CLINICAL STUDY PROTOCOL

Primary Study Intervention(s)	HFA-152a (1 – Difluoroethane) and HFA-134A (1,1,1,2 – Tetrafluoroethane) 1 – Difluoroethane and 1,1,1,2 – Tetrafluoroethane
Other Study Intervention(s)	NA
Study Identifier	221781
Approval Date	14 May 2024
Title	A randomized, double-blind, single-site, two-way crossover Phase 1 study to assess the effect of repeated doses of Test propellant (HFA-152a) on mucociliary clearance as compared to Reference propellant (HFA-134a) in healthy male and female participants
Compound Number/Name	AH3365 - Salbutamol
Brief title	Study of the effect of HFA-152a and HFA-134a propellants on mucociliary clearance in healthy participants
Acronym	NA
Sponsor	GlaxoSmithKline Research & Development Limited 980 Great West Road, Brentford, Middlesex, TW8 9GS, UK
Sponsor signatory	Oscar Della Pasqua Executive Director, Head Clinical Pharmacology Lifecyle Management

Medical monitor name and contact can be found in local study contact information document.

Protocol Investigator Agreement

- **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 clinical study site agreement.**
- **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 cooperate 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.**

Study identifier	221781
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Investigator name	_____
Signature	_____
Date of signature (DD Month YYYY)	_____

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADE	Adverse device effect
AE	Adverse event
ALT	Alanine transaminase
ARSAC	Administration of Radioactive Substances Advisory Committee
AUC	Area under the curve
AUC(0-4h)	Area under the percent radiolabeled particle retention -time curve up to 4 hours
BID	Bis in die (twice daily)
BMI	Body mass index
CFR	Code of Federal Regulations
CI	Confidence interval
CIOMS	Council for International Organizations of Medical Sciences
COPD	Chronic obstructive pulmonary disease
COVID-19	Coronavirus disease 2019
CSR	Clinical study report
CV	Coefficient of variation
CVb	Between-subject coefficient of variation
CVw	Within subject coefficient of variation
ECG	Electrocardiogram
eCRF	Electronic case report form
ED	Early discontinuation
EMA	European Medicine Agency
FEV1	Forced expiratory volume in 1 second

Abbreviation	Definition
FSFV	First subject first visit
FSH	Follicle stimulating hormone
FVC	Forced vital capacity
GCP	Good clinical practices
GM	Geometric mean
GMR	Geometric mean ratio
GSK	GlaxoSmithKline
GWP	Global Warning Potential
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HFA-134a	1,1,1,2 – Tetrafluoroethane (Reference propellant)
HFA-152a	1 – Difluoroethane (Test propellant)
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
HRT	Hormonal Replacement Therapy
ICE	Intercurrent event
ICF	Informed consent form
ICH	International Council for Harmonization
ICSR	Individual case safety reports
IEC	Independent ethics committee
IMP	Investigational medicinal product
INR	International normalized ratio
IRB	Institutional review board
LSLV	Last subject last visit

Abbreviation	Definition
MCC	Mucociliary clearance
MDI	Metered dose inhaler
MDR	(European) medical device regulation
MedDRA	Medical Dictionary for Regulatory Activities
MSDS	Material Safety Data Sheet
PD	Pharmacodynamic
PI	Principal Investigator
PK	Pharmacokinetic
PR	Pulse rate
QT	QT interval
QTc	Corrected QT interval
QTcF	QT interval corrected using Fredericia formula
ROI	Region of interest
SADE	Severe adverse device effect
SAE	Severe adverse event
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome-corona virus type 2
SD	Standard deviation
SoA	Schedule of activities
TEAE	Treatment-emergent adverse event
THC	Tetrahydrocannabinol
TP	Treatment period
ULN	Upper limit of normal
USADE	Unexpected severe adverse device effect

Abbreviation	Definition
WOCBP	Woman of childbearing potential
WONCBP	Woman of nonchildbearing potential

Term	Definition
Blinding:	A procedure in which 1 or more parties to the study are kept unaware of the intervention assignment in order to reduce the risk of biased study outcomes. The level of blinding is maintained throughout the conduct of the study, and only when the data are cleaned to an acceptable level of quality will appropriate personnel be unblinded or when required in case of a SAE. In a double-blind study, the participant, the investigator and sponsor staff who are involved in the treatment or clinical evaluation of the participants and the review or analysis of data are all unaware of the intervention assignment.
Certified copy	A copy (irrespective of the type of media used) of the original record that has been verified (i.e. by a dated signature or by generation through a validated process) to have the same information, including data that describe the context, content, and structure, as the original.
Combination product	Combination product comprises any combination of • drug • device • biological product Each drug, device and biological product included in a combination product is a constituent part.
Eligible	Qualified for enrollment into the study based upon strict adherence to inclusion/exclusion criteria.
Essential documents	Documents which individually and collectively permit evaluation of the conduct of a study and the quality of the data produced
Intervention number	A number identifying an intervention to a participant, according to intervention allocation.

Term	Definition
Investigator	A person responsible for the conduct of the clinical study at a study site. If a study is conducted by a team of individuals at a study site, the investigator is the responsible leader of the team and may be called the principal investigator. The investigator can delegate study-related duties and functions conducted at the study site to qualified individual or party to perform those study-related duties and functions
Participant	Term used throughout the protocol to denote an individual who has been contacted to participate or who participates in the clinical study as a recipient of the study intervention (vaccine(s)/product(s)/control). Synonym: subject
Participant number	A unique identification number assigned to each participant who consents to participate in the study.
Primary Completion Date	The date on which the last participant in a clinical study was examined or received an intervention to collect final data for the primary outcome measure. Whether the clinical study ended according to the protocol or was terminated does not affect this date. For clinical studies with more than one primary outcome measure with different completion dates, this term refers to the date on which data collection is completed for all the primary outcome measures.
Randomization	Process of random attribution of intervention to participants to reduce selection bias.
Self-contained study	Study with objectives not linked to the data of another study.
Source data	All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the study. Source data are contained in source documents (original records or certified copies).
Study completion date	The date on which the last participant in a clinical study was examined or received an intervention/treatment to

Term	Definition
	collect final data for the primary outcome measures, secondary outcome measures, and AEs (that is, the last participant's last visit or LSLV).
Study intervention	Term used throughout the clinical study to denote a set of investigational product(s) or marketed product(s) or placebo intended to be administered to a participant. Note: “Study intervention” and “study treatment” are used interchangeably unless otherwise specified.
Study monitor	An individual assigned by the sponsor and responsible for assuring proper conduct of clinical studies at 1 or more investigational sites.

1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A randomized, double-blind, single-site, two-way crossover Phase 1 study to assess the effect of repeated doses of Test propellant (HFA-152a) on mucociliary clearance as compared to Reference propellant (HFA-134a) in healthy male and female participants

Brief Title: Study of the effect of HFA-152a and HFA-134a propellants on mucociliary clearance in healthy participants

Rationale: A new Ventolin formulation (low carbon Ventolin) is under development, in which the 1,1,1,2 – Tetrafluoroethane (HFA-134a) propellant is substituted by 1,1-Difluoroethane (aka HFA-152a), to reduce the effect on climate change. The purpose of this study is to investigate the effect of the new propellant HFA-152a (Test, T) on mucociliary clearance (MCC) in comparison to that of the current propellant HFA-134b (Reference, R) in healthy participants, as requested by regulatory requirements. Refer to Section 2.1.

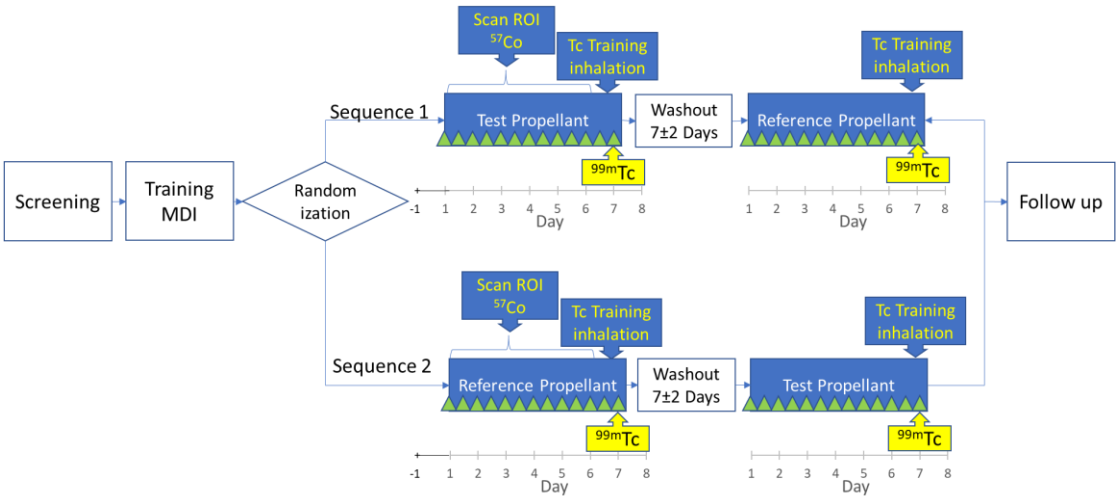
Objectives, Endpoints, and Estimands: The primary objective of the study is to assess MCC after 7-day administration of HFA-152a (Test) or HFA-134a (Reference) propellants to healthy male and female participants. The primary endpoint is the area under the percent radiolabeled particle retention-time curve up to 4 hours (AUC[0-4h]) after nebulized ^{99m}Tc-sulphur colloid inhalation measured on Day 7. For additional information on the primary, secondary, and exploratory objectives, endpoints and estimands, refer to Section 3.

Overall Design: This is a randomized, double-blind, single-site, 2-way crossover study to investigate the effect of HFA-152a and HFA-134a propellants on MCC in healthy participants. Refer to Section 4.1.

Number of Participants: The study has planned to enrol a total of 24 healthy participants to ensure at least 20 participants with at least 10 randomized to each 1 of 2 treatment sequences (T-R and R-T). Refer to Section 9.5.

Data Monitoring/Other Committee: Refer to Section 10.1.6.

1.2. Study Schema



Notes: Training MDI concerns the initial training of the inhalation from MDI (propellants); additional training will be provided during the treatment periods. Between Day 1 to Day 6 of Period 1, the ROI encompassing the right lung will be defined based on a single ^{57}Co transmission scan of the participant chest. Green triangles represent propellant administrations (4 inhalations BID for 6 days + single morning administration on Day 7). Tc Training inhalation concerns the training of inhalation of nebulized saline solution (without radiolabeled ^{99m}Tc); Yellow boxes represent inhalation of the nebulized labelled ^{99m}Tc for the assessment of MCC. Abbreviations: BID=twice daily, Co=Cobalt, MDI=metered dose inhaler, ROI=region of interest, Tc=Technetium.

