Protocol

Study ID: 223166

Official Title: A Randomized, Non-inferiority, Double-blind, Controlled, Single-dose, 2-way Cross-over Study to Assess the Potential for Airway Sensitivity Reactions With Propellants HFA-152a (Test) and HFA-134a (Reference) Administered Via Pressurized Metered Dose Inhalers in Adults Aged 18-45 With Mild Asthma

NCT ID: NCT06702462

Date of Document: 08-Oct-2024

CLINICAL STUDY PROTOCOL

Primary study intervention(s)	Propellant HFA-152a administered via pMDI (Test)
Other study intervention(s)	Propellant HFA-134a administered via pMDI (Reference)
Study identifier	223166
Approval date	08 Oct 2024
Title	A randomized, non-inferiority, double-blind, controlled, single-dose, 2-way cross-over study to assess the potential for airway sensitivity reactions with propellants HFA-152a (Test) and HFA-134a (Reference) administered via pressurized metered dose inhalers in adults aged 18-45 with mild asthma
Compound number/Name	AH3365 - Salbutamol
Brief title	A study to assess the potential for airway sensitivity reactions with propellants HFA-152a (Test) and HFA-134a (Reference) administered via pressurized metered dose inhalers in adults with mild asthma
Sponsor	GlaxoSmithKline Research & Development Limited 79 New Oxford Street London WC1A 1DG United Kingdom
Sponsor signatory	Oscar Della Pasqua Executive Director, Clinical Pharmacology

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

Based on TMF-14732712 Protocol v3.0.

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.

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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
ACQ	Asthma Control Questionnaire
ADE	Adverse device effect
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of special interest
AUC	Area under the curve
AxMP	Auxiliary medicinal product
CA	Competent authority
CCI	Commercially confidential information
CFR	Code of Federal Regulations
CI	Confidence interval
Cmax	Maximum concentration
CONSORT	Consolidated standards of reporting trials
CRF/eCRF	Case report form/electronic case report form
CSR	Clinical study report
CV	Cardiovascular
DNA	Deoxyribonucleic acid
DRE	Disease-related event
ECG	Electrocardiogram
ED	Early discontinuation
eDiary	electronic Diary
EMA	European Medicines Agency
EoS	End-of-study
FAS	Full Analysis Set
FCAS	Fully compliant analysis set
FDA	Food and Drug Administration
FEV1	Forced expiratory volume in 1 second
FEV1 AUC0-15min	Area under the forced expiratory volume in 1 second-time curve from zero to 15 minutes
FSFV	First subject first visit
FSH	Follicle stimulating hormone
GC	Gas Chromatography
GCP	Good clinical practices
GMR	Geometric mean ratio
GWP	Global warming potential
H0	Null Hypothesis
H1	Alternative Hypothesis
HFA-134a	1,1,1,2-Tetrafluoroethane (Reference)
HFA-152a	1,1-Difluoroethane (Test)
HHS	Home healthcare services
HIV	Human immunodeficiency virus
HR	Hazard ratio
HRT	Hormonal replacement therapy

Abbreviation	Definition
IB	Investigator's brochure
ICE	Intercurrent event
ICF	Informed consent form
ICH	International Council on Harmonisation
ICS	Inhaled corticosteroids
ICSR	Individual case safety reports
IEC	Independent Ethics Committee
IMP	Investigational medicinal product
INR	International normalized ratio
IRB	Institutional review board
LABA	Long-acting beta-agonists
LAR	Legally acceptable representative
LTRA	Leukotriene receptor antagonist
MAO	Monoamine oxidase
MAR	Missing at random
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
MSDS	Material safety data sheet
PD	Pharmacodynamic
PFT	Pulmonary function test
PI	Personal information
PIP	Pediatric investigation plan
PK	Pharmacokinetic
pMDI	Pressurized metered dose inhalers
QTc	QT interval corrected
QTcB	QT interval corrected for heart rate using Bazett's formula
QTcF	QT interval corrected for heart rate using Fridericia's formula
QTL	Quality tolerance limit
RNA	Ribonucleic acid
SABA	Short-acting beta-agonists
SADE	Serious adverse device effect
SAE	Serious adverse event
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SD	Standard deviation
SIB	Suicidal ideation behavior
SmPC	Summary of product characteristics
SoA	Schedule of activities
SRT	Safety review team
SUSAR	Suspected unexpected serious adverse reaction
Sw	Within-participant variability
T1/2	Terminal phase half-life
TEAE	Treatment-emergent adverse event
TM	Telemedicine

Abbreviation	Definition
Tmax	Time to maximum concentration
TP1	Treatment period 1
TP2	Treatment period 2
ULN	Upper limit of normal
USADE	Unanticipated serious adverse device effect
WOCBP	Woman of childbearing potential
WONCBP	Woman of non-childbearing potential

Term	Definition
ADR	An AE where a causal relationship between a medicinal product and the AE is at least a reasonable possibility, i.e., the relationship cannot be ruled out. In the context of a clinical trial, an ADR can be serious or nonserious. Serious ADRs may be subject to expedited reporting if they are considered unexpected (see SUSAR definition). For marketed products, ADRs are subject to expedited reporting within the country where they are authorized.
AxMP	Medicinal products used in the context of a clinical trial but not as IMPs, such as medicinal products used for background treatment, challenge agents, rescue medication, or used to assess endpoints in a clinical trial. AxMPs should not include concomitant medications, that is medications unrelated to the clinical trial and not relevant for the design of the clinical trial. Authorized AxMP = Medicinal product authorized in accordance with Regulation (EC) No 726/2004, or in any member state concerned in accordance with Directive 2001/83/EC, irrespective of changes to the labelling of the medicinal product. Note: Safety reporting with regard to authorized AxMPs shall be made in accordance with Chapter 3 of Title IX of Directive 2001/83/EC. Unauthorized AxMP = Medicinal product not authorized in accordance with Regulation (EC) No 726/2004. Safety reporting for unauthorized AxMPs will follow the same processes and procedures as SUSAR safety reporting.
Background treatment	Type of medicinal product administered to each of the clinical trial participant, regardless of randomization group, to treat the indication that is the object of the study. Background treatment is generally considered to be the current standard of care for the particular indication. In these trials, the IMP is given in addition to the background treatment and safety/efficacy are assessed. The protocol may require that the IMP plus the background treatment is compared with an active comparator or with placebo plus background treatment.
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 (e.g., 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.
Challenge agent	A product given to trial participants to produce a physiological response that is necessary before the pharmacological action of the IMP can be assessed.

