device deficiencies occurring with any medical device provided for use in the study in order for the sponsor to fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.
- The investigator, or responsible person according to local requirements (e.g., the head of the medical institution), will comply with the applicable local regulatory requirements relating to the reporting of device deficiencies to the IRB/IEC.

8.5. Pharmacokinetics

Blood samples of approximately 6 mL will be collected for measurement of plasma concentrations of salbutamol as specified in the SoA (Section 1.3).

Plasma salbutamol will be analyzed by solid phase extraction in combination with LC-MS-MS with a lower limit of quantification of 50 pg/mL.

Instructions for the collection and handling of plasma samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

Details of PK blood sampling collection, processing, storage and shipping procedures are provided in the Lab Manual to be prepared by GSK.

8.6. Pharmacodynamics

The following PD parameters will be evaluated and compared: serum potassium weighted means and minimum serum potassium.

Blood samples of approximately 3.5 mL will be collected for measurement of potassium concentrations in serum as specified in the SoA (Section 1.3).

Serum potassium concentrations will be assessed by the [redacted]

8.7. Genetics

Genetics are not evaluated in this study.

8.8. Biomarkers

Biomarkers are not evaluated in this study.

8.9. Immunogenicity assessments

Immunogenicity is not evaluated in this study.

8.10. Health economics or medical resource utilization and health economics

Health economics OR medical resource utilization and health economics parameters are not evaluated in this study.

8.11. Timing of assessments

8.11.1. Timing of dosing

The study intervention will be administered between 08:00 and 10:00 hours in the morning. Dosing for each individual participant will be at around the same time (±1 hour) on each dosing day.

8.11.2. PK blood sampling

For PK blood samples, pre-dose samples will be obtained between waking up and dosing. Post-dose samples up to 30 minutes post-dose will be obtained with a time window of ±1 minute. Thereafter, post-dose samples will be obtained with time margins of ±5% of the time that has passed since (last) dosing.

8.11.3. PD blood sampling

For PD blood samples, pre-dose samples will be obtained between waking up and dosing. Post-dose samples up to 30 minutes post-dose will be obtained with a time window of ±2 minutes. Thereafter, post-dose samples will be obtained with time margins of ±5% of the time that has passed since (last) dosing.

8.11.4. Safety assessments

For safety assessments, pre-dose assessments will be performed between waking up and dosing. For safety assessments up to 2.5 hours post-dose, a time window of ±15 minutes is allowed. Thereafter, serial post-dose assessments (e.g., multiple assessments within

any given day) will be performed with time margins of ±10% of the time that has passed since (last) dosing.

When assessments are planned for the same scheme time, the order of the assessments should be arranged in such a way that ECG and vital signs will be done first followed by the PK (then PD) blood sampling, with PK blood sampling exactly on time.

9. STATISTICAL CONSIDERATIONS

The statistical analysis plan will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints. The statistical analysis plan will be finalized prior to database lock.

Any deviation from the statistical analysis plan will be reported in the Section "Changes in Planned Analysis" in the CSR.

9.1. Statistical hypotheses

This study is designed to compare the PK profile of salbutamol HFA-152a MDI and salbutamol HFA-134a MDI (currently marketed Ventolin product). For each primary PK endpoint (AUC[0-30], AUC[0-∞], AUC[0-t] and Cmax), 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).

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

Refer to Section 9.3.1 for the statistical analysis.

9.2. Analysis sets

Analysis Set	Definition / Criteria	Analyses Evaluated
Enrolled	• All participants who entered the study (who were randomized or received study intervention 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
Screened	• All Participants who were screened for eligibility	• Study Population
Safety	• All participants who received at least one dose of study intervention.	• Safety

Analysis Set	Definition / Criteria	Analyses Evaluated
PK	• 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). • Data will be reported according to the actual study intervention.	• PK
PD	• All participants who received at least one dose of study intervention and have at least 1 non-missing potassium concentration result.	• PD

9.3. Statistical analyses

9.3.1. Pharmacokinetic analysis

PK analysis will be the responsibility of the CCI [redacted] Plasma concentration-time data will be analysed by noncompartmental methods with WinNonlin 8.3. Calculations will be based on the actual sampling times recorded during the study. From the plasma concentration-time data, the PK parameters will be determined as indicated in Table 7, as data permit.