1.3. Schedule of Activities (SoA)

The Schedules of Activities (SoA) are presented in the following Table 1.

Table 1 Schedule of Activities

Visit	Screening	Treatment Period 1				Washout	Treatment Period 2				Follow up or early withdrawal
Visit Window	**Day -21 to Day-7**	**Day -1**	**Day 1 to Day 6**	**Day 7**	**Day 8**	**7 days ± 2 days**	**Day -1**	**Day 1 to Day 6**	**Day 7**	**Day 8**	**8 days ± 2 days after last TP (discharge)**
Confinement[a]		X	X	X	X		X	X	X	X	
Admission		X					X				
Discharge from site					X					X	
Informed Consent	X										
Inclusion and exclusion criteria	X	X					X				
Demography	X										
Physical examination[b]	X										X
Body weight	X										
Height and BMI calculation	X										
Medical history (includes substance usage)	X										
Pulmonary tests[c]	X	X			X		X			X	
FSH	X										
Serology (HBsAg, anti-HCV, anti-HIV 1 and 2)	X										

Visit	**Screening**	**Treatment Period 1**				**Washout**	**Treatment Period 2**				**Follow up or early withdrawal**
Visit Window	**Day -21 to Day-7**	**Day -1**	**Day 1 to Day 6**	**Day 7**	**Day 8**	**7 days ± 2 days**	**Day -1**	**Day 1 to Day 6**	**Day 7**	**Day 8**	**8 days ± 2 days after last TP (discharge)**
Drug and alcohol screen, cotinine test	X	X					X				
Clinical laboratory assessments[d]	X			X					X		X
Vital signs[e]	X	X	X	X	X		X	X	X	X	X
12-lead ECG[f]	X	X	X	X			X	X	X		X
MDI training[g]	X		◄	——►				◄	——►		
Randomization		X									
Randomization criteria[h]		X					X				
Administration of study intervention (propellants)[i]			X	X				X	X		
^{57}Co transmission scan[j]			X								
Inhalation training[k] (saline without ^{99m}Tc)				X					X		
Nebulized ^{99m}Tc administration and percent radiolabeled particle retention measurements[l]				X					X		

Visit	**Screening**	**Treatment Period 1**				**Washout**	**Treatment Period 2**				**Follow up or early withdrawal**
Visit Window	**Day -21 to Day-7**	**Day -1**	**Day 1 to Day 6**	**Day 7**	**Day 8**	**7 days ± 2 days**	**Day -1**	**Day 1 to Day 6**	**Day 7**	**Day 8**	**8 days ± 2 days after last TP (discharge)**
AE review[m]			←	←	←	←	←	←	←	←	→
SAE review[n]	←	←	←	←	←	←	←	←	←	←	→
Concomitant medication review	X	X	X	X			X	X	X		X

a. Participants will be in the clinic for 2 periods, from Day -1 until Day 8; they will be discharged from site on Day 8, 24 h after nebulized 99mTc in both TP 1 and TP 2.
b. Complete physical examinations will be conducted at screening and at the follow-up visit. Symptom-driven physical examinations may be conducted on Day -1 and 8 of each TP, at follow up, or any other time, per the investigator's discretion.
c. FVC, FEV1
d. Clinical laboratory assessments (including clinical chemistry, hematology, and urinalysis): at screening, on Day 7 of each TPs, and at discharge.
e. Vital signs (systolic and diastolic blood pressure, and pulse rate): vital signs will be recorded at screening, admission, on each propellant morning dosing day at pre-dose and at the following time point post-dose: 20±10 min post-dose, 24 hours post last dose in each period and at follow up visit. Participants will be discharged by the investigator based on normal vitals, or in case of abnormal values judged to be not clinically significant and not representing a safety concern.
f. 12-lead ECG: 12-lead ECG will be recorded as single assessments at screening, admission, on each morning dosing day of each TP at pre-dose, and at the following time points post-dose: 20±10 min post-dose, and at follow up. Participants will be discharged from the study by the investigator based on normal ECG or in case of abnormal values judged to be not clinically significant and not representing a safety concern. In case of QT abnormalities, ECGs will be repeated in triplicate assessments.
g. Inhaler Training will be performed at screening, at least 7 days before the start of the multiple dosing, and again during the mornings of Day 1 to Day 7 of each treatment period. Once the participant is comfortable with using the training device, practice completing a sequence of 8 puffs. Provide feedback as necessary until proper technique is observed before conducting the full dose administration using the investigational inhaler.
h. At the start of treatment period 1 and 2, the randomization criteria (aka treatment period criteria) (see section 5.3) should be reviewed to ensure no changes in participant's health status. Please see section 5.3 for further details
i. Propellants will be given 4 actuations BID (morning and evening, 12±3 hours apart) by oral inhalation using MDI. Note: Propellant devices need to be primed before use.
j. Single transmission scan of the chest using 57Co.
k. Training to nebulized 99mTc inhalation: Participants will be trained to nebulized 99mTc inhalation by using saline inhalation (without 99mTc) on Day 7 of each TP, before propellant dosing.
l. Administration of nebulized 99mTc inhalation given 30±10 min after the last propellant intake. Measurement of retained radioactivity will be performed immediately after nebulized 99mTc administration (scintigraphic time="0") and then at 15, 30, 45, 60, 90, 120, 150, 180, 210, 240 min after nebulized 99mTc administration.
m. All AEs will be collected from the start of study intervention until final discharge from the study (including washout period). All SAEs will be collected from the signing of the Informed consent form (ICF) until final discharge from the study (including washout period).

2. INTRODUCTION

2.1. Background and Study Rationale

Ventolin (aka salbutamol, albuterol) is a beta2-adrenergic receptor agonist providing short-acting (4 to 6 hour) bronchodilation with fast onset (within 5 minutes) in reversible airways obstruction. It is indicated in the treatment or prevention of bronchospasm in chronic conditions such as asthma and COPD and in the prevention of exercise-induced bronchospasm [Ventolin, 2021]. Ventolin is frequently administered via an MDI currently formulated with hydrofluorocarbon 1,1,1,2 – Tetrafluoroethane (aka HFA-134a) as propellant. This propellant agent is characterized by a large GWP, being responsible for trapping solar heat in the atmosphere, thus contributing to climate change. To reduce this impact, GSK is developing a new Ventolin formulation (low carbon Ventolin), in which the HFA-134a propellant is substituted by 1,1-Difluoroethane (aka HFA-152a). HFA-152a is characterized by a >10-fold lower GWP compared to HFA-134b. The new propellant is also characterized by shorter atmospheric life (1.4 years vs. 14 years), which further reduces its potential effect on climate change. CCI [redacted]
CCI [redacted]
CCI [redacted]

To assure that these changes are not leading to potential modifications of Ventolin clinical efficacy or safety and tolerability characteristics, a development program was planned, incorporating in vitro and in vivo assessments. In particular, following the publication of the relevant guidance from EMA [EMA, 2009; Lee, 2009; Lu, 2015; EMA, 2017; EMA, 2023] comparative studies aiming at assessing relative bioavailability, similar PD effects (methacholine challenge), and long-term safety of the 2 formulations (Test=HFA-152a and Reference=HFA-134b) are being implemented.

The available guidance, related to the requirements for clinical documentation for orally inhaled products, also indicate the need to assess the effect of the new propellant on MCC [EMA, 2009], which was specifically required by EMA for low carbon Ventolin. MCC is an innate host defence mechanisms freeing up the airways from dust, bacteria, and other irritants [Munkholm, 2014; Bustamante-Marin, 2017]. This MCC assessment can therefore be considered part of the safety and tolerability characterization of the propellant and, in turn of the new Ventolin formulation. The fact that MCC after the exposure to the new Test propellant is similar to that observed after the Reference propellant, which has been in clinical use for many years, would provide additional confidence on the safety and tolerability characterization of the new Ventolin formulation.

The purpose of this study is to investigate the effect of the new propellant HFA-152a (Test) on MCC in comparison to that of the current propellant HFA-134b (Reference) in healthy male and female participants using the percent radiolabeled particle retention following inhalation of a radiolabeled compound (colloidal ^{99m}Tc sulphur) after a short repeated exposure to the Test and Reference propellants [Bennett, 2015; Bennett, 2013; Bennett, 2022].

2.2. Benefit/Risk Assessment

More detailed information about the known risks and reasonably expected AEs on used propellants may be found in the corresponding MSDS.

2.2.1. Risk Assessment

Ventolin formulated with the Reference propellant, has been on the market for many years and, thus, has a well characterized tolerability profile. 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, and was rapidly cleared from the blood [Kuehl, 2022]. The Sponsor's assessment of known and potential risks of this study are summarized in Table 2. Concerning exposure to radiolabeled compounds, see Section 10.9.

^{99m}Tc sulphur colloid injection is marketed in the USA for intravenous, subcutaneous, intraperitoneal and oral administration for imaging studies. Full details on adverse reactions using the approved routes of administration can be found in the prescribing information for ^{99m}Tc sulphur colloid injection. The most frequently reported adverse reactions, across all categories of use and routes of administration, include rash, allergic reaction, urticaria, anaphylaxis/anaphylactic shock, and hypotension. Less frequently reported adverse reactions are fatal cardiopulmonary arrest, seizures, dyspnea, bronchospasm, abdominal pain, flushing, nausea, vomiting, itching, fever, chills, perspiration, numbness, and dizziness. Local injection site reactions, , have also been reported.

^{99m}Tc sulphur colloid injection can be used to identify pulmonary aspiration, therefore although it is not licensed to be administered into the lungs, this route is known to be tolerated. Additionally, the use of inhaled ^{99m}Tc sulphur colloid in 0.9% sodium chloride to assess lung MCC has been safely performed in clinical studies since the 1980s [Bennett, 2015].