Term	Definition
Co-administered product	A product given to clinical trial participants as required in the protocol as part of their standard care for a condition that is not the indication for which the IMP is being tested and is therefore not part of the objective of the study.
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.
Comparator	Any product used as a reference (including placebo, marketed product, GSK, or non-GSK) for an investigational product being tested in a clinical trial. This is any product that is being used to assess the safety, efficacy, or other measurable value against the test product (IMP).
eDiary	Electronically recorded patient data and automated data entries on, for example, a handheld mobile device, tablet, or computer.
Eligible	Qualified for enrollment into the study based upon strict adherence to inclusion/exclusion criteria.
Essential documents	Documents that individually and collectively permit evaluation of the conduct of a study and the quality of the data produced.
HHS	Deployment of mobile health care professional(s) (nurses or phlebotomists) to perform study activities remotely.
Intercurrent event	Event occurring after study intervention initiation that affects either the interpretation or the existence of the measurements associated with the clinical question of interest.
Intervention number	A number identifying the intervention assigned to a participant, according to intervention allocation.
IMP	A pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorization but used or assembled (formulated or packaged) in a way different from the authorized form, or when used for an unauthorized indication, or when used to gain further information about the authorized form.
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.
LAR	An individual, judicial or other body authorized under applicable law to consent on behalf of a prospective participant to the participant's participation in the clinical study. The terms legal representative or legally authorized representative are used in some settings.
LSLV	The date on which the last participant in a clinical study was examined or received an intervention/treatment to collect final data for the primary outcome measures, secondary outcome measures, and AEs (that is, the last participant's last visit or LSLV).
Medicinal products used to assess endpoints	A product given to the participant in a clinical trial as a tool to assess a relevant clinical trial endpoint; it is not being tested or used as a reference in the clinical trial.
Non-IMP	Any products used in a clinical trial (other than the investigational product being tested) which are stipulated to be used to evaluate the efficacy and safety of the investigational drug in the protocol including comparators, co-administration drugs, rescue drugs and premedication drugs. • Non-IMPs products can be approved in Japan or other countries, or can be products that are not approved.
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 identifier	A unique identification number assigned to each participant who consents to participate in the study.
Placebo	An inactive substance or treatment that looks the same as, and is given in the same way as, an active drug or intervention/treatment being studied.

Term	Definition
Primary completion date	This is the date that the final participant in the study was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical study concluded according to the pre-specified protocol or was terminated. In other words, Primary Completion Achieved is the date of the last contact with the participant when data has been collected/intervention done for the purpose of data collection for analysis of all primary endpoints. In the case of clinical studies with more than 1 primary outcome measure with different completion dates, this term refers to the date on which data collection is completed for all of the primary outcomes. This date may occur prior to the study end or be the same date as the study end milestone.
Randomization	Process of random attribution of intervention to participants to reduce selection bias.
Remote visit	A visit conducted in the place other than the study site.
Rescue medication	Medicine(s) identified in the protocol as those that may be administered to the participants when the efficacy of the IMP is not satisfactory, or the effect of the IMP is too great and is likely to cause a hazard to the participant, or to manage an emergency situation.
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).
Standard of care	Medicine(s) for a specific indication, or a component of the standard care for a particular medical indication, based on national and/or international consensus; there is no regulatory significance to this term. Products/regimens considered standard of care may differ country to country, depending on consensus in individual countries.
Study intervention	Term used throughout the clinical study to cover all types of investigational and non-investigational products including medical devices and vaccines intended to be administered to the study participants during the study conduct. Procedures conducted to manage participants or to collect data are excluded from the usage of this term.
Study monitor	An individual assigned by the sponsor and responsible for assuring proper conduct of clinical studies at 1 or more investigational sites.
Subcohort	A group of participants for whom specific study procedures are planned as compared with other participants or a group of participants who share a common characteristic (e.g., ages, vaccination schedule) at the time of enrollment.
SUSAR	In a clinical trial, a serious adverse reaction that is considered unexpected, i.e., the nature or severity of which is not consistent with the reference safety information (e.g., IB for an unapproved IMP). All ADRs that are both serious and unexpected are subject to expedited reporting.
TM	The use of electronic information and telecommunications technologies (both video-based and audio-only) to facilitate remote health care delivery, participant and professional health-related education, public health and health administration.
Virtual visit	This term refers to study visits conducted using multimedia or technological platforms.

1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol title: A randomized, non-inferiority, double-blind, controlled, single-dose, 2-way cross-over study to assess the potential for airway sensitivity reactions with propellants HFA-152a (Test) and HFA-134a (Reference) administered via pressurized metered dose inhalers in adults aged 18-45 with mild asthma.

Brief title: A study to assess the potential for airway sensitivity reactions with propellants HFA-152a (Test) and HFA-134a (Reference) administered via pressurized metered dose inhalers in adults with mild asthma.

Rationale: In current pMDIs, micronized particles are suspended in propellant HFA-134a which has a significant GWP. GSK is seeking to develop a low carbon footprint alternative propellant, HFA-152a, which will have a lower impact on global warming. Refer to Section 2 for further information.