Table 7 Pharmacokinetic parameters

Parameter	Description
AUC(0-30min)	Area under the plasma concentration-time curve up to 30 minutes post-dose
AUC(0-∞)	Area under the plasma concentration-time curve from time 0 to infinity calculated as: $AUC_{0\text{-}inf}=AUC_{0\text{-}t}+C_{last}/k_{el}$, where C_{last} is the last measurable plasma concentration and Kel is the elimination rate constant
AUC(0-t)	Area under the plasma concentration-time curve up to time t, where t is the last point with concentrations above the LLOQ
Cmax	Maximum observed plasma concentration
tmax	Time to Cmax
$t_{1/2}$	Apparent terminal phase half-life

The primary PK parameters are AUC(0-30min), AUC(0-t), AUC(0-∞) and Cmax.

PK data will be summarized, listed and may be presented in graphical form and will be summarised descriptively.

The PK parameters AUC(0-30min), AUC(0-∞), AUC(0-t) (where it is the last point with concentrations above the LLOQ), and Cmax will be statistically analysed. The comparison of interest is described in Section 9.1.

Following log(e)-transformation, AUC parameters and Cmax will be separately analysed using a mixed effects model with fixed effect terms for period and treatment. Participant will be treated as a random effect in the model. Point estimates and their associated 90% CI will be constructed for the comparisons stated in Section 9.1. The point estimates and their associated 90% CI will then be back-transformed to provide point estimates and 90% CI for the ratios, as described in Section 9.1.

9.3.2. Safety analysis

Safety and tolerability will be assessed through AEs, clinical laboratory, vital signs, and ECGs, and any other parameter that is relevant for safety assessment. Safety analysis is described in further detail below.

Safety data will be presented in tabular and/or graphical format and summarized descriptively.

9.3.2.1. Adverse events

Frequency and percentages for incidence of AEs and SAEs will be provided. Absolute and changes from baseline values for 12-lead ECG, and absolute values for clinical laboratory values, 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). A listing of all individual AEs and SAEs will be provided. Summary tables of TEAEs (eg. including tremor, palpitations, tachycardia, flushing and headache) and SAEs will be presented by system organ class based on the MedDRA terminology list (preferred terms): 1 containing the number of TEAEs (frequency and percentage for incidence by treatment and 1 containing the number of drug-related TEAEs (frequency of occurrence, number of participants experiencing the event) per treatment. Additional tables of total counts by treatment and relationship and by treatment and severity will be given.

9.3.2.2. Clinical laboratory

Clinical laboratory data (absolute values) will be listed accompanied by an indication of whether the parameter is outside the reference range. A summary of all data outside the reference range of the clinical laboratory will be provided. Clinical laboratory data will be presented descriptively, where applicable. If a clinical laboratory value is clinically significant as judged by the investigator, then the clinical laboratory value will be recorded as an AE.

9.3.2.3. Vital signs and electrocardiograms

Absolute values for vital signs (systolic and diastolic blood pressure and pulse rate) will be listed and will be presented descriptively (arithmetic mean, SD, median, minimum, and maximum).

Absolute and changes from baseline values for ECG parameters detailed in Section 8.3.3 will be listed and will be presented descriptively (arithmetic mean, SD, median, minimum, and maximum), where applicable.

In addition, the following ECG parameters will be summarised by treatment groups: QTc interval and HR (change from baseline and absolute values), and peak HR and peak QTc interval (absolute values). Three pre-dose measures will be averaged for QTc interval and HR to derive one baseline value.

If an absolute value for vital signs or ECG parameters is clinically significant as judged by the investigator, then the value will be recorded as an AE.

9.3.3. Pharmacodynamic analysis

The following PD parameters will be evaluated and compared: serum potassium HR and QTcF, as weighted means and minimum or maximum.

All PD data will be summarized using descriptive statistics (arithmetic mean, geometric mean, %CV, SD, median, minimum, and maximum) and will be listed and summarized in tabular and/or graphical form.