Table 2 Summary of Potential Risks of Clinical Significance

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study intervention [Test and Reference propellants and radiolabeled compound]		
Local respiratory irritation	The risk would be that the Test propellant has a local tolerability profile different from that of the Reference propellant, which has been on the market for many years and, thus, has a well-known tolerability profile.	During the clinical conduct, close monitoring of all participants according to the Schedule of Assessment will be performed to evaluate the occurrence and severity of any local irritation and actions taken according to the protocol and stopping criteria if breached. No local respiratory irritation was observed in a pilot PK study of the new formulation of Ventolin and other studies evaluating HFA-152a have found the propellant to be well tolerated by study participants.
Risks related to exposure to radiolabelled ^{99m}Tc and ^{57}Co	The risk would be that the amount of radioactivity carries a risk of later developing serious and possibly fatal conditions.	Over both administrations, the estimated radiation dose that each participant will receive is 1.22 mSv defined using the principle of "as low as reasonably practicable. If repeat transmission scans (up to 2) are required, the maximum possible radiation dose that each participant will receive is 1.42 mSv. While any increase in the amount of radiation that is received above natural radiation carries a risk of later developing serious and possibly fatal conditions, the risk associated with the maximum possible dose of radiation in this study is very small indeed and is considered to be acceptable. Extrapolation from epidemiological studies indicated that the lifetime risk of inducing a fatal cancer in a healthy individual from the total exposure of 1.0 mSv is approximately 1 in 20 000, which indicates that the additional risk from this amount of radiation exposure is minimal, compared with the lifetime risk for being diagnosed with cancer in the UK (1 in 2). See Section 10.9. Subjects at risk (women of child-bearing potential, age <30 years, age >55 years) have been excluded from the study.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Risks related to sulphur colloid inhalation	The risk would be that colloidal particle inhalation may give rise to local tolerability issues, bronchospasm and although unlikely, of allergic or anaphylactic reactions.	During the clinical conduct, close monitoring of all participants according to the Schedule of Assessment will be performed to evaluate the occurrence and severity of any local irritation and actions taken according to the protocol and stopping criteria if breached. In addition to hypersensitivity reactions, inhaled particulates can rarely trigger bronchospasm. In the unlikely event that a patient suffers an episode of bronchospasm after inhaling any of the study interventions they will be promptly and appropriately managed according to clinical judgement e.g., administration of inhaled or nebulized bronchodilator such as salbutamol or ipratropium, and they will be withdrawn from the study. Oxygen will be given if required to maintain oxygen saturations >90%. If judged clinically necessary by the investigator participants could be transferred to hospital for ongoing treatment and monitoring.

2.2.2. Benefit Assessment

This study is performed with Test and Reference propellants in healthy participants.

While not a direct benefit, participants in this study will contribute to the process of developing a new, more environmentally friendly formulation of Ventolin that contributes less greenhouse gas emissions.

Participants may benefit from information about their general health status through medical evaluations/assessments associated with this study (i.e., physical examinations and blood testing [hematology and biochemistry data]).

2.2.3. Overall Benefit-Risk Conclusion

This study is performed with Test and Reference propellants in healthy participants. The tolerability profile of the Reference propellant HFA-134a, which has been part of the Ventolin formulation for many years, is well characterized. The change in propellant from HFA-134a to HFA-152a is supported by a nonclinical toxicology program. The test propellant was well tolerated in human exposure studies thus far, and in GSK's PK study was rapidly cleared from the blood. The test propellant is under evaluation by other companies as well (see Study to Assess the Effect of the New HFA-152a Propellant on Mucociliary Clearance - Full Text View - ClinicalTrials.gov, accessed 21/11/2023).

The risk related to the exposure to radioactivity is characterized and manageable. The maximum possible dose of radiation in this study is very small indeed and is considered to be acceptable. The risk related to nebulized ^{99m}Tc sulphur colloid inhalation is characterized and manageable.

Women of child-bearing potential (WOCBP) are excluded to protect from risk associated with administration of radioactivity. Adult subjects (from 18 up to 55 years) are typically used in this kind of studies; exclusion of subjects younger than 30 years is justified based on the recommendations of the ARSAC for the exposure to radiation.

Taking into account the measures taken to minimize any risk to participants in this study (exclusion of WOCBP, exclusion of subjects of younger age), the potential risks recognized are justified by the anticipated benefits to all ongoing and future programs with HFA-152a as a propellant as well as the anticipated environmental and societal benefits of introducing a salbutamol inhaler with a new propellant (HFA-152a) with greatly reduced GWP, compared to the current propellant HFA-134a.

3. OBJECTIVES, ENDPOINTS AND ESTIMANDS

The study objectives and endpoints are presented in Table 3.

Table 3 Objectives and endpoints

Objectives	Endpoints
Primary	
To assess MCC expressed as integrated measurements of retained radioactivity in the right lung up to 4 h after 7-day administration of Test and Reference propellants to healthy male and female participants	• AUC0-4h after nebulized ^{99m}Tc inhalation on Day 7
Secondary	
(MCC) To assess MCC expressed as retained radioactivity in the right lung at individual times after 7-day administration of Test and Reference propellants to healthy male and female participants	• Percent radiolabeled particle retention at 1 h after nebulized ^{99m}Tc inhalation on Day 7 • Percent radiolabeled particle retention at 1.5 h after nebulized ^{99m}Tc inhalation on Day 7 • Percent radiolabeled particle retention at 3 h after nebulized ^{99m}Tc inhalation on Day 7
(Safety) To assess the safety and tolerability after 7-day administration of Test and Reference propellants in healthy male and female participants.	• Incidence of AEs and SAEs

Primary Estimand

The primary clinical question of interest is:

What is the GMR in primary parameter AUC0-4h after repeated dosing for 7 days of HFA-152a, aka 1 – Difluoroethane (Test propellant) and HFA-134a, aka 1,1,1,2 – Tetrafluoroethane (Reference propellant) in healthy participants?

The estimand is described by the following attributes:

- Population:

  Healthy male or female participants aged 30 to 55 years.

- Endpoint:

  AUC(0-4h) in the right lung after nebulized ^{99m}Tc inhalation on Day 7.

- Treatment condition:

  Administration of repeated doses of Test propellant (HFA-152a) or Reference propellant (HFA-134a) for 6 days, given as 4 inhalations BID and last administration on the morning of Day 7.

- Intercurrent events (ICEs) and estimand strategies:

  1. Treatment discontinuation due to any reasons (Principal stratum strategy)

2. Participants unable to take all doses as prescribed (Principal stratum strategy)
3. Dosing error in propellants (Principal stratum strategy)

The principal stratum strategy is a commonly accepted strategy for MCC studies. For all ICEs, interest lies in evaluating primary parameter and comparison of the ratio of 2 formulations for AUC(0-4h) after nebulized ^{99m}Tc inhalation in a principal stratum strategy for participants completed the study and who achieved 100% compliance with no dosing error.

- Population-level summary:

  Ratio of adjusted GM for AUC(0-4h) (for logarithmic transformed values) following repeated dosing of the 2 formulations (HFA-152a and HFA-134a), with 90% CI.

  Rationale for estimand: The Test formulation is being developed with the aim to have comparable AUC(0-4h) after nebulized ^{99m}Tc inhalation characteristics as the reference formulation, under the scenario where participants are required to have the desired levels of exposure to study intervention. Interest lies in the AUC(0-4h) values obtained in the scenarios had the participant been exposed to correct dose as prescribed, completed the study and 100% compliance.

Estimands Supporting Secondary MCC Objectives

The secondary clinical question of interest is:

What is the mean difference in percent radiolabeled particle retention at 1, 1.5, and 3 hours after nebulized ^{99m}Tc inhalation, after repeated dosing for 7 days of HFA-152a , aka 1 – Difluoroethane (Test propellant) and HFA-134a, aka 1,1,1,2 – Tetrafluoroethane (Reference propellant) in healthy participants?

This secondary MCC estimand has the same estimand attributes as the primary estimand (population, treatment condition, ICEs strategy, rationale for the estimand), except for the following attributes:

- Endpoint:
  - Right lung percent radiolabeled particle retention at 1 h after nebulized ^{99m}Tc inhalation on Day 7
  - Right lung percent radiolabeled particle retention at 1.5 h after nebulized ^{99m}Tc inhalation on Day 7
  - Right lung percent radiolabeled particle retention at 3 h after nebulized ^{99m}Tc inhalation on Day 7
- Population-level summary:

  Adjusted mean difference in percent radiolabeled particle retention at 1, 1.5 and 3 h following repeated dosing of the 2 formulations (HFA-152a and HFA-134a), with 90% CI.

Estimands Supporting Secondary Safety Objectives

The clinical question of interest for the safety secondary objective is:

What is the safety and tolerability profile of HFA-152a (Test propellant) compared to HFA-134a (Reference propellant) in healthy participants?

This secondary safety estimand has the same estimand attributes as the primary estimand (population, treatment condition), except for the following attributes:

- Endpoint:

  Incidence of AE and SAEs.
- ICEs and estimand strategies:
  1. Treatment discontinuation due to any reasons – (Treatment policy strategy)
  2. Participants unable to take all doses as prescribed (Treatment policy strategy)
  3. Dosing error in propellants (Treatment policy strategy)
- Population-level summary:

  Number and percentages for incidence of AEs and SAEs

  Rationale for estimand: This is a study in healthy volunteers with short follow-up duration. Therefore, all AEs and SAEs data are of interest, regardless of ICEs to support completeness of reporting and transparency of the clinical study.

4. STUDY DESIGN

4.1. Overall Design

This is a randomized, double-blind, single-site, 2-way crossover study to assess the effect of repeated doses of Test propellant (HFA-152a, aka 1 – Difluoroethane) on MCC as compared to Reference propellant (HFA-134a, aka 1,1,1,2 – Tetrafluoroethane) in healthy male and female participants.

The study has planned to enrol a total of 24 healthy participants to ensure at least 20 participants are included in the principal stratum analysis set with at least 10 participants randomized to each treatment sequence.

Participants will be randomly assigned to 1 of 2 treatment sequences in 2 TPs using a cross-over design. The following treatment sequences will be tested:

- Treatment Sequence 1: T-R
- Treatment Sequence 2: R-T

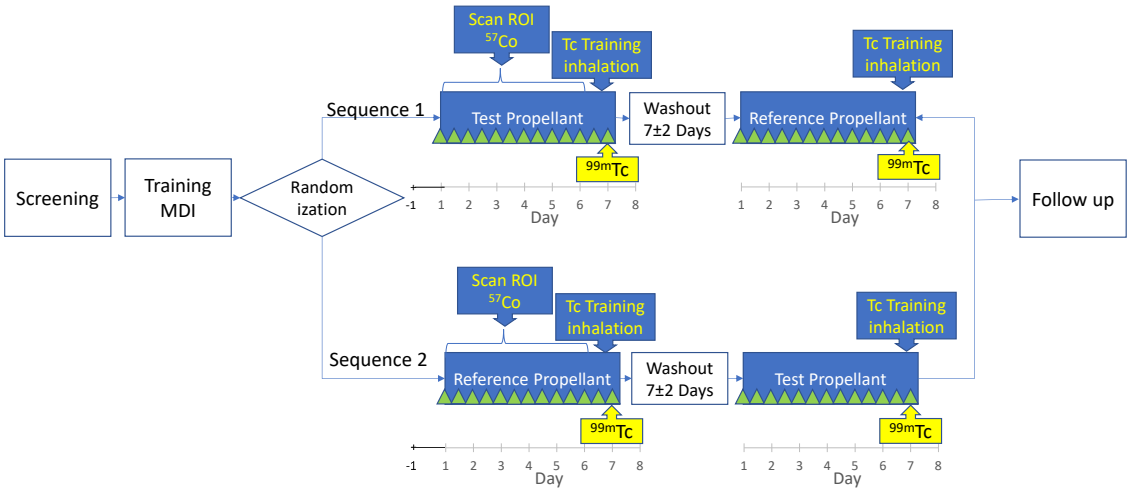
Where T is HFA-152a, aka 1 – Difluoroethane (Test) and R is HFA-134a, aka 1,1,1,2 – Tetrafluoroethane (Reference).