Objectives, Endpoints, and Estimands: The primary objective of this study is to demonstrate non-inferiority for bronchoconstriction in pMDIs containing HFA-152a (Test) and HFA-134a (Reference) propellants. The primary endpoint will be percentage change from baseline in FEV1 at 15 minutes post-dose. Secondary endpoints will evaluate FEV1 AUC0-15 minutes, safety variables linked to the potential for bronchoconstriction in pMDIs containing HFA-152a (Test) and HFA-134a (Reference) propellants as well as the general safety and tolerability of both propellants containing pMDIs. For further information on the objectives, endpoints and estimands, refer to Section 3.

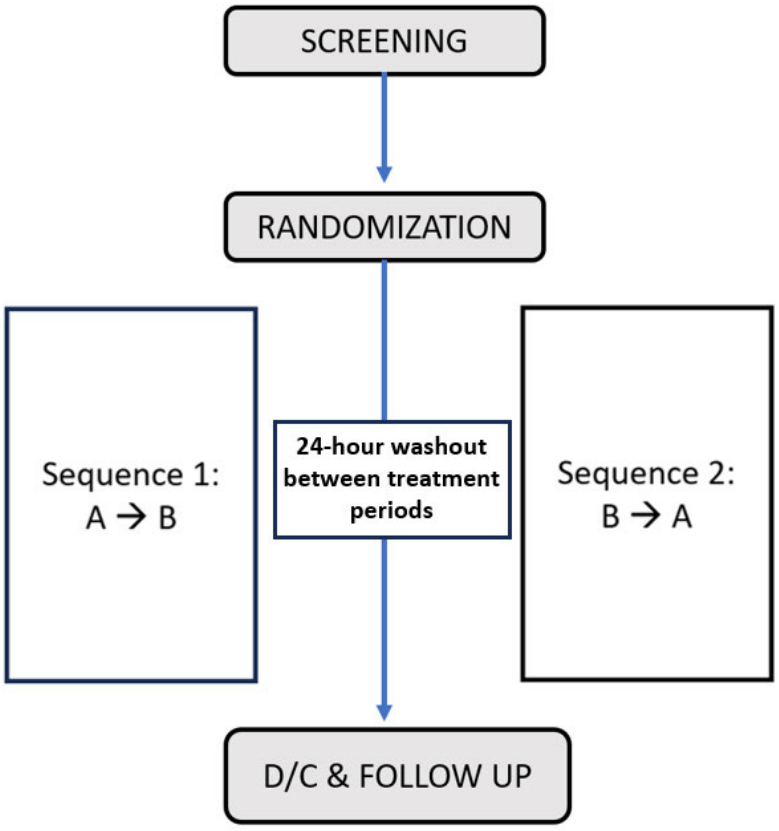
Overall Design: This is a randomised, non-inferiority, double-blind, controlled, single-dose, 2-way cross-over study to assess the potential for bronchoconstriction with propellants HFA-152a (Test) and HFA-134a (Reference) administered via pMDI (i.e. no active medicine) in adults with mild asthma. Subjects will be randomized to 2 possible treatment sequences, AB and BA, where A is the Test propellant and B is the Reference. There will be a 24 hour washout period between study treatment periods. Spirometry, ECG and vital signs data will be recorded to assess for bronchoconstriction, safety and tolerability of each propellant. Refer to Section 4.1. for further information regarding the study design.

Number of Participants: A minimum of 16 participants (approximately n = 18 enrolled to account for potential ICEs) will be randomly assigned with 8 randomized to each treatment sequence. Participants will be randomized to 1 of the 2 treatment sequences AB or BA.

Data Monitoring/Other Committee: Not Applicable.

1.2. Schema

Figure 1 Study design overview



Treatment A = Propellant HFA-152a pMDI; Treatment B = Propellant HFA-134a pMDI; pMDI= Pressurized metered dose inhaler, D/C = Discharge.

1.3. Schedule of activities

Table 1 Schedule of activities

Procedure	Screening		TP1	TP2	ED	Follow up[a]
Day	Day -28 to Day-2	Day -1	Day 1	Day 2		7 days after TP2
Visit Window						±2 Days
Admission & Confinement[b]		←	—	→		
Discharge from site				X	X	
Informed consent	X					
Inclusion and exclusion criteria	X	X				
Demography	X					
Drugs of abuse test	X	X				
Full physical examination including height and weight[c]	X	X			X	
Medical history	X	X				
Highly sensitive serum or urine pregnancy test (females only)[d]	X	X			X	
FSH and estradiol (females only)	X					
HIV, Hepatitis B and C screening	X					
SARS-CoV-2 PCR test[e]		X				
Laboratory assessments (including liver chemistries)[f]	X	X		X	X	
12-lead ECG[g]	X	X		X	X	
Vital signs[h]	X	X		X	X	
Randomization			X			
ACQ-6	X	X				
Inhaler Training		X	X	X		
Administration of study intervention[i]			X	X		
Spirometry tests[j]	X	X	X	X	X	
Participant experience questionnaire				X	X	
AE review[k]			←	—	—	→
SAE review[l]	←	—	—	—	—	→
Concomitant medication review	←	—	—	—	—	→

ACQ = Asthma Control Questionnaire; AE = Adverse event; ECG = Electrocardiogram; ED = Early discontinuation; FSH = follicle stimulating hormone; HIV = Human immunodeficiency virus; ICF = Informed consent form; SAE = Serious adverse event; SARS-CoV-2 PCR = Severe acute respiratory syndrome coronavirus 2 polymerase chain reaction; TP1 = Treatment period 1; TP2 = Treatment period 2.