PD parameters (serum potassium, HR and QTcF as weighted means and minimum or maximum) will be separately analysed using a mixed effects model with fixed effect terms for period and treatment. Participant will be treated as a random effect in the model. Point estimates and their associated 90% CI will be constructed for the comparisons stated above. If necessary, additional analysis will be performed in accordance with current regulatory guidelines.

9.4. Interim analyses

Not applicable.

9.5. Sample size determination

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 8 below 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 8 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-∞).

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).

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, ethical, and study oversight considerations

10.1.1. Regulatory and ethical considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and CIOMS international ethical guidelines
  - Applicable ICH GCP guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, IB, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any substantial amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following, as applicable:
    - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
    - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
    - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

10.1.2. Financial disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the study and for 1 year after completion of the study.

10.1.3. Informed consent process

- The investigator or the investigator's representative will explain the nature of the study, including the risks and benefits, to the participants and answer all questions regarding the study.
- Potential participants must be informed that their participation is voluntary. They will be required to physically or digitally sign a statement of informed consent that meets the local regulations, ICH guidelines, privacy, and data protection requirements, where applicable, and the IRB/IEC or study centre.
- The medical record must include a statement that physical or digital informed consent was obtained before the participant was enrolled in the study and the date the physical or digital consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be reconsented to the most current version of the ICF(s) during their participation in the study.
- A physical or digital copy of the ICF(s) must be provided to the participant.

Participants who are rescreened are required to sign a new ICF and will be assigned a new participant number.

In case of unexpected pregnancy, participant must be informed that personal information such as date of birth and sex of the baby will be collected as part of safety follow-up.

Consent for the baby may be obtained from the participant and/or their partner as per local regulations.

If partners of male participants become pregnant during the study, consent will be needed to be obtained or notification given as per local regulation to the partner before collecting their personal information such as last menstrual period and year of birth, or personal information such as date of birth as sex of their baby as part of safety follow-up.

10.1.4. Recruitment strategy

Participants will be identified for potential recruitment using clinical database, and IEC/IRB-approved newspaper/radio/social media advertisements, prior to consenting to take part in this study.

10.1.5. Data protection

- Participants will be assigned a unique identifier by the investigator. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- GSK will ensure protection of the personal data of the investigator and site staff which is collected within the framework of and for the purpose of the study.
- The participant must be informed that their personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant that data will be used as described in the informed consent.
- The participant must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- The contract between sponsor and study sites specifies responsibilities of the parties related to data protection, including handling of data security breaches and respective communication and cooperation of the parties.
- Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.

10.1.6. Committees structure

Not Applicable.

10.1.7. Dissemination of Clinical Study Data

- The key design elements of this protocol and results summaries will be posted on www.ClinicalTrials.gov and/or GSK Clinical Study Register in compliance with applicable regulations/GSK policy. GSK will aim to register protocols summaries prior to study start and target results summaries submission within 12 months of primary/ study completion date. Where external regulations require earlier disclosure, GSK will follow those timelines.
- Where required by regulation, summaries will also be posted on applicable national or regional clinical study registers.
- Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the study report, and provided reasonable access to statistical tables, figures, and relevant reports. GSK will also provide the investigator with the full summary of the study results, including a summary of trial results understandable to laypersons. The investigator is encouraged to share the plain language summary with the study participants, as appropriate. The full study report will be made available upon request, after decision on marketing authorization by regulatory authorities.
- GSK will provide the investigator with the randomization codes and participant-level line listings for their site only after completion of the full statistical analysis.
- GSK intends to make anonymized participant-level data from this study available to external researchers for scientific analyses or to conduct further research that can help advance medical science or improve patient care. This helps ensure the data provided by study participants are used to maximum effect in the creation of knowledge and understanding.

10.1.8. Data quality assurance

- All participant data relating to the study will be recorded on printed or electronic CRFs unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- Guidance on completion of eCRFs will be provided in eCRF completion guidelines.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source documents.
- **QTLs will be predefined in the Action Item Key Decision Log to identify systematic issues that can impact participant safety and/or reliability of study results. These predefined parameters will be monitored during the study, and important deviations from the QTLs and remedial actions taken will be summarized in the CSR.**
- Monitoring details describing strategy, including definition of study critical data items and processes (e.g., risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance

issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan.