In each study period, Test or Reference propellants will be administered by oral inhalation BID on Days 1-6 and as a single dose on the morning of Day 7. MCC will be determined using gamma-scintigraphy following the administration of nebulized colloidal ^{99m}Tc-sulphur colloid by inhalation after the final dose of the propellant on Day 7. The

study will comprise a Screening Period of up to 21 days prior to first dosing; 2 TPs of 8 days each, with a 7±2 days Washout Period between the 2 TPs; and a final safety Follow-up Visit up to 8 ± 2 days after the final dose administration in TP2 (maximal duration 56 days).

A schema of the study is provided in Figure 1.

Figure 1 Schematic of the Study



Notes: Training MDI concerns the initial training of the inhalation from MDI (propellants); additional training will be provided during the treatment periods. Between Day 1 to Day 6 of Period 1, the ROI encompassing the right lung will be defined based on a single 57Co transmission scan of the participant chest. Green triangles represent propellant administrations (4 inhalations BID for 6 days + single morning administration on Day 7). Tc Training inhalation concerns the training of inhalation of nebulized saline solution (without radiolabeled 99mTc); Yellow boxes represent inhalation of the nebulized labelled 99mTc for the assessment of MCC.
Abbreviations: BID=twice daily, Co=Cobalt, MDI=metered dose inhaler, ROI=region of interest, Tc=Technetium.

4.2. Scientific Rationale for Study Design

A reformulated 'low carbon' Ventolin is under development, in which the HFA-134a propellant is replaced by 1,1-Difluoroethane (aka HFA-152a), to reduce the effect on climate change. In addition to other assessments (relative bioavailability, PD similarity in the methacholine challenge model, and long-term safety study characterization of the Test vs Reference formulation), during interactions with EMA; the assessment of the effect of the new propellant HFA-152a (Test) on MCC in comparison to that of the current propellant HFA-134b (Reference) was required. Considering that MCC is an important host defence mechanism freeing up the airways from dust, bacteria and other irritants, the assessment of MCC is part of the safety characterization of the new (Test) propellant. The demonstration that the Test propellant has similar effect on MCC compared to the Reference Propellant (tested in years of commercial use of Ventolin) will provide additional confidence concerning the safety and tolerability of the new formulation of Ventolin.

The study is based on a randomized 2-way crossover design as the potential, differential effect of the Test and Reference propellants can be suitably tested in the same subjects,

i.e., the design is suited to reduce the influence of confounding covariates as each participant serves as their own control. The crossover design typically requires a smaller number of participants compared to a parallel group design. Carryover effects are expected to be eliminated by introducing a suitable washout phase; considering the very short residence of the propellant in the body [Kuehl, 2022], a washout period of 7±2 days is considered appropriate.

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. In addition, the study involves the administration of propellants only, and no patient benefit is expected from the administration of propellants, so that the study can be suitably performed in healthy participants. 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. Subjects at risk for radioactivity administration (WOCBP, subjects <30 years, see section 2.2) have been excluded.

As the assessment of safety and tolerability is among the secondary objectives of the study, it is preferred that the study is double blinded, i.e., both the investigators and the healthy participants do not know the actual propellant used in a particular occasion, to allow for a more objective identification and collection of the AEs after administration.

4.2.1. Participant Input to the Design

Not applicable.

4.3. Justification for Dose and Duration of the Treatment

Effects on MCC are not expected to be elicited after a single dose of propellants, so MCC assessment will be conducted after a short-term (7-day) repeated dosing of the propellants. For the chronic therapy of asthma, Ventolin can be administered as 2 inhalations up to 4 times a day, resulting in a maximum of 8 inhalations/day [Ventolin HFA, 2021]. Therefore, in this MCC study, the propellants will be given as 4 inhalations BID (i.e., matching the maximal daily exposure of the propellant in the clinical use of Ventolin), for a total 13 administrations, i.e., final administration on the morning of Day 7 of each treatment period. Of note, no salbutamol will be included in the formulation for this assessment. The amount of propellant given per single actuation is the same for both propellants . For the dose of radiolabelled material, see Section 8.7 and, Section 10.9.

4.4. End-of-Study Definition

A participant is considered to have completed the study if the participant has completed the 2 treatment periods of the study including the last visit or the last scheduled procedure shown in the SoA (see Section 1.3).

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. The Ethics Committee should be notified of the conclusion of the study within 90 days of the end of the study, or within 15 days if the study is terminated early, clearly explaining the reasons for the termination. The ARSAC Practitioner will also be notified of the end of trial or early termination of the trial within an appropriate timeframe.

5. STUDY POPULATION

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

It is aimed to enroll up to 24 healthy male and female participants to have at least 20 completers.

5.1. Inclusion Criteria

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

1. Sex: male or female.
2. Age: 30 to 55 years, inclusive, at screening
3. BMI: 18.0 to 32.0 kg/m^2, inclusive, at screening
4. Weight: ≥50 kg
5. Nonsmokers or ex-smokers for more than 6 months with a smoking history of <10 pack years
6. Status: healthy participants
7. Spirometry data;
   - FEV1≥80% of predicted values;
   - FEV1:FVC ratio >70%.
8. Females must be of nonchildbearing potential, as defined in Section 10.4.1.2.
9. A female participant is eligible to participate if:
   - She is a WONCBP, as defined in Section 10.4.
   - She agrees not to donate eggs (ova, oocytes) for the purpose of reproduction during the study intervention period and at least 30 days after the last dose of study intervention. She must also not be involved in the process of donating eggs prior to consenting to the study.
10. Male participants are eligible to participate if they agree to the following during the study intervention period and for at least 90 days after the last dose of study intervention:
    - Refrain from donating sperm

- Either be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent
- Or must agree to use a male condom when having sexual intercourse with a WOCBP who is not currently pregnant. The female partner should additionally use a highly effective contraceptive method with a failure rate of <1% per year as described in Section 10.4.

11. All prescribed medication must have been stopped at least 30 days prior to admission to the clinical research center based on investigator judgment (see Section 6.9). An exception is made for HRT, and occasional paracetamol which may be used throughout the study.
12. Ability and willingness to abstain from alcohol from 48 hours (2 days) prior to screening, and from 48 hours (2 days) prior to each admission until discharge from the clinical research center at each study period.
13. Ability and willingness to abstain from methylxanthine-containing beverages or food (coffee, tea, cola, chocolate, energy drinks) from 48 hours (2 days) prior to each admission to the clinical research center at each study period.
14. Good physical and mental health on the basis of medical history, physical examination, clinical laboratory, ECG, and vital signs, as judged by the investigator.
15. Capable of giving written informed consent which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.
16. Capable of using inhaler device with no physical or other issues which would impair the participant's ability to successfully use a pMDI inhaler as instructed in this study.
17. Ability to comply with the protocol. Subjects have capacity and no issues which would impair their ability to comply with all aspects of the protocol during the study.

The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

5.2. Exclusion Criteria

Individuals who meet any of the following exclusion criteria at screening will not be eligible to participate in the study:

1. Radiation exposure, including that from the present study, excluding background radiation but including diagnostic x-rays and other medical exposures, exceeding 5 mSv in the last 12 months or 10 mSv in the last 5 years. No occupationally exposed worker, as defined in the Ionising Radiation Regulations 2017, shall participate in the study.
2. History or presence of any form of asthma, including childhood asthma and exercise induced asthma.
3. Respiratory disorders other than asthma. A history of respiratory diseases to include (but not limited to): pneumothorax, pulmonary fibrotic disease, bronchopulmonary

dysplasia, chronic bronchitis, cystic fibrosis, bronchiectasis, interstitial lung disease, emphysema, COPD, tuberculosis, known alpha 1 antitrypsin deficiency and other respiratory abnormalities other than asthma that, in the opinion of the investigator, could put the participant at risk through study participation or could affect the study analyses and data interpretation.

4. History or presence of any cardiovascular, respiratory, hepatic, renal, gastrointestinal, endocrine, hematologic, or neurological disorders that could, in the opinion of the investigator, put the participant at risk through study participation or that would affect the study analyses and data interpretation.
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. Also, any other history of previous malignancy that could, in the opinion of the investigator, put the participant at risk through study participation or which could affect the study analyses and data interpretation.
6. Recent history of mild conditions potentially affecting MCC (viral infections, cough, cold, active hayfever etc.) in the last 14 days (see also Section 5.5).
7. Recent use of drugs for treating conditions potentially affecting MCC (viral infections, cough, cold, etc.) in the last 30 days (see also Section 5.5).
8. Systolic blood pressure <90 mmHg or >140 mmHg, or diastolic blood pressure <50 mmHg or >90 mmHg at screening or Day -1 of each treatment period.
9. History of pathological tachycardia, or a pulse rate >100 bpm at screening or Day -1.
10. Current or chronic history of liver disease or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones).
11. Vaccine(s) within 2 weeks prior to admission or plans to receive such vaccines during the study.
12. Exposure to more than 4 new chemical entities within 12 months prior to the first dosing day or participation in a clinical study within 90 days of study start, or 5 half-lives of study drug if that is longer.
13. Current enrollment or past participation in this clinical study.
14. 12-Lead ECG abnormality: Significant abnormality in the 12-lead ECG performed at screening that, in the investigator's opinion, would affect safety evaluations or place the subject at risk.
15. QTc >450 msec (or >480 msec in participants with bundle branch block) performed at screening.

    Notes: The QTc is the QT interval corrected for heart rate according to QTcF. It is either machine-read or manually over-read. The specific formula used to determine eligibility and discontinuation for an individual participant should be determined prior to initiation of the study and used throughout the study for the individual participant. In other words, several different formulas cannot be used to calculate the QTc for an individual participant and then the lowest QTc value used to include or discontinue the participant from the trial.