a. The Follow-Up visit will be conducted virtually (i.e. by telephone or videocall)
b. Participants will be in the clinic from Day -1 until end of TP2. Participants will be discharged from site, after the last assessment scheduled for TP2. Participants will be discharged by the investigator based on normal vitals, lung function, and ECG parameters or if any abnormal values are judged to be not clinically significant and not representing a safety concern.
c. Complete physical examinations will be conducted at screening, Day -1 and at the ED visit. Symptom-driven physical examinations may be conducted at any other time, per the investigator's discretion. Height and weight will be collected only at screening.
d. Serum pregnancy testing will be done at screening and urine testing at Day -1 and ED visit.
e. Sampling of nasal and throat mucosal cells for PCR testing for SARS-CoV-2 may be performed at the discretion of the site based on local guidelines
f. Clinical laboratory assessments (including clinical chemistry, hematology, and urinalysis): at screening, on Day -1 and during TP2 at 20 min±10 min after propellant dosing, or ED.
g. 12-lead ECG: 12-lead ECG will be recorded as single assessments at screening, on Day -1 and TP2 after final spirometry assessment (+2hr window), or ED. Participants will be discharged 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.
h. Vital signs (systolic and diastolic blood pressure, and pulse rate): vital signs will be recorded at screening, on Day -1 and TP2 after final spirometry assessment (+2hr window) or ED.
i. Administration of study intervention: 8 inhalations of study intervention, with the inhalations administered at 20-second intervals. There will be a 24-hour washout period (i.e., treatment with the propellants will be given on 2 consecutive days). Note: All post-dose time points will be from start of dosing (first inhalation)
j. At Screening and Day -1, participants should demonstrate FEV1 ≥60% of predicted. On Treatment Days, FEV1 Spirometry will be performed at pre-dose (the measurement taken immediately preceding the dosing [0 minutes]), then at 5, 15, 60 and 180 minutes post-dose. If the participant requires early discharge, only one FEV1 assessment is required.
k. All AEs will be collected from the start of study intervention until final discharge from the study (completion of the Follow-up visit).
l. All SAEs will be collected from the signing of the ICF until final discharge from the study (completion of the Follow-up visit)

2. INTRODUCTION

2.1. Study rationale

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

GSK is seeking to develop a sustainable version of the current Ventolin Evohaler to address global climate change. This study, in accordance with EMA guidance, will evaluate propellants HFA-152a (Test) and HFA-134a (Reference) administered via pMDIs (i.e., without active salbutamol to evaluate the potential for bronchoconstriction caused by the Test and Reference propellants only).

Hereafter, the pMDIs containing propellant HFA-152a (Test) will be referred to as propellant HFA-152a and pMDIs containing propellant HFA-134a (Reference) will be referred to as propellant HFA-134a.

2.2. Background

In humans, a study was performed to determine the uptake, distribution, and elimination of HFA-152a during and after short-term inhalation exposure [Ernstgård, 2012]. Healthy participants were exposed to 0 ppm, 200 ppm or 1000 ppm HFA-152a for 2 hours at light exercise in an exposure chamber. Capillary blood, urine, and exhaled air were sampled up to 22 hours post-exposure and analyzed for HFA-152a. Fluoride and other potential metabolites were analyzed in urine. Symptoms of irritation and central nervous system effects were rated, and inflammatory markers were analyzed in blood. Within a few minutes of exposure to 200 and 1000 ppm, HFA-152a increased rapidly in blood and reached average levels of 7.4 and 34.3 µM, respectively. The post-exposure decreases in blood were fast and parallel (on semi-log plots) to those in exhaled air with a slower decline phase half-life of approximately 3 h. Within 4 h post-dose HFA-152a concentration in blood was less than 1% of the concentrations achieved following steady-state conditions; blood concentrations were below the detection limit 22 h post-exposure. The estimated net uptake during exposure to 1000 ppm of 6.6 mmol (6.7%) equates to the amount exhaled post-exposure. About 20 µmol excess fluoride (0.013% of inhaled HFA-152a on a molar basis) was excreted in urine after exposure to 1000 ppm, compared to control. No fluorine-containing metabolites were detected in urine. Symptom ratings and changes in inflammatory markers revealed no exposure-related effects.

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Salbutamol + HFA-152a: To date, there has been only one clinical study completed for the combination of salbutamol with HFA-152a. GSK Study 219430 was a pilot study utilizing a single dose 2-way cross-over design in healthy participants to compare the PK of salbutamol administered via pMDIs containing propellants HFA-152a and HFA-134a. This study evaluated 28 healthy male and female adults (19 to 53 years). Each participant received a single 800 ug dose of salbutamol HFA-152a pMDI or salbutamol HFA-134a pMDI delivered as 8 actuations of 100 ug each, administered at 20 second intervals. Following a minimum washout period of 72 hours, the participant received a single dose of the alternative propellant i.e., each participant (except for one) received one 800 ug dose of each pMDI.

The primary objective was to characterize AUC and Cmax parameters following single doses of salbutamol in healthy participants delivered via a pMDI containing propellant HFA-152a, compared with a pMDI containing propellant HFA-134a. Secondary endpoints included additional PK parameters (Tmax and half-life [T1/2]), PD endpoints (mean weighted serum potassium, HR, QTc values) and general safety evaluations including AEs, other ECG parameters, clinical laboratory assessments, and vital signs.

The results of this preliminary PK characterization study indicated that as a proxy of lung absorption, the AUC(0-30 min) of salbutamol when administered with HFA-152a was only slightly higher than reference (geometric mean ratio [GMR; 90% CI], 1.16 [1.02, 1.32]). Overall exposure as measured by AUC(0-inf) was somewhat higher with the Test HFA-152a (GMR [90% CI], 1.41 [1.30,1.53]). Importantly, the rate and extent of exposures of salbutamol observed in this study when administered with propellant HFA-152a were well within the range of historical exposures of salbutamol when administered with HFA-134a known to be safe and effective over the extensive clinical and post-marketing experience with salbutamol HFA-134a.

No clinically significant differences in effect on serum potassium concentrations, HR, or QTcF between administration with salbutamol HFA-152a pMDI and salbutamol HFA-134a pMDI, were observed.