- The sponsor or designee is responsible for the data management of this study, including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (e.g., contract research organizations).
- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 25 years from the issue of the final CSR/ equivalent summary unless local regulations or institutional policies require a different retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.1.9. Source documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the eCRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data and its origin can be found in e.g. source data acknowledgment or monitoring guidelines.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The sponsor or designee will perform monitoring to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.10. Study and site start and closure

Start of study and first act of recruitment

The start of study is defined as FSFV (first ICF signature date).

Study/Site Termination

GSK or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of GSK. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

For study termination:

- Discontinuation of further study intervention development

For site termination:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the investigator
- Total number of participants included earlier than expected

If the study is prematurely terminated or temporarily suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or temporary suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.11. Publication policy

The results of this study may be published in peer reviewed scientific literature and/or presented at scientific meetings. The sponsor will comply with the requirements for publication of study results in accordance with standard editorial and ethical practice and as per the sponsor's internal policy. Authorship will be determined by mutual agreement and in line with ICMJE authorship requirements.

10.2. Appendix 2: Clinical laboratory tests

- The tests detailed in Table 9 will be performed at the CCI [redacted]
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.
- Investigators must document their review of each laboratory safety report.

Table 9 Protocol-required safety laboratory tests

Laboratory Tests	Parameters
Hematology	• Platelet count

Laboratory Tests	Parameters	
	• Red blood cell (RBC) count	
	• RBC indices	○ Mean corpuscular volume (MCV) ○ Mean corpuscular hemoglobin (MCH) ○ %Reticulocytes
	• Absolute white blood cell (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 by dipstick • Microscopic examination (urine sediment examinations will only be performed if there is an abnormality in urinalysis in accordance with CCI [redacted]	
Pregnancy test	• Highly sensitive serum human chorionic gonadotropin (hCG) pregnancy test (as needed for WOCBP)	

Laboratory Tests	Parameters
Other screening tests	• Follicle stimulating hormone (FSH) and estradiol (as needed in WONCBP only) • Cotinine, alcohol and drug screen (to include at minimum: amphetamines [including XTC], methadone, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines) • Serology [(HIV antibody 1/2 antibody test, hepatitis B surface antigen [HBsAg], and hepatitis C virus antibody)] • PCR testing for SARS-CoV-2

* To assess the kidney function, use the estimated glomerular filtration rate (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 and 4) and at the following time points: pre-dose and 15 and 30 minutes, 1, 1.5, 2 and 4 hours post dose

10.3. Appendix 3: AEs and SAEs: Definitions and procedures for recording, evaluating, follow-up, and reporting

10.3.1. Definition of AE

AE definition
• An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of a study intervention, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention.

Events meeting the AE definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New condition detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected intervention- intervention interaction.

• Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • Events that occur as a result of protocol-mandated procedures (i.e. invasive procedures, modification of participant's previous therapeutic regimen).
Events <u>NOT</u> meeting the AE definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital, admission for routine examination). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen. Pre-existing diseases will be recorded in the medical history section of the eCRF. • Hospitalization for elective treatment of a pre-existing condition (known or diagnosed before signing the informed consent) that did not worsen from baseline.

10.3.2. Definition of SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed:
a. Results in death
b. Is life threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization • In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AE. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. • Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in persistent or significant disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect in the offspring of a study participant
f. Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy)
g. Is a suspected transmission of any infectious agent via an authorized medicinal product
h. Other situations: • Possible Hy's Law case: ALT ≥ 3x ULN AND total bilirubin ≥ 2x ULN (>35% direct bilirubin) or international normalized ratio (INR) >1.5 must be reported as SAE • Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. o Examples of such events include invasive or malignant cancers, intensive treatment for allergic bronchospasm, blood dyscrasias, convulsions, or development of intervention dependency or intervention abuse.