16. ALT >1.5× ULN at screening.
17. Total bilirubin >1.5×ULN at screening. Participants with Gilbert's syndrome can be included with total bilirubin >1.5×ULN as long as direct bilirubin is <1.5×ULN
18. Presence of HBsAg at screening or within 3 months prior to first dose of study intervention.
19. 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.
20. Positive hepatitis C RNA test result at screening or within 3 months prior to first dose of study intervention. **Note:** Test is optional and participants with negative hepatitis C antibody test are not required to also undergo hepatitis C RNA testing.
21. Positive HIV antibody test.
22. Positive pre-study drug/alcohol screen, including THC.
23. Regular use of known drugs of abuse, including THC.
24. Cotinine levels indicative of smoking or history or use of tobacco- or nicotine containing products within 6 months prior to screening.
25. Use of combustible tobacco products, and noncombustible nicotine delivery systems, inclusive of cigarettes, cigars, pipes, and materials used to "vape" within 6 months prior to screening.
26. Average intake of more than 21 units of alcohol per week in males and 14 units per week in females (clinical site standard: unit of alcohol equals approximately 250 mL of beer, 100 mL of wine, or 35 mL of spirits) based on breath alcohol test.
27. 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.
28. Presence or history of clinically significant allergy requiring treatment, as judged by the investigator.
29. 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 e.g.,xample, herbal medicine, health supplements, traditional medicine, homeopathic remedies, etc.) within 14 days prior to first dose of propellant in treatement period 1.
30. Subjects who are study site employees, or immediate family members of a study site or sponsor employee.
31. Failure to satisfy the investigator of fitness to participate for any other reason.

5.3. Randomization criteria

Participants meeting any of the following criteria must not be randomized. Similarly, the following criteria 1 and 2 should also be reviewed and confirmed again at the start of

treatment period 2 to ensure no changes since the participant completed treatment period 1.

1. Occurrence of a culture-documented or suspected bacterial or viral infection of the upper or lower respiratory tract, sinus or middle ear occurring between screening and randomization that, in the opinion of the investigator, may put the safety of the participant at risk or impact the participant's ability to participate in the study or that may impact analyses and interpretation of the study results. See Section 5.5 for information on rescreening.
2. Any other change in health status since screening or short course of medications taken since screening, which could, in the opinion of the investigator, put the safety of the participant at risk through study participation, impact the participant's ability to participate or confound the interpretation of the study results. See Section 5.5 for information on rescreening.

5.4. Lifestyle Considerations

5.4.1. Meals and Dietary Restrictions

There are no meal or dietary restrictions, except those reported under Section 5.4.2. On Days -1 to Day 6 and Day 8 meals will be provided at appropriate times. On Day 7, breakfast will be provided after safety bloods have been taken and prior to administration of any study treatment. Lunch will be provided after completion of all scintigraphy imaging at approximately 4 hours post dose. The evening meal will be provided at approximately 10 hours post dose. Water consumption will be controlled.

5.4.2. Caffeine Alcohol and tobacco

- Due to the potential effects on pulmonary function, 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 each admission until discharge from the site at the end of each treatment period
- During the study, participants will abstain from alcohol from 48 hours prior to admission until discharge from the site at the end of each treatment period.
- Use of tobacco products will not be allowed from 6 months prior to screening until after the final follow up visit.

5.4.3. Exercise

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).

5.4.4. Other Restrictions

- Participants must not donate blood during the study until discharge (other than the blood sampling planned for this study). Participants should refrain from donating sperm or eggs during the study intervention period and for at least 90 days or 30 days, respectively, after the last dose of study intervention.

5.5. Screen Failures

A screen failure occurs when a participant who consents to participate in the clinical study is not subsequently entered into the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, any protocol deviations, 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.

Participants who were considered screen failure for recent history of mild temporary conditions potentially affecting MCC (exclusion criterion 6) or for taking drugs for treating mild temporary conditions affecting MCC (exclusion criterion 7) may be rescreened and enrolled at later times if time allows. Rescreened participants should be assigned a new participant number for every screening/rescreening event. Previously assigned participant numbers are to be recorded in the participants' eCRF.

5.6. Criteria for Temporarily Delaying Administration of Study Intervention

Not applicable

6. STUDY INTERVENTIONS AND CONCOMITANT THERAPY

The definition of study intervention is provided in the table of definitions.

6.1. Study Intervention Administered

Study intervention is presented in Table 4.

Table 4 Study Intervention Administered

Intervention Label	Test Treatment	Reference Treatment	MCC gamma scintigraphy assessment
Intervention Name	Test propellant: HFA-152a, aka 1 – Difluoroethane	Reference propellant (HFA-134a, aka 1,1,1,2 – Tetrafluoroethane	Nebulized radiolabelled saline solution
Intervention Description	repeated doses: 6 days, 4 inhalations twice daily (BID)+last administration on the morning of Day 7	repeated doses: 6 days, 4 inhalations twice daily (BID)+last administration on the morning of Day 7	Saline solution containing radiolabeled ^{99m}Tc colloidal sulphur
Route of administration	Oral inhalation	Oral inhalation	Oral inhalation
Use	Propellant for Ventolin	Propellant for Ventolin	Enable assessment of MCC via scintigraphy imaging
Source	GSK	GSK	Clinical site CCI
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.	Labelled as per the country requirements

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 in the morning and in the evening (time interval 12±3 hour) BID on each dosing day.

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, which is used to administer the study intervention.
- MDIs need to be primed before use. The priming of MDIs should not be done in the vicinity of the participants, as unintended inhalation needs to be avoided.

- 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 10.7) and appropriately managed by GSK.

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, institution, the head of the medical institution (where applicable), 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.
- A MSDS/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 Interactive response technologies 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

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

Type of Study	
Blinding of laboratory testing	The laboratory in charge of sample testing will be blinded to the study intervention assignment. Codes will be used to link the participant and study to each sample. There will be no link between the study intervention groups and the identity of the participant.
Emergency unblinding	This is a double-blind study in which participants investigators/outcomes assessors, and investigational site staff are blinded to the study interventions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participants' 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 in the eCRF. If the investigator is unable to access RAMOS they can contact the GSK helpdesk based on the information provided in the pharmacy manual. A physician other than the investigator (e.g., an emergency room physician) or participant/participant's caregiver or family member may also request emergency access to the participant's study intervention information as per participant card.

A participant may continue in the study if that participant's intervention assignment is unblinded. 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.

6.5. Study Intervention Compliance

Participants 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. 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] or similar) which provide flow and co-ordination coaching. An overdose is any dose of propellant given to a participant that exceeds the planned dose for an individual within a given dose group. In the event of an overdose, the [investigator or designee] should:

- Closely monitor the participant for any AE/SAE and laboratory abnormalities for 1 week.
- Document the quantity of the excess dose in the eCRF.

6.6. Dose Modifications

Not applicable.

6.7. Continued Access to Study Intervention after the End of the Study

Not applicable.

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.

GSK does not recommend specific treatment for an overdose.

6.9. Prior and Concomitant Medications

The use of all prescribed medication is not allowed from 30 days prior to admission to the clinical research center until discharge from the study at the final follow up visit or ED. An exception is made for HRT, which are allowed throughout the study and occasional use of up to 4 g/day paracetamol. 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 30 days prior to admission to the clinical research center until discharge from the study at the final follow up visit.

Vaccination (including vaccination against SARS-CoV-2) is not allowed from 2 weeks prior to admission until discharge. Acetaminophen (paracetamol), at doses of 4 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. 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.

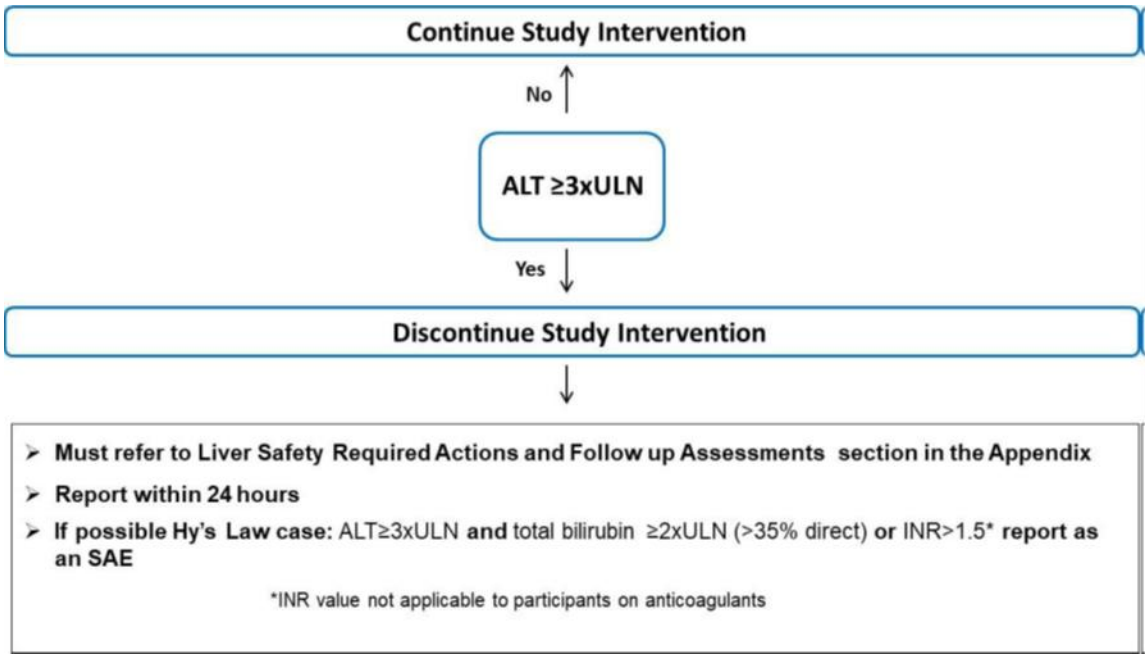
See the SoA for data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed. The primary reason for premature discontinuation of the study intervention will be documented in the eCRF based on the list below:

Reason	Additional Items/Sub-reasons
AE	
Lost to follow-up	Participant relocated Participant was incarcerated Other, specify Unknown
Participant achieved protocol-defined stopping criteria	Liver chemistry stopping criteria QTc stopping criteria Bronchospasm stopping criteria
Physician decision	Specify
Protocol deviation	Specify
Site terminated by the Sponsor	
Study treatment terminated by the Sponsor	
Study terminated by the Sponsor	
Withdrawal by participant	Burden of procedure Participant relocated COVID-19 pandemic Other, specify
Other	Specify
Death	

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 2 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 2 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 10.6 for required liver safety actions and follow-up.

7.1.2. QTc Stopping Criteria

If a clinically significant finding is identified (including, but not limited to, changes from 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-reported 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

For participants with underlying bundle branch block, follow the discontinuation criteria listed below:

Baseline QTc with Bundle Branch Block	Discontinuation QTc with Bundle Branch Block
<450 msec	>500 msec
450 – 480 msec	≥530 msec

Note: Baseline referred to Day -1 of the relevant treatment

7.1.3. Bronchospasm Stopping Criteria

In the unlikely event that a participant suffers an episode of significant bronchospasm after inhaling any of the study interventions, participants will be discontinued from any further study interventions and withdrawn from the study. This assessment of bronchospasm will be made by the investigator. Significant bronchospasm is defined as symptomatic requiring treatment and/or showing a decrease in FEV1 >30% from baseline (baseline will be considered to be the most recent pre-therapy measurement i.e., Day -1 test of the relevant treatment period). Treatment of bronchospasm should include an inhaled or nebulised bronchodilator such as salbutamol and/or ipratropium and oxygen to maintain peripheral oxygen saturation >90%. If, at any time, it is believed that participant safety would be improved by transfer to hospital, this will be arranged.