Other Sponsor Studies: A study specifically evaluating HFA-152a's potential to cause airway sensitivity reactions (compared to HFA-134a) using pMDIs was undertaken, which indicated that FEV1 at 15 min after HFA-152a administration (primary endpoint) was equivalent to that of HFA-134a, adjusted mean and corresponding 95% confidence CI being 1.86% and -0.48; 4.20, respectively. No bronchoconstriction and SAEs were reported. HFA-152a was demonstrated to have a reassuring and comparable safety profile to HFA-134a [Salvadori, 2023].

2.3. Benefit-risk assessment

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

2.3.1. 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 the below table.

Potential risk of clinical significance	Summary of data/Rationale for risk	Mitigation strategy
Study intervention(s) [Test and Reference propellants]		
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 accordingly. 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.
Study procedures		
There are no risks associated with the study design and/or procedures.		

2.3.2. Benefit assessment

- The mild asthmatic participant will receive medical assessments associated with study procedures. For example, physical examination, spirometry, ECG, and labs. They may, as a result, derive some benefit related to information about their general health status and asthma control status.
- The mild asthmatic participant will be contributing to characterising the safety and tolerability profile of the new propellant HFA-152a. In doing so they are contributing to the process of developing a therapy which has a reduced impact on global warming.

2.3.3. Overall benefit-risk conclusion

Taking into account the measures taken to minimize risk to participants participating in this study, the potential risks identified in administration of pMDIs containing propellants HFA-152a and HFA-134a are justified by the anticipated benefits to all ongoing and future programs with HFA-152a as a propellant. This includes the anticipated environmental and societal benefits of introducing a new propellant (HFA-152a) with greatly reduced GWP compared to the current propellant HFA-134a.

3. OBJECTIVES, ENDPOINTS AND ESTIMANDS

Table 2 Objectives and endpoints

Objective(s)	Endpoint(s)
Primary	
To evaluate the potential for bronchoconstriction in pMDIs containing HFA-152a (Test) and HFA-134a (Reference) propellants.	• Percentage change from baseline in FEV1 (at 15 mins) after administration of a single dose (8 puffs) of pMDIs containing HFA-152a (Test) and HFA-134a (Reference) propellants
Secondary	
To evaluate variables linked to the potential for HFA-152a to cause bronchoconstriction when administered via a pMDI containing HFA-152a (Test) and HFA-134a (Reference) propellants.	• FEV1 AUC0-15min after administration of a single dose (8 puffs) of pMDIs containing HFA-152a (Test) and HFA-134a (Reference) propellants • Percentage change from baseline in FEV1 (at timepoints, 5, 60 and 180 minutes) after administration of a single dose (8 puffs) of pMDIs containing HFA-152a (Test) and HFA-134a (Reference) propellants • Participants with a percentage change from baseline in FEV1 <-15% (at timepoints 5, 15, 60 and 180 minutes) after administration of a single dose (8 puffs) of pMDIs containing HFA-152a (Test) and HFA-134a (Reference) propellants
To assess the safety and tolerability of single doses of pMDIs containing HFA-152a (Test) and HFA-134a (Reference) propellants.	• Incidence of AEs and SAEs

AE = Adverse event; FEV1 = Forced expiratory volume in 1 second; FEV1 AUC0-15 mins = Area under the forced expiratory volume in 1 second-time curve from zero to 15 minutes; HFA-134a = 1,1,1,2-Tetrafluoroethane (Reference); HFA-152a = 1,1-Difluoroethane (Test); pMDI = Pressurized metered dose inhalers; SAE = Serious adverse event.

3.1. Primary estimand

The primary clinical question of interest is:

What is the adjusted mean difference in percentage change from baseline in FEV1 (at 15 mins post-dose) in pMDIs containing HFA-152a (Test) and HFA-134a (Reference) propellants, in participants aged between 18 and 45 years with mild asthma who completed the study treatments without the use of rescue medication or making an incorrect number of actuations?

The estimand is described by the following attributes:

Population:

Male or female participants aged 18 to 45 years with mild asthma.

Endpoint:

Percentage change from baseline in FEV1 (at 15 mins) after administration of a single dose (8 puffs) of pMDIs containing HFA-152a (Test) and HFA-134a (Reference) propellants.

Treatment condition:

Administration of a single dose of propellant HFA-152a (Test) or HFA-134a (Reference) administered via a pMDI.

ICEs and estimand strategies:

1. Treatment discontinuation due to any reasons (Principal stratum strategy)
2. Use of rescue medication (Principal stratum strategy)
3. Incorrect number of actuations (Principal stratum strategy)

For all ICEs, interest lies in evaluating the primary parameter and comparison of the mean percentage change from baseline in FEV1 (at 15 mins) after administration of a single dose of pMDIs containing HFA-152a (Test) and HFA-134a (Reference) propellants using a principal stratum strategy for participants who completed the study without the use of rescue medication or dosing error of propellant.

Population-level summary:

Adjusted mean difference in percentage change from baseline in FEV1 (at 15 mins post-dose) between pMDIs containing HFA-152a (Test) and HFA-134a (Reference) propellants, with 95% CI.

Rationale for estimand:

The Test propellant is being developed with the aim to have comparable percentage change in FEV1 (at 15 mins post-dose) as the Reference propellant, under the scenario where participants are required to have the desired levels of exposure to study intervention. Interest lies in participants who adhere to the treatment sequence. The estimation will be based on the set of participants who received treatment in both periods, given the small sample size and the low likelihood of participants failing to complete the treatment sequence.

3.2. Secondary estimands

3.2.1. Estimands Supporting Secondary Objectives

3.2.1.1. FEV1 AUC0-15mins

The key secondary clinical question of interest is:

What is the adjusted mean difference in FEV1 AUC0-15min, in pMDIs containing HFA-152a (Test) and HFA-134a (Reference) propellants, in participants aged between 18 and 45 years with mild asthma who completed the study treatments without the use of rescue medication or making an incorrect number of actuations?