10.3.3. Solicited events

• Definition of solicited event
• Solicited AEs are predefined local and systemic events for which the participant is specifically questioned, and which are noted by the participant in their diary.

10.3.4. Unsolicited AE

• Definition of unsolicited AE
• An unsolicited AE is an AE that was not solicited using a participant diary and that is communicated by a participant who has signed the informed consent. Unsolicited AEs include serious and nonserious AEs. • Potential unsolicited AEs may be medically attended (i.e., symptoms or illnesses requiring a hospitalization, emergency room visit, or visit to/by a healthcare provider). The participant will be instructed to contact the site as soon as possible to report medically attended event(s), as well as any events that, though not medically attended, are of participant concern. Detailed information about reported

unsolicited AEs will be collected by qualified site personnel and documented in the participant's records.

- Unsolicited AEs that are not medically attended nor perceived as a concern by the participant will be collected during an interview with the participant and by review of available medical records at the next visit.

10.3.5. Definition of TEAE

TEAE definition:
• A TEAE is an event that emerges during treatment having been absent pre-treatment or worsens relative to the pre-treatment state.

10.3.6. Recording, assessment and follow-up of AE, SAE, and pregnancies

10.3.6.1. AE and SAE recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information.
- It is not acceptable for the investigator to send photocopies of the participant's medical records to GSK in lieu of completion of the GSK, AE/SAE required form.
- There may be instances when copies of medical records for certain cases are requested by GSK. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to GSK.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

10.3.6.2. Assessment of intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to one of the following categories:

- Mild:
  A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- Moderate:
  A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing

discomfort but poses no significant or permanent risk of harm to the research participant.

- Severe:
  A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

10.3.6.3. Assessment of causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. The investigator will use clinical judgment to determine the relationship.
- A *reasonable possibility* of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.
- For causality assessment, the investigator will also consult the IB and/or product information, for marketed products.
- The investigator must review and provide an assessment of causality for each AE/SAE and document this in the medical notes There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. **However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to GSK.**
- The investigator may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

10.3.6.4. Assessment of outcomes

The investigator will assess the outcome of all serious and nonserious unsolicited AEs recorded during the study as:

- Recovered/resolved
- Recovering/resolving
- Not recovered/not resolved
- Recovered with sequelae/resolved with sequelae
- Fatal (SAEs only).

10.3.6.5. Follow-up of AEs, SAEs, pregnancies or any other events of interest

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by GSK to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide GSK with a copy of any postmortem findings including histopathology.
- New or updated information will be recorded in the originally submitted documents.
- The investigator will submit any updated SAE data to GSK within 24 hours of receipt of the information.

After the initial AE/SAE/pregnancy or any other event of interest, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up.

Other nonserious AEs must be followed until follow-up or until the participant is lost to follow-up.

Follow-up during the study

AEs documented at a previous visit/contact and defined as not recovered/not resolved or recovering/resolving will be reviewed at subsequent visits/contacts until follow-up or lost to follow-up.

If a participant dies during their participation in the study or during a recognized follow-up period, GSK will be provided with any available post-mortem findings, including histopathology.

Follow-up of pregnancies

Pregnant participants will be followed to determine the outcome of the pregnancy. At the end of the pregnancy, whether full-term or premature, information on the status of the mother and child will be forwarded to GSK using the paper pregnancy report and the Adverse Events Report if applicable. Generally, the follow-up period does not need to be longer than 6 to 8 weeks after the estimated date of delivery.

Regardless of the reporting period for SAEs in this study, if the pregnancy outcome is an SAE, it should always be reported as such.

Furthermore, the investigator must report any SAE occurring as a result of a poststudy pregnancy that is considered by the investigator to be reasonably related to the study intervention, to GSK as described in the Section 10.3.7.

10.3.6.6. Updating of SAE and pregnancy information after removal of write access to the participant's eCRF

When additional SAE or pregnancy information is received after write access to the participant's eCRF is removed, new or updated information should be recorded on the appropriate paper report, with all changes signed and dated by the investigator. The updated report should be sent to the Study contact for reporting SAEs (refer to Section 8.4.6).