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, behavioral, or compliance reasons.

During the clinical conduct, close monitoring of all participants according to the Schedule of Assessment will be performed to evaluate the occurrence and severity of any local irritation; appropriate actions will be taken, including the removal from the study.

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, if required. The participant will be discharged from the clinical unit if safe to do so and will be asked to quarantine at home according to local guidelines.

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 ED 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:

Reason	Additional Items/Sub-reasons
AE	
Lost to follow-up	Participant relocated, Participant was incarcerated Other, specify Unknown
Participant achieved protocol-defined stopping criteria	Liver chemistry stopping criteria QTc stopping criteria Bronchospasm stopping criteria
Physician decision	Specify
Protocol deviation	Specify
Site terminated by the Sponsor	
Study terminated by the Sponsor	
Withdrawal by participant	Burden of procedure Participant relocated COVID-19 pandemic Other, specify
Other	Specify
Death	

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 10.3.5.5).

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 SoA (Section 1.3). 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. Subjects who have signed informed consent but are not eligible to proceed should be recorded in the eCRF with a status of 'screen failure'.
- Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the timeframe defined in the SoA (see Section 1.3).
- 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 age, 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 history by interviewing the participant 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

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

8.2.1. Inhaler training

Participants' MDI proficiency will be reviewed by the investigator or delegate. Inhaler proficiency will be assessed during the Screening Visit and during subsequent treatment period visits at the timepoints specified in the SoA (Section 1.3). If a participant is unable to demonstrate inhaler use in a satisfactory and repeatable manner, they will be excluded from the study.

8.3. Safety Assessments

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

8.3.1. Physical Examinations

- A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal (including liver and spleen), dermatologic, and neurological systems. Height and weight (on an empty bladder and wearing light clothing) 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.

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

8.3.3. Electrocardiograms

- Screening and post-dose will be conducted via single 12-lead ECG(s) as outlined in the SoA (see Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc 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.
- All ECGs will be performed in single assessment. In case of any QT abnormalities ECGs will be repeated in triplicate.
- If an absolute value for parameters is clinically significant as judged by the investigator, then the value will be recorded as an AE.

8.3.4. Spirometry

Spirometry will be performed at the study site to assess FEV1 and FVC.

To enroll in this study, participants must demonstrate a baseline FEV1 ≥80% of predicted and a FEV1:FVC ratio >70% at screening. At least 3 acceptable spirometry maneuvers (from a maximum of 8 attempts) should be achieved on each occasion that spirometry assessments are performed, in accordance with the American Thoracic Society/European Respiratory Society standards [Graham, 2019]. The highest of 3 technically acceptable measurements will be recorded at each visit. Global Lung Function Initiative equations will be used [Quanjer, 2012] to determine predicted values. Predicted values will be corrected for gender, age, height and race.

8.3.5. Clinical Safety Laboratory Tests

- Clinical laboratory tests will be performed in accordance with laboratory manual 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 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 Section 10.3).

- 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 nonprotocol-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.

8.3.6. Pregnancy Testing

Not applicable, as only women of nonchildbearing potential (WONCBP) are eligible to participate in 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 10.3). 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. 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 10.3.5.5 and Section 10.7.4.4.

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

All SAEs will be collected from the signing of the ICF until final discharge from the study (see SoA, Section 1.3).

All AEs will be collected from the start of study intervention until final discharge from the study (see SoA, Section 1.3).

Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded as medical history/current medical conditions, 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.

A poststudy AE/SAE is defined as any event that occurs outside of the AE/SAE reporting period defined in Section 8.4.1.

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, after a participant has been discharged from the study, the investigator must record it in the medical records. If the investigator considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.4.3. 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.

8.4.4. Adverse event of special interests

Not Applicable.

8.4.5. 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 Table 5 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 10.3.5.3.
- 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 investigational directions for use, or package insert will notify the IRB/IEC, if appropriate according to local requirements.
- The ARSAC practitioner will be notified of any SAE that is considered related to the exposure of radioactivity.

Table 5 Timeframes for submitting SAE, pregnancy and other events 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/Electronic AEs Report	24 hours*	Paper/Electronic AEs Report
Pregnancies	24 hours*	Paper pregnancy notification report	24 hours *	Paper pregnancy follow-up report

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

8.4.6. Pregnancy

- Details of all pregnancies in female partners of male participants will be collected after the start of study intervention and until 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 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, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.
- The pregnant female partner will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the 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 8.4.5. While the investigator is not obligated to actively seek this information in former pregnant female partners, he or she may learn of an SAE through spontaneous reporting.
- Any male participant whose partner becomes pregnant while participating in the study will discontinue study intervention or be withdrawn from the study.

8.4.7. Cardiovascular and Death Events

Cardiovascular Events

Not Applicable.

Death Events

The Death eCRF is provided immediately after the occurrence or outcome of death is reported. Initial and follow-up reports regarding death must be completed within one week of when the death is reported.

8.4.8. Disease-related events and/or disease-related outcomes not qualifying as AEs or SAEs

Not Applicable.

8.4.9. Contact information for reporting SAEs and pregnancies

Table 6 Contact information for reporting SAEs and pregnancies

Study contact for questions regarding SAEs and pregnancies Contact GSK's local and/or medical contacts
Contacts for reporting SAEs and pregnancies. Available 24/24 hours and 7/7 days fax # +44(0) 20 81814780. Available during working hours oax37649@gsk.com

8.4.10. Participant Card

The investigator or delegate must provide the participant with a "participant card" containing information about the clinical study. The participant must be instructed to always keep the participant card in their possession for the duration of the study. In an emergency, this card serves to inform the responsible attending physician that the participant is in a clinical study and that relevant information may be obtained by contacting the investigator(s) or their back up.

8.4.11. Medical device deficiencies

Medical devices are being provided for use in this study to administer the study intervention. To fulfill 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 10.7.

Note. Deficiencies fulfilling the definition of an AE/SAE will follow the processes outlined in Section 10.7 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 10.7.

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 by email/facsimile equipment. If email/facsimile equipment is unavailable, then notification by telephone with a copy of data collection tool sent by overnight courier service should be utilized.
- 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 or designee 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

No PK data will be collected in this study.

8.6. Pharmacodynamics

No PD data will be collected in this study.

8.7. Imaging Assessments

8.7.1. Assessment of MCC using nebulized ^{99m}Tc and scintigraphy Assessments

After Day 7 Test or Reference Propellant inhalation, MCC will be assessed in each TP. Sulphur colloid containing NMT 20 MBq ^{99m}Tc will be delivered to the lungs via the PARI LC PLUS nebulizer with PARI TubroBO SX compressor using relaxed tidal breathing (with a nose clip) according to the study specific dosing instructions. Immediately after nebulization (prior to the acquisition of any scintigraphic images), participants will rinse their mouth with at least 120mL of water and will expel the rinse to minimize the amount of radioactivity that may be swallowed, after which a further volume of 120mL of water is to be taken and drunk to clear any radioactivity from the oropharynx and esophagus.

From the start time of the nebulization, a record of coughs will be kept for each subject up until completion of the final scintigraphy assessment at approximately 4 h following completion of the nebulization.

To enable the gamma scintigraphic assessment of MCC, up to 2 anatomical markers containing ^{99m}Tc will be taped to the skin, so they are visible within the gamma camera field of view without overlapping regions of interest. Immediately post-nebulization (and the subsequent rinsing and consumption of water), posterior and anterior images will be collected (T0), with subsequent images collected at defined intervals over a 4-hour period, as indicated in the SoA (Section 1.3). Where necessary, any items external to the body of the subject will be retained and imaged (as soon as is feasible around the imaging schedule of the participant) e.g., apron, tissues, mucociliary excretions, if it is believed to benefit for the subsequent data analysis.

All images will be acquired using a gamma camera with a 54 × 40 cm field of view and fitted with a low energy parallel hole collimator. For all images, subjects will be in a standing position in front of the gamma camera, in both posterior and anterior orientations.

The gamma scintigraphic images collected up to 4 h following the controlled inhalation of nebulized ^{99m}Tc-sulphur colloid, will be used to derive the percent of radioactivity that is retained in the right lung (as a percent of initial amount of radioactivity delivered at T0) across all imaging time points (as indicated in the SoA).

The imaging schedule provided in the SoA may be altered based on emerging scintigraphic data (for e.g., additional images may be acquired if deemed necessary for the purposes of the data analysis). Actual image times will always be recorded. Adjustments to the schedule may also be made to allow time to alter the position of the anatomical markers, or to adjust the camera positioning in order to maintain image quality.

Whole lung clearance is strongly dependent on the site of particle deposition within the lung. To characterize regional deposition by providing a clear outline of the lungs, and in order to correct for the attenuation of gamma rays by overlying tissues, each participant will undergo a transmission scan of the thorax using a flood field source containing ^{57}Co. The transmission scans will be planned to be performed on Day 1 to Day 6 of TP 1, as per the SoA (Section 1.3).

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.

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

9.1. Statistical Hypotheses

No formal hypothesis testing will be performed for the primary and secondary endpoints. This study is designed to estimate MCC of orally inhaled HFA-152a MDI (Test propellant) and HFA-134a MDI (Reference propellant). For this aim, the GMR will be calculated by taking the ratio of the GMs of the Test (T) to the Reference propellant (R) for primary endpoint; 90% Confidence Interval of GMR (T/R) will also be calculated.

9.1.1. Multiplicity adjustment

The primary or secondary endpoints will be analyzed in a descriptive manner with no formal hypothesis testing and therefore no multiplicity adjustments will be applied.

9.2. Analysis Sets

Analysis Set	Definition / Criteria	Analyses Evaluated
Screened	• All participants who were screened for eligibility.	• All Screened, Reason for Screen Failures
Enrolled	• All participants who screen passed and entered in the study (who were randomized). • 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	• Study Population

Analysis Set	Definition / Criteria	Analyses Evaluated
	as they did not enter the study.	
MCC (Principal Stratum)	• All participants who were able to adhere to all doses of study intervention as prescribed and completed the study	• Estimand for primary and secondary objective of MCC parameters
Safety	• All participants who received at least one dose of study intervention.	• Estimand for secondary safety objective

9.3. Statistical Analyses

9.3.1. General considerations

Calculations will be based on the actual sampling times recorded during the study. From the retained radioactivity data, the following parameters will be estimated: retained radioactivity at all different timepoints and AUC0-4h of the retained radioactivity.