This secondary 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:

FEV1 AUC0-15mins after administration of a single dose (8 puffs) of pMDIs containing HFA-152a (Test) and HFA-134a (Reference) propellants.

Population-level summary:

Adjusted mean difference in FEV1 AUC0-15min between pMDIs containing HFA-152a (Test) and HFA-134a (Reference) propellants, with 95% CI.

3.2.1.2. Percentage Changes from Baseline in FEV1

The secondary clinical question of interest is:

What is the adjusted mean difference in percentage change from baseline in FEV1 (at 5, 60 and 180 minutes post-dose) for pMDIs containing HFA-152a (Test) and HFA-134a (Reference) propellants, in participants aged between 18 and 45 years with mild asthma who completed the study treatments without the use of rescue medication or making an incorrect number of actuations?

This secondary 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:

Percentage change from baseline in FEV1 (at timepoints 5, 60 and 180 minutes) after administration of a single dose (8 puffs) of pMDIs containing HFA-152a (Test) and HFA-134a (Reference) propellants.

Population-level summary:

Adjusted mean difference in percentage change from baseline in FEV1 (at 5, 60 and 180 minutes post-dose) between pMDIs containing HFA-152a (Test) and HFA-134a (Reference) propellants, with 95% CI.

3.2.1.3. Participants with a Percentage Change from Baseline in FEV1 <-15%

The secondary clinical question of interest is:

What is the proportion of participants with a percentage change from baseline in FEV1 <-15% (at timepoints 5, 15, 60 and 180 minutes), in pMDIs containing HFA-152a (Test) and HFA-134a (Reference) propellants, in participants aged between 18 and 45 years with mild asthma who completed the study treatments without the use of rescue medication or making an incorrect number of actuations?

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

Endpoint:

Participants with a percentage change from baseline in FEV1 <-15% (at timepoints 5, 15, 60 and 180 minutes) after administration of a single dose of pMDIs containing HFA-152a (Test) and HFA-134a (Reference) propellants.

Population-level summary:

Number and percentage of participants with a percentage change from baseline in FEV1 <-15% (at timepoints 5, 15, 60 and 180 minutes) after administration of a single dose of pMDIs containing HFA-152a (Test) and HFA-134a (Reference) propellants.

3.2.2. Estimands Supporting Secondary Safety Objectives

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

What is the safety and tolerability of single doses of pMDIs containing HFA-152a (Test) and HFA-134a (Reference) propellants in participants aged between 18 and 45 years with mild asthma, regardless of whether they completed the study treatments, used rescue medication, or made incorrect number of actuations?

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. Use of rescue medication (Treatment policy strategy)
3. Incorrect number of actuations (Treatment policy strategy)

Population-level summary:

Number and percentages for incidence of AEs and SAEs

Rationale for estimand:

This is a study in mild asthma patients 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 dose (8 puffs), 2-way cross-over study in mild asthmatic subjects with administration of pMDIs containing propellants HFA-152a (Test) and HFA-134a (Reference).

A single dose will be administered, to deliver 8 actuations of either Test or Reference propellant. Participants will be randomly assigned to one of 2 treatment sequences in 2 treatment periods using a cross-over design. The following treatment sequences will be tested: Treatment Sequence 1: AB Treatment Sequence 2: BA (where A is the Test propellant and B is the Reference).

There will be a 24-hour washout period (i.e., treatment with the propellants will be given on 2 consecutive days). Spirometry assessments will be recorded during the study treatment periods to assess for bronchoconstriction. ECG, clinical laboratory tests and vital signs will be recorded as safety assessments.

The period between randomization and screening will be maximum of 28 days. Participants will arrive at the clinic on Day-1 and will remain confined to the clinic for TP1 and TP2, which are consecutive treatment days. Subjects will exit the study when deemed safe for discharge following all assessments on TP2 by the investigator.

4.2. Scientific rationale for study design

Study population

Mild Asthmatics 18-45 years of age have been chosen as an appropriate cohort in whom it will be safe to assess the risk of bronchoconstriction. This has been done in line with EMA guidance [EMA, 2009], which recommended collection of data on possible airway sensitivity reactions by studying lung function in younger (18-45 years) asthmatic patients.

Randomization and crossover design

A randomized, crossover study is a suitable strategy to evaluate the impact of an inhaled substance on bronchoconstriction. The crossover design will be employed to minimize, as much as possible, the influence of confounding covariates as each participant serves as their own control. The cross-over design requires a smaller number of participants compared to a parallel group design. Carryover effects are expected to be eliminated by introducing a washout phase of a minimum of 24 hours between study inhaler administration.

Crossover designs are recommended by Regulatory Authorities i.e., FDA to demonstrate PD bioequivalence of Test and Reference pMDIs containing salbutamol [Draft Guidance on Albuterol Sulfate, 2023].

Active device blinding regime

An active-device-blinding regime was chosen to minimize participant burden, inhaler technique errors and treatment allocation errors. Each treatment period will have matched numbers of actuations for HFA-152a and HFA-134a. 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 characterization of the safety and tolerability profile of the 2 propellants.

4.2.1. Participant input into design

Not applicable.

4.3. Justification for dose

For the chronic therapy of asthma, currently marketed salbutamol HFA-134a (Ventolin) can be administered as 2 inhalations up to 4 times a day, resulting in a maximum of 8 inhalations/day [Ventolin SmPC, 2024]. Therefore, in this airway sensitivity study, the propellants will be given as a single dose of 8 inhalations (i.e., matching the maximal daily exposure of the propellant in the clinical use of Ventolin). 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.

4.4. End-of-study definition

A participant is considered to have completed the study if the participant has completed all periods of the study including the last visit.

The EoS is defined as the date of the last subject contact.