10.3.7. Reporting of SAEs and pregnancies

SAE reporting to GSK via an electronic data collection tool

- The primary mechanism for reporting an SAE to GSK will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken offline to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken offline, then the site can report this information on a paper SAE form (see next section) or to the medical monitor by telephone.
- If the site during the course of the study becomes aware of any serious, nonserious AEs, pregnancy exposure, related to any GSK non-IMP they will report these events to GSK or to the concerned competent authority via the national spontaneous reporting system. These will be classified as spontaneous ICSRs.
- Contacts for SAE reporting can be found in Section 8.4.6.

SAE reporting to GSK via paper data collection tool

- Email/facsimile transmission of the SAE paper data collection tool is the preferred method to transmit this information to the medical monitor.
- In rare circumstances and in the absence of email/facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE data collection tool within the designated reporting timeframes.
- Contacts for SAE reporting can be found in Section 8.4.6.

10.4. Appendix 4: Contraceptive and barrier guidance

10.4.1. Definitions

10.4.1.1. Woman of childbearing potential (WOCBP)

Women in the following categories are considered WOCBP (fertile):

Adolescents of childbearing potential: Tanner stage ≥2 (post-thelarche) irrespective of the occurrence of menarche or following menarche.

From the time of menarche until becoming postmenopausal unless permanently sterile (see below)

Note: Menarche is the first onset of menses in a young female. Menarche is normally preceded by several changes associated with puberty including breast development and pubic hair growth.

10.4.1.2. Woman of nonchildbearing potential (WONCBP)

Women in the following categories are considered WONCBP:

Permanently sterile due to one of the following procedures:

a. Documented hysterectomy

b. Documented bilateral salpingectomy

c. Documented bilateral oophorectomy

   For permanently sterile individuals due to an alternate medical cause other than the above, (e.g., Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), investigator discretion should be applied to determining study entry. If reproductive status is questionable, additional evaluation should be considered.

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

Postmenopausal female

A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

- A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
- Females on HRT and whose menopausal status is in doubt must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.4.2. Contraception guidance

Female participants of childbearing potential with fertile male partners must use one of the following contraceptive methods from at least 4 weeks prior to first study intervention until 90 days post-dose of last study intervention.

- Abstinence, defined as sexual inactivity consistent with the preferred and usual lifestyle of the participant. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
- Use of a highly effective contraceptive (see list below) plus partner use of a condom.

Male participants with female partners of childbearing potential must use one of the following contraceptive methods for 48 hours post-dose of last study intervention. Investigators are responsible for consulting with participants on selection of contraceptive methods.

- Abstinence, defined as sexual inactivity consistent with the preferred and usual lifestyle of the participant. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
- Condom plus partner use of a highly effective contraceptive (see list below).

Highly effective contraceptive methods with a failure rate of < 1%

- Oral contraceptive, either combined or progestogen alone
- Injectable progestogen
- Implants of etonogestrel or levonorgestrel
- Percutaneous contraceptive patches
- Intra-urine devices (hormonal or copper)

10.5. Appendix 5: Liver safety: suggested actions and follow-up assessments

Phase 1 liver chemistry increased monitoring criteria have been designed to assure participant safety and to evaluate liver event aetiology (in alignment with the FDA premarketing clinical liver safety guidance). http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf.

Phase 1 liver chemistry increased monitoring criteria and required follow-up assessments

Liver Chemistry Increased Monitoring Criteria	
ALT-absolute	ALT≥3xULN If ALT≥3xULN **AND bilirubin**[1,2] ≥ 2xULN (>35% direct bilirubin) or **INR** >1.5, Report as an SAE. See additional Actions and Follow-Up Assessments listed below

Required Actions and Follow-up Assessments following Liver Event	
Actions	**Follow-Up Assessments**
• Report the event to GSK **within 24 hours** • Complete the liver event CRF, and complete an SAE data collection tool if the event also meets the criteria for an SAE[2] • Perform liver event follow-up assessments • Monitor the participant until liver chemistries resolve, stabilize, or return to within baseline (see **MONITORING** below)	• Viral hepatitis serology[3] • Blood sample for PK analysis, obtained within 72 hrs of identified liver event.[4] • Serum CPK and LDH. • Fractionated bilirubin (i.e., direct and indirect bilirubin), if total bilirubin≥2xULN • Obtain complete blood count with differential to assess eosinophilia • Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form • Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over-the-counter medications. • Record alcohol use on the liver event alcohol intake case report form