The MCC parameters data will be summarized using descriptive statistics (N, n, arithmetic mean, 95% CI of arithmetic mean, GM, 95% CI of GM, SD, SD (log_e) median, CVb in %, minimum and maximum), and will be listed and summarized in tabular and/or graphical form. Where appropriate, listings and graphical presentation will also be produced for MCC parameters endpoints.

Discrete data (safety) will be summarized by counts and percentages as appropriate.

9.3.1.1. Definition of MCC endpoints

The definitions of MCC parameters are described in the following table:

Parameter	Description
AUC_{0-4h} (primary)	Area under the right lung percent radiolabeled particle retention -time curve up to 4 h after dosing with nebulized ^{99m}Tc on Day 7
R1h (secondary)	Right lung Percent radiolabeled particle retention at 1 h after dosing with nebulized ^{99m}Tc on Day 7
R1.5h (secondary)	Right lung Percent radiolabeled particle retention at 1.5 h after dosing with nebulized ^{99m}Tc on Day 7
R3h (secondary)	Right lung Percent radiolabeled particle retention at 3 h after dosing with nebulized ^{99m}Tc on Day 7

9.3.1.2. Main Analytical Approach

The primary MCC parameter is area under the percent radiolabeled particle retention-time curve up to 4 hours (AUC[0-4h]) after nebulized ^{99m}Tc inhalation. The primary analysis will evaluate the primary estimand in the MCC analysis set. In cases where reliable estimation of AUC(0-4h) is not possible due to last nonreportable measurable radioactivity retention data, the corresponding AUC(0-4h) data will be treated as missing data.

Log_e-transformed data of AUC(0-4h) will be analyzed using mixed effect model approach with fixed effect such as period, treatment group and participants as random effects The point estimates and their associated 90% CI will then be back-transformed to provide point estimates and 90% CI for the ratios (GMR) of HFA-152a , aka 1 – Difluoroethane (Test)/ HFA-134a, aka 1,1,1,2 – Tetrafluoroethane (Reference).

Strategies for handling ICEs is described in Section 3. Further details of the planned analysis of primary estimands will be described in the SAP.

9.3.1.3. Sensitivity Analysis

If missing data is more than 10% then a sensitivity analysis will be conducted by using AUC0-4h estimated by linear extrapolation method of the log-transformed data.

9.3.1.4. Supplementary/supportive Analysis

No supplementary/supportive analysis will be performed.

9.3.1.5. Secondary Endpoints Analyses

The secondary MCC endpoints are as follows:

- Right lung percent radiolabeled particle retention at 1 h after dosing with nebulized ^{99m}Tc on Day 7
- Right lung percent radiolabeled particle retention at 1.5 h after dosing with nebulized ^{99m}Tc on Day 7
- Right lung percent radiolabeled particle retention at 3 h after dosing with nebulized ^{99m}Tc on Day 7

The secondary endpoint analysis, like the primary analysis, will assess the secondary estimand in the MCC population. In cases where the measurement is not performed, it will be treated as missing data.

Secondary endpoints will be analyzed using mixed effect model approach with fixed effect such as period, treatment group and participants as random effects. The point estimates of mean difference and their associated 90% CI will be provided for HFA-152a, aka 1 – Difluoroethane (Test) and HFA-134a, aka 1,1,1,2 – Tetrafluoroethane (Reference).

ICEs will be managed in the same way as primary endpoint.

Further details of the planned analysis of secondary estimands will be described in the SAP.

9.3.1.6. Sensitivity Analysis for secondary endpoint

If the distribution of the secondary endpoints' (percent radiolabeled particle retention at 1, 1.5, 3 h after dosing with nebulized ^{99m}Tc on Day 7) data does not follow normal distribution, then $\log_e$ transformation will be applied.

Log_e transformed data of secondary endpoints will be analyzed using mixed effect model approach with fixed effect such as period, treatment group and participants as random effects. The point estimates and their associated 90% CI will then be back-transformed to provide point estimates and 90% CI for the ratio (GMR) of HFA-152a, aka 1 – Difluoroethane (Test) / HFA-134a, aka 1,1,1,2 – Tetrafluoroethane (Reference).

If missing data of percent radiolabeled particle retention at either timepoint (1h, 1.5h, and 3h) is >10% then sensitivity analysis will be performed using log-linear/linear (depending if data are normally or log-normally distributed, respectively) interpolation/ extrapolation imputation of available measurements similarly to what reported under Section 9.3.1.3).

9.3.2. Safety Analysis

All safety analyses will be performed on the Safety analysis set.

Safety and tolerability will be assessed through AEs, SAEs, clinical laboratory, vital signs, and ECGs, and any other parameter that is relevant for safety assessment.

Safety data will be presented in tabular and/or graphical format and summarized descriptively according to GSK's SDTM standards.

Treatment policy strategy (as described in Section 3) for the ICE of study treatment discontinuation due to any reason will be used for summarizing safety data of the study.

Safety analysis is described in further detail in below sections.

9.3.2.1. Adverse Events

All reported AEs will be coded using the standard GSK dictionary (MedDRA) and grouped by body system and preferred terms. Counts and percentages for AEs, and SAEs will be produced by system organ class and preferred terms. AEs and SAEs will also be presented for overall and on-treatment period. The number and percentages will be provided for all AEs, study treatment – related AEs, and SAEs, deaths, fatal AEs, non-fatal SAEs, and AEs leading to study treatment or study withdrawal. AEs and SAEs will be summarized by severity.

9.3.2.2. Clinical Laboratory

A summary of all data outside the reference range of the clinical laboratory will be provided to monitor participants' safety. Absolute values of clinical laboratory data will be presented descriptively (arithmetic mean, SD, median, minimum, and maximum), where applicable.

9.3.2.3. Vital signs and ECG

Absolute and changes from baseline values for vital signs (systolic and diastolic blood pressure, and pulse rate) will be summarized 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 presented descriptively (arithmetic mean, SD, median, minimum, and maximum), where applicable.

9.4. Interim Analyses

No interim analysis will be performed for this study.

9.5. Sample Size Determination

Up to 24 healthy participants will be randomly assigned to ensure at least 20 participants are included in the MCC analysis set with at least 10 randomized to each treatment sequence.

The target number of participants is chosen to achieve half width (refer to Table 7) of the 90% CI, in the estimate of the GMR for the primary endpoint.

An MCC study [Donno, 1988] reported a CVw of 8.5% for the AUC(0-6h) parameter. The within-participant CVw for the AUC(0-4h) parameter was thus assumed to range from 8.5% to 11.5%.

Using a sample size 20 and CVw of 10.5% in AUC(0-4h), the half width of the upper bound of 90% CI for observed treatment ratio of AUC(0-4h) between 2 treatment arms is 5.93 % (Table 7). Considering for example, that the GMR between Test and Reference is 1.05 for n = 20 and CVw = 10.5%, then the upper bound of the 90% CI for observed treatment ratio is 1.05*(1+0.0593)=1.11 and the lower bound is 1.05/(1+0.0593)=0.99 (Table 8).

Table 7 Half-width Expected for Different Sample Size and Intra-Subjects Variability

Sample size	Intra subject variability SD (CVw%)	Half-width (%) of the upper bound of 90% CI for Observed Treatment Ratio
16	0.0849 (8.5%)	5.44
18		5.07
20		4.77
22		4.52
16	0.0948 (9.5%)	6.09
18		5.68
20		5.35
22		5.06
16	0.1047 (10.5%)	6.76
18		6.30
20		5.93
22		5.61
16	0.1146 (11.5%)	7.42
18		6.92
20		6.51
22		6.16

Abbreviations: CI=confidence interval; CVw=coefficient of variation within subjects.

Table 8 Lower and Upper Bound GMR for Different Values of GMR

GMR (T/R)	Lower and Upper bound for observed GMR (T/R)	
	Lower Bound	**Upper Bound**
0.9	0.85	0.95
0.95	0.90	1.01
1	0.94	1.06
1.05	**0.99**	**1.11**
1.1	1.04	1.17

Note: n = 20 & CVw = 10.5%
Abbreviations: CVw=coefficient of variation within subjects, GMR=geometric mean ratio, R=reference, T=test

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
  - Health and Safety. The Ionising Radiations Regulations 2017. Statutory Instrument 2017 No. 1075.
  - Health and Safety. The Ionising Radiations (Medical Exposure) Regulations 2017. Statutory Instrument 2017 No. 1322.
- The protocol, protocol amendments, ICF, 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.
- 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. Any amendments relating to the administration of radioactive substances will be reviewed by the ARSAC practitioner prior to submission to ARSAC as required by the current ARSAC Notes for Guidance. The ARSAC practitioner will also be notified of any substantial amendments to the PIS and ICF and/or protocol.
- 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, if applicable
  - 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), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations

- The ARSAC practitioner for this study will administer the radiation at CCI Administration will be conducted in accordance with the ARSAC practitioner's current licence and CCI current ARSAC Employer licence. Additionally, a research application will be submitted to ARSAC to obtain approval for the conduct of the study before test product administration.
- The protocol will be reviewed and the final version will be approved by the ARSAC practitioner.

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 course of 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 requirements of 21 CFR 50, local regulations, ICH guidelines, HIPAA requirements, privacy and data protection requirements, where applicable, and the IRB/IEC or study center.
- 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.

In case of unexpected pregnancy, participant must be informed that PI such as date of birth, 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.

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 their 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 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 right, 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, involvement of central reading mechanism) 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 and the first act of recruitment are 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, ARSAC practitioner and ARSAC, 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 clinical safety laboratory tests detailed in Table 9 will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- 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	
	• Red blood cell (RBC) count	
	RBC indices	• Mean corpuscular volume (MCV) • Mean corpuscular hemoglobin (MCH) • %Reticulocytes
	Absolute WBC count with differential:	• Neutrophils • Lymphocytes • Monocytes • Eosinophils • Basophils
	• **Hemoglobin**	
	• **Hematocrit**	
Clinical chemistry[1]	• Urea • Potassium • Creatinine* • Sodium • Calcium • Glucose fasting • Creatine phosphokinase (CPK)	• Aspartate aminotransferase (AST)/serum glutamic-oxaloacetic transaminase (SGOT)[1] • Alanine aminotransferase (ALT)/serum glutamic-pyruvic transaminase (SGPT)[1] • Alkaline phosphatase[2] • Total bilirubin[1] • Direct bilirubin, only if total bilirubin is elevated • Total protein
Routine urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, [bilirubin, urobilinogen, nitrite, leukocyte esterase] by dipstick • Microscopic examination. Please note, this will only be performed if there is an abnormality in accordance with Clinical Laboratory standard procedures at investigator discretion. • Culture at investigator discretion (if positive: specify pathogen)	
Other screening tests	• 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)] • Testing for SARS-CoV-2 may be performed at the discretion of the physician and based on local guidelines.	