5. STUDY POPULATION

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

5.1. Inclusion criteria

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

- Male or female; females may be of childbearing potential, of nonchildbearing potential, or postmenopausal. **INC#1**
- Participant must be 18 to 45 years of age inclusive, at the time of screening. **INC#2**
- Confirmed diagnosis of asthma: documented, established diagnosis of asthma for at least 6 months. **INC#3**
- Receiving 1 of the following asthma treatments, at a stable dose, for at least 12 weeks prior to the screening visit and is anticipated to remain stable for the duration of the study: **INC#4**
    - As needed SABA only
    - As needed SABA plus low-dose ICS (defined as 100-250 µg/day fluticasone propionate or equivalent taken whenever SABA is taken).
    - Daily maintenance low-dose ICS, plus as needed SABA or ICS-SABA single inhaler combination therapy
    - Low dose combination single inhaler ICS-formoterol or single inhaler ICS-SABA as needed for symptom relief (and if needed, before exercise)
    - LTRAs in combination with any of the above therapies

    Note: LABA medications other than formoterol are not allowed.

- Participants taking SABA-containing medications must be able to withhold their SABA containing medication for ≥6 hours prior to screening and each treatment period. **INC#5**
- Participants taking formoterol containing medications must be able to withhold their formoterol or ICS/formoterol ≥12 hours prior to screening and study visit days. **INC#6**
- ACQ-6 score <1.5 at screening and Day -1. **INC#7**

- No severe asthma exacerbations within 6 months prior to screening and ≤1 severe exacerbation during the 12 months prior to screening. **INC#8**

  Note: Severe Asthma Exacerbation is defined as a deterioration of asthma requiring the use of systemic corticosteroids (tablets, suspension, or injection) for at least 3 days (or a single depo injection), or an in-patient hospitalization or emergency department visit due to asthma that required systemic corticosteroids.

- Lung function: subjects with a pre-bronchodilator FEV1 ≥60% predicted at Screening and Day-1. **INC#9**
- Demonstrates ability to use a pMDI in a satisfactory and repeatable manner, as judged visually by the Investigator or designee using a CCI or similar device. Participant has no physical or other impairment which would impact their ability to use their pMDI. **INC#10**
- A female participant is eligible to participate if she is not pregnant or breastfeeding, and one of the following conditions applies: **INC#11**
  - Is a WONCBP as defined in Section 10.4.1

OR

  - Is a WOCBP and using a contraceptive method that is highly effective, with a failure rate of <1%, as described in Section 10.4, 28 days prior to and during the study intervention period and for at least 30 days after the last dose of study intervention. The investigator should evaluate potential for contraceptive method failure (e.g., noncompliance, recently initiated) in relationship to the first dose of study intervention.

- Female participants must have a negative highly sensitive pregnancy test (urine or serum as required by local regulations) within 28 days before the first dose of study intervention (see Section 8.3.5 Pregnancy testing). **INC#12**
- If a urine test cannot be confirmed as negative (e.g., an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive. **INC#13**
- Additional requirements for pregnancy testing during and after the study intervention are located in Section 8.3.5. **INC#14**
- 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. **INC#15**
- For male participants, no contraceptive measures are required. **INC#16**
- Non-smokers, or previous smokers who have not used any tobacco containing-products or vaping products within 12 months prior to study start, and with a total pack year history of ≤10 pack years. **INC#17**
- The use of marijuana, even with a valid prescription, is prohibited within 12 months prior to study start. **INC#18**

- Capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the ICF and in this protocol. **INC#19**
- Full capacity and no issues which would impair their ability to comply with all aspects of the protocol during the study. **INC#20**

5.2. Exclusion criteria

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

- A history of life-threatening asthma or asthma that is unstable in the opinion of the investigator. Note: Life-threatening asthma is defined as an asthma episode that required intubation and/or was associated with hypercapnia, respiratory arrest, or hypoxic seizures within the last 5 years. **EXC#1**
- Asthma treatment requiring use of biologic agents (e.g. mepolizumab or dupilumab), chronic systemic corticosteroids, or oral controller agents other than LTRAs. **EXC#2**
- 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, chronic obstructive pulmonary disease, tuberculosis and other respiratory abnormalities other than asthma that, in the opinion of the investigator, would put the participant at risk through study participation, or would affect the study analyses if the disease exacerbates and/or requires additional therapy during the study. This includes history of lung cancer and previous thoracic surgery such as lung resection. **EXC#3**
- Respiratory infection: Culture-documented or suspected bacterial or viral infection of the upper or lower respiratory tract (Including COVID-19) e.g., pneumonia, bronchitis, sinusitis and sinus or middle ear that is not resolved within 6 weeks of screening that: **EXC#4**

  led to a change in asthma management.

  OR

  in the opinion of the investigator, is expected to affect the participant's asthma status.

  OR

  in the opinion of the investigator, is expected to affect the participant's ability to participate in the study.

- Asthma Exacerbation: Any severe asthma exacerbation within 6 months prior to screening. (Severe asthma exacerbation defined as a deterioration of asthma requiring the use of systemic corticosteroids (tablets, suspension, or injection) for at least 3 days, or a single depo injection or an in-patient hospitalization or ED visit due to asthma that required systemic corticosteroids). **EXC#5**

- Biologic/immunosuppressive therapies that can be used for the treatment of respiratory diseases during the 6 months, or 5 half-lives–whichever is longer-prior to start of the study. **EXC#6**
- Participants undergoing de-sensitization therapy. **EXC#7**
- Any other prescription or over the counter medication which would significantly affect the course of asthma, or interact with sympathomimetic amines, including but not limited to: certain classes of anticonvulsants (barbiturates, hydantoins, carbamazepine); beta-adrenergic blockers; phenothiazines; MAO inhibitors. **EXC#8**
- Administration of systemic, oral, or depot corticosteroids for asthma treatment within 12 weeks of Visit 1. Intranasal corticosteroids are permitted if at a stable dose for at least 3 months prior to screening). **EXC#9**
- Exposure to more than 4 new chemical entities within 12 months prior to the first dosing day or participation in a clinical study within 30 days of study start, or 5 half-lives of study drug if that is longer. **EXC#10**
- Twelve-Lead ECG abnormality: Significant abnormality in the 12-lead ECG performed at screening. **EXC#11**
- QTc >450 msec or QTc > 480 msec in participants with bundle branch block. **EXC#12**