MONITORING: **<u>If</u> ALT≥3xULN AND <u>bilirubin</u> ≥ 2xULN <u>or INR</u> >1.5:** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow-up assessments within **24 hrs** • Monitor participants twice weekly until liver chemistries resolve, stabilise or return to within baseline • A specialist or hepatology consultation is recommended **<u>If</u> ALT≥3xULN <u>AND bilirubin</u> < 2xULN <u>and INR</u> ≤1.5:** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow-up assessments within **24-72 hrs** • Monitor participants weekly until liver chemistries resolve, stabilize or return to within baseline	**<u>If</u> ALT≥3xULN AND <u>bilirubin</u> ≥ 2xULN <u>or INR</u> >1.5:** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total IgG (or gamma globulins). • Assess history of acetaminophen usage in the past week. • Liver imaging (ultrasound, magnetic resonance, or computerized tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy CRF forms.

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT ≥ 3xULN and bilirubin ≥ 2xULN (>35% direct bilirubin) or ALT ≥ 3xULN and INR>1.5, if INR measured, which may indicate severe liver injury (possible 'Hy's Law'), must be reported as an SAE INR measurement is not required and the threshold value stated will not apply to participants receiving anticoagulants
3. Includes: Hepatitis A IgM antibody; Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM); Hepatitis cRNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody; Hepatitis E IgM antibody
4. Record the date/time of the PK blood sample draw and the date/time of the dose of study intervention prior to blood sample draw on the CRF. Instructions for sample handling and shipping are in the Lab Manual.

10.6. Appendix 6: Medical device AEs, ADEs, SAEs, SADEs, USADEs and device deficiencies: Definitions and procedures for recording, evaluating, follow-up, and reporting in medical device studies

- The definitions and procedures detailed in this appendix are in accordance with ISO 14155 and the European Medical Device Regulation (MDR) 2017/745 for clinical device research (if applicable).
- Both the investigator and the sponsor will comply with all local reporting requirements for medical devices.

- The detection and documentation procedures described in this protocol apply to all sponsor medical devices provided for use in the study. See Section 6.1.1 for the list of sponsor medical devices.

10.6.1. Definition of medical device AE and ADE

Medical device AE and ADE definition
• A medical device AE is any untoward medical occurrence, in a clinical study participant, users, or other persons, temporally associated with the use of study intervention whether or not considered related to the investigational medical device. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of an investigational medical device. This definition includes events related to the investigational medical device or comparator and events related to the procedures involved except for events in users or other persons, which only include events related to investigational devices. • An ADE is defined as an AE related to the use of an investigational medical device. This definition includes any AE resulting from insufficient or inadequate instructions for use, or any malfunction of the investigational medical device as well as any event resulting from use error or from intentional misuse of the investigational medical device.

10.6.2. Definition of medical device SAE, SADE and USADE

A medical device SAE is any serious adverse event that:
a. Led to death
b. Led to serious deterioration in the health of the participant, that either resulted in: • A life-threatening illness or injury. The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death, if it were more severe. • A permanent impairment of a body structure or a body function. • Inpatient or prolonged hospitalization. Planned hospitalization for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered an SAE. • Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function • Chronic disease (MDR 2017/745).
c. Led to fetal distress, fetal death or a congenital abnormality or birth defect
SADE definition

• A SADE is defined as an adverse device effect that has resulted in any of the consequences characteristic of an SAE. • Any device deficiency that might have led to an SAE if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate.
Unanticipated SADE (USADE) definition
• An USADE (also identified as UADE in US Regulations 21 CFR 813.3), is defined as a serious adverse device effect that by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report (see Section 2.3).

10.6.3. Definition of device deficiency

Device deficiency definition
• A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. Device deficiencies include malfunctions, use errors, and inadequacy of the information supplied by the manufacturer.