NOTES

1. Details of liver chemistry stopping criteria and required actions and follow-up are given in Section 10.6: Liver Safety: Suggested Actions and Follow-up Assessments [and Study Intervention Rechallenge Guidelines]. All events of ALT [or AST] ≥3 × ULN and total bilirubin ≥2 × ULN (>35% direct bilirubin) or ALT [or AST] ≥3 × ULN and INR >1.5 (if INR measured), which may indicate severe liver injury (possible Hy's law), must be reported to [sponsor] in 24hours (excluding studies of hepatic impairment or cirrhosis).
2. If alkaline phosphatase is elevated, consider fractionating.

* To assess the kidney function, use eGFR 2009 calculator (CKD-Epi creatinine equation). eGFR (based on CKD-Epi) will be measured at all time points when creatinine is measured.

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 NOT 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, which 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 INR (if INR is measured) >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. – 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. Definition of Cardiovascular events

Not Applicable.

10.3.4. 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.

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

10.3.5.1. 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 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.

10.3.5.2. Assessment of intensity

The investigator will make an assessment of intensity for each AE, SAE and device deficiency 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.

10.3.5.3. Assessment of causality

- The investigator is obligated to assess the relationship between the study interventions as described in Table 4 and each occurrence of each AE/SAE/device deficiency. 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 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.

- Where multiple interventions are administered in the same visit, the investigator should specify, when possible, if the AE/SAE could be causally related to a specific study intervention. When a causal relationship to a specific study intervention cannot be determined, the investigator should indicate the AE/SAE to be related to all interventions
- 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.

10.3.5.4. 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).

10.3.5.5. 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 if available.
- 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 visit 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 visit or until the participant is 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 postmortem findings, including histopathology, if available.

Follow-up of pregnancies

Pregnant partners of male 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 follow-up report and the AE 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 10.3.5.7.

10.3.5.6. 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 8.4.1).

10.3.5.7. 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 or poststudy 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 (CA) via the national spontaneous reporting system. These will be classified as spontaneous ICSRs.
- Contacts for SAE reporting can be found in Section 8.4.9.

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 8.4.9.

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 1 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 partners of childbearing potential with fertile male participants must use a highly effective contraceptive (see list below) plus participant use of a condom from the start of first study intervention until 90 days post-dose of last study intervention.

• **CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:**
• **Highly Effective Methods[b] That Have Low User Dependency** Failure rate of <1% per year when used consistently and correctly.
Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c]
Intrauterine device (IUD)
Intrauterine hormone-releasing system (IUS)[c]
Bilateral tubal occlusion/ligation
Azoospermic participant (vasectomized or due to a medical cause) • Azoospermia is a highly effective contraceptive method provided that the partner is the sole sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days. Note: documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
• **Highly Effective Methods[b] That Are User Dependent** Failure rate of <1% per year when used consistently and correctly.

Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c] • oral • intravaginal • transdermal • injectable
Progestogen-only hormone contraception associated with inhibition of ovulation[c] • oral • injectable
Sexual abstinence • Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
a. Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies. b. Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly. c. [Male condoms must be used in addition to hormonal contraception]. If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action. Note: Periodic abstinence (calendar, sympto-thermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception. Male condom and female condom should not be used together (due to risk of failure from friction)

10.5. Appendix 5: Genetics

Not Applicable. Genetics are not evaluated in this study.

10.6. Appendix 6: Liver safety: suggested actions and follow-up assessments

Phase 1 Liver chemistry stopping criteria have been designed to assure participant safety and to evaluate liver event etiology.

Phase 1 Liver Chemistry Stopping Criteria and Required Follow Up Assessments

Liver Chemistry Stopping Criteria	
ALT-absolute	ALT≥3xULN If ALT≥3xULN AND total bilirubin≥2xULN (>35% direct bilirubin) or INR (if measured) >1.5, report as an SAE[1,2].
Required Actions, Monitoring and Follow up Assessments	
Actions	**Follow Up Assessments**
• Immediately discontinue study intervention	• Viral hepatitis serology[3]

Liver Chemistry Stopping Criteria	
• Report the event to GSK within 24 hours • Complete the liver event form and complete an SAE data collection tool if the event also meets the criteria for an SAE[2] • Perform liver event follow up assessments as described in the Follow Up Assessment column • Do not restart or rechallenge participant with study intervention • Monitor the participant until liver chemistries resolve, stabilize, or return to within baseline (see MONITORING) **MONITORING:** **If ALT ≥3×ULN AND total bilirubin ≥2×ULN or INR >1.5:** • Repeat liver chemistries (include ALT, aspartate transaminase [AST], alkaline phosphatase, total bilirubin and INR) and perform liver event follow up assessments within 24 hours • Monitor participant twice weekly until liver chemistries resolve, stabilize or return to within baseline • A specialist or hepatology consultation is recommended **If ALT ≥3×ULN AND total bilirubin <2×ULN and INR ≤1.5:** • Perform liver chemistries (include ALT, AST, alkaline phosphatase, total bilirubin and INR) and perform liver event follow up assessments within 24-72 hours • Monitor participant weekly until liver chemistries resolve, stabilize or return to within baseline	• Obtain INR and recheck with each liver chemistry assessment until the aminotransferases values show downward trend • Obtain serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH), • Fractionate 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 liver event form • Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, recreational drugs, and other over-the-counter medications • Record alcohol use on the liver event alcohol intake form **If ALT ≥3×ULN AND total bilirubin ≥2×ULN or INR >1.5 obtain the following in addition to the assessments listed above:** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG) or gamma globulins • Liver imaging (ultrasound, magnetic resonance, or computed tomography) and /or liver biopsy to evaluate liver disease, complete Liver Imaging form. • Liver biopsy may be considered and discussed with local specialists if available, for instance:

Liver Chemistry Stopping Criteria	
	○ In participants when serology raises the possibility of autoimmune hepatitis (AIH) ○ In participants when suspected DILI progresses or fails to resolve on withdrawal of study intervention ○ In participants with acute or chronic atypical presentation. • If liver biopsy is conducted, then complete liver biopsy form

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation testing is unavailable, record the absence/presence of detectable urinary bilirubin on dipstick, which is indicative of direct bilirubin elevations suggesting liver injury.
2. All events of ALT ≥3xULN and total bilirubin 2×ULN (>35% direct bilirubin) or ALT 3×ULN and INR >1.5, which may indicate severe liver injury (possible 'Hy's Law'), must be reported as an SAE, the INR threshold value stated will not apply to participants receiving anticoagulants
3. Includes: hepatitis A immunoglobulin (IgM) antibody; HBsAg and HBcAb; hepatitis C RNA; cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, heterophile antibody or monospot testing) and hepatitis E IgM antibody.

10.7. Appendix 7: 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 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.

10.7.1. 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 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 a medical device. This definition includes events related to the 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 devices.

- An ADE is defined as an AE related to the use of a medical device. This definition includes any AE resulting from insufficient or inadequate instructions for use or any malfunction of the medical device as well as any event resulting from use error or from intentional misuse of the medical device.

10.7.2. Definition of medical device SAE, SADE and USADE

A Medical Device SAE is any serious AEs 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, which 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 ADE 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 ADE that by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report (see Section 2.2).

10.7.3. 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.

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

10.7.4.1. 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 competent authority via the national spontaneous reporting system. These will be classified as spontaneous ICSRs.

10.7.4.2. Assessment of intensity

Refer to Section 10.3.5.2.

10.7.4.3. Assessment of causality

Refer to Section 10.3.5.3.

10.7.4.4. 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 postmortem findings including histopathology, if available.
- 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.

10.7.5. 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 (see next table) 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 table) or to the medical monitor by telephone.
- If the site during the course of the study or poststudy becomes aware of any serious, nonserious AEs, pregnancy exposure, related to any GSK device 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 8.4.9.

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 8.4.9.

10.7.6. 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 8.4.9.

10.7.7. Reporting of medical device deficiencies for associated person

• **Reporting to GSK**
If an Associated Person (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 8.4.9 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.

10.8. Appendix 8: Country-specific requirements

Not Applicable.

10.9. Appendix 9. Risk Assessment for Gamma Scintigraphy Studies using nebulized ^{99m}Tc

This is a gamma scintigraphy study using a nebulized ^{99m}Tc labelled sulphur colloid product containing not more than 20 MBq, so participants will be exposed to ionising radiation. The effective dose per administration will be 0.5 mSv and 0.03 mSv per ^{99m}Tc anatomical marker. The effective dose per transmission scan will be 0.1 mSv.

The effective dose that each participant will receive from each administration of 20 MBq ^{99m}Tc (including 2 anatomical markers) will not exceed 0.56 mSv. Over both administrations the estimated radiation dose that each participant will receive is 1.22 mSv*. This is approximately 5.5 months of the average radiation exposure received in the UK each year (2.7 mSv; data obtained from UK Health Security Agency Ionising Radiation Exposure of the UK Population: 2010 Review [PHE, 2016]) and is equivalent to slightly less than the radiation dose that would result from 3 x-rays of the abdomen (0.47 mSv per procedure). It is believed that any increase in the amount of radiation that is received above natural radiation carries a risk of later developing serious and possibly fatal conditions. The risk associated with the maximum possible dose of radiation in this study is very small indeed and is considered to be acceptable.

The dose of radioactivity has been determined in accordance with the current approved ARSAC Employer Licence Application for CCI [redacted] CCI and the current Practitioner Licence for the ARSAC practitioner. The associated radiation exposure will fall within International Commission on Radiological Protection (ICRP) (1992) Guidelines for Category IIb studies (1 to 10 mSv).

*Note: Transmission scans can be repeated up to 2 times, if the first is considered not suitable for use due to unforeseen circumstances. Each transmission scan results in 0.1 mSv of radiation. Accordingly the maximum amount of radiation that any participant may receive (if the scan is repeated a maximum of 2 times) will be 1.42mSv. This is not expected to result in a significant increase in risk.

Radiation Exposure per Participant

[redacted]	[redacted] CCI	[redacted]	Effective Dose (mSv)
Transmission Scan (^{57}Co)			0.1
^{99m}Tc Sulphur Colloid			0.5
^{99m}Tc anatomical marker (per marker)			0.03
Total per administration*	[redacted]		0.56
Total over 2 administrations**			1.22

*Representative of one radiolabelled dose with the use of 2 anatomical markers
**Representative of both radiolabelled doses with the use of 2 anatomical markers per dose, and a transmission scan

Extrapolation of data from epidemiological studies of cancers induced by radiation exposure indicates that the risk factor for an adult UK population of both sexes (age range 18 to 64) is 5×10^{-2} per Sv [NRPB, 1993]. From this it can be estimated that the lifetime risk of inducing a fatal cancer in a healthy individual from a total exposure of 1.0 mSv is approximately 1 in 20,000. The lifetime risk for being diagnosed with cancer in the UK is around 1 in 2 [Cancer Research, 2021], indicating that this additional risk from this amount of radiation exposure is minimal.

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