10.6.4. Recording and follow-up of medical device AE and/or SAE and device deficiencies

10.6.4.1. Medical device AE, SAE, and device deficiency recording

- When an AE/SAE/device deficiency occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE/device deficiency information in the participant's medical records, in accordance with the investigator's normal clinical practice and on the appropriate form.
- It is not acceptable for the investigator to send photocopies of the participant's medical records to GSK in lieu of completion of the AE/SAE/device deficiency form.
- There may be instances when copies of medical records for certain cases are requested by GSK. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to GSK.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
- For device deficiencies, it is very important that the investigator describes any corrective or remedial actions taken to prevent recurrence of the deficiency.

- A remedial action is any action other than routine maintenance or servicing of a medical device where such action is necessary to prevent recurrence of a device deficiency. This includes any amendment to the device design to prevent recurrence.

- If the site during the course of the study becomes aware of any serious, nonserious incident (including device deficiencies and malfunctions) related to any GSK non-IMP product they will report these events to GSK or to the concerned CA via the national spontaneous reporting system. These will be classified as spontaneous ICSRs.

10.6.4.2. Assessment of intensity

Refer to Section 10.3.6.2.

10.6.4.3. Assessment of causality

Refer to Section 10.3.6.3.

10.6.4.4. Follow-up of medical device AE/SAE and device deficiency

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by GSK to elucidate the nature and/or causality of the AE/SAE/device deficiency as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide GSK with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed form.
- The investigator will submit any updated SAE data to GSK within 24 hours of receipt of the information.

10.6.5. Reporting of medical device SAEs

Medical device SAE reporting to GSK via an electronic data collection tool

- The primary mechanism for reporting an SAE to GSK will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken offline to prevent the entry of new data or changes to existing data.

- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken offline, then the site can report this information on a paper SAE form or to the medical monitor by telephone.
- Contacts for SAE reporting can be found in Section 8.4.6.

Medical Device SAE Reporting to GSK via Paper Data Collection Tool

- Email/Facsimile transmission of the SAE paper data collection tool is the preferred method to transmit this information to the medical monitor.
- In rare circumstances and in the absence of email/facsimile equipment, notification by telephone is acceptable with a copy of the SAE paper data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE paper data collection tool within the designated reporting time frames.

Contacts for SAE reporting can be found in Section 8.4.6.

10.6.6. Reporting of SADEs

SADE reporting to GSK

NOTE: There are additional reporting obligations for medical device deficiencies that are potentially related to SAEs that must fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.

- Any device deficiency that is associated with an SAE must be reported to the sponsor within 24 hours after the investigator determines that the event meets the definition of a device deficiency.
- The sponsor will review all device deficiencies and determine and document in writing whether they could have led to an SAE. These device deficiencies will be reported to the regulatory authorities and IRBs/IECs as required by national regulations.
- Contacts for SAE reporting can be found in Section 8.4.6.

10.6.7. Reporting of medical device deficiencies for associated person

• **Reporting to GSK**
If an Associated Person (i.e. e.g., spouse, caregiver, site staff) experiences a device deficiency, the medical device deficiency information, and any associated AE/SAE information will be reported to GSK. The associated person will be provided with the authorization to contact physician letter.

If follow-up information is required, authorization to contact physician (or other licensed medical practitioner) must be signed to obtain consent.

- Medical device deficiencies that are not related to an AE or SAE should be reported via email to gsk-rd.complaints@gsk.com, using the medical device deficiency report form.
- If the medical device deficiency is related to a nonserious AE and not linked to an SAE, please send the medical device deficiency report form with details of the associated AE via email to gsk-rd.complaints@gsk.com only.
- If the device incident is linked to an SAE, please email the medical device deficiency report form, within 24 hours. Refer to Section 8.4.6 for reporting.
- GSK will review all device deficiencies and determine and document in writing whether they could have led to an SAE. These device deficiencies will be reported to the regulatory authorities and IRBs/IECs as required by national regulations.

10.7. Appendix 7: Country-specific requirements

Not applicable.

10.8. Appendix 8: Protocol amendment history

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents.

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