  Notes:

  - The QTc is the QT interval corrected for heart rate according to Bazett's formula (QTcB), Fridericia's formula (QTcF), and/or another method. 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.
- CV disease. History or current evidence of any clinically significant CV disease or abnormality including MI, congestive heart failure, uncontrolled hypertension, uncontrolled coronary heart disease, cardiac dysrhythmia, or ECG with evidence of ischemic heart disease that, in the opinion of the investigator, would put the participant at risk through study participation, or would affect the study analyses if the disease exacerbates during the study. **EXC#13**
- Other diseases**:** History or current evidence of hematologic, neurologic, psychiatric, or any other disease or condition, including cancer, that in the opinion of the investigator, would put the participant at risk through study participation, or would affect the study analyses if the disease exacerbates during the study and required increased or additional treatment. **EXC#14**

- Any prescription medication which, in the opinion of the investigator, could adversely affect asthma control, interact with asthma medications or increase the risk of bronchoconstriction or airway sensitivity. **EXC#15**
- Any medication which, in the opinion of the investigator, could put the safety of the participant at risk through study participation or that risks confounding interpretation of study results if taken during the study. **EXC#16**
- Stable doses (3 months or longer) of the following are permitted: **EXC#17**
    - Intranasal corticosteroids
    - Oral anti-histamines
- Positive HIV antibody test. **EXC#18**
- ALT >1.5x ULN at screening. **EXC#19**
- Total bilirubin >1.5xULN 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. **EXC#20**
- Current or chronic history of liver disease or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones) that, in the opinion of the investigator, would put the participant at risk through study participation, or would affect the study analyses if the disease exacerbates during the study. **EXC#21**
- Presence of HBsAg at screening or within 3 months prior to first dose of study intervention. **EXC#22**
- Positive hepatitis C antibody test result at screening or within 3 months prior to starting study intervention. Note: Participants with positive hepatitis C antibody due to prior resolved disease can be enrolled, only if a confirmatory negative hepatitis C RNA test is obtained. **EXC#23**
- 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. **EXC#24**

5.3. Randomization exclusion criteria

After the screening visit, any participants meeting any of the following criteria on study visit Day 1 for TP1 must not be randomized:

- Participants who experience a protocol-defined severe exacerbation (refer to Section 5.1 for severe exacerbation definition) since the screening visit. **REC#1**
- Changes in asthma maintenance medication occurring between screening and Treatment Periods suggestive of a worsening of asthma control in the opinion of the investigator. **REC#2**
- Worsening asthma control or symptoms since screening which in the opinion of the investigator requires additional asthma treatment. Participants with increased use of reliever medication between screening and randomization possibly suggestive of a worsening of asthma control should be discussed with the GSK Medical Monitor and safety team. **REC#3**
- Any new medications started since screening which could, in the opinion of the investigators, impact the patient's asthma control, put the safety of the participant at risk through study participation or confound the interpretation of the study results if the medication was continued during the study. **REC#4**
- Clinically significant abnormal laboratory tests or ECG findings (including QTcF) since screening, which are still abnormal upon repeat analysis. Each investigator will use his/her own discretion in determining the clinical significance of the abnormality. When in doubt, the GSK study medical monitor should be notified in order to facilitate a joint decision. **REC#5**
- Occurrence of a culture-documented or suspected bacterial or viral infection of the upper or lower respiratory tract, sinus or middle ear during the run-in period that leads to a change in asthma management, or in the opinion of the investigator is expected to affect the subject's asthma status or the subject's ability to participate in the study. **REC#6**
- Any other change in overall health status since screening that could, in the opinion of the investigator, impact the patient's asthma control, put the safety of the participant at risk through study participation or confound the interpretation of the study results. **REC#7**

5.4. Lifestyle considerations

5.4.1. Meals and dietary restrictions

- Participants will be advised not to consume any foods containing poppy seeds within 48 hours (2 days) prior to admission to the clinical research centre as this could cause a false positive drug screen result.
- Meals and snacks (such as decaffeinated coffee, herbal tea, fruit, biscuits) will be provided according to the standard operating procedures of the clinical research centre during the intervention period.
- Study drug will be administered to participants after a light breakfast. Water is allowed *ad libitum* throughout.

5.4.2. Caffeine, alcohol, and tobacco

- Alcohol consumption within 6 months prior to the study greater than average weekly intake of >21 units for males or >14 units for females.
- A positive test result for drugs of abuse (including tetrahydrocannabinol) at screening or Day –1. Marijuana, even with a valid prescription, is prohibited within 12 months of the start of the study and throughout the study period.
- Use of combustible tobacco products, and non-combustible nicotine delivery systems, inclusive but not limited to cigarettes, cigars, pipes,materials used to "vape," dissolvable and non-dissolvable products within 12 months prior to the start of the study.
- Cotinine levels indicative of current smoking or recent history of use of tobacco- or nicotine containing products.
- During the study, participants will abstain from alcohol from 48 hours prior to admission until after discharge.
- During each dosing session, participants will abstain from ingesting caffeine- or xanthine-containing products (e.g., coffee, tea, cola drinks, and chocolate).

5.4.3. Activity

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

5.4.4. Other restrictions

Participants must not donate blood from the screening period until discharge from the study (other than the blood sampling planned for this study).

Recent eye surgery: Recent eye surgery or any other condition in which raised intracranial pressure (caused by forceful exhalation) would be harmful.

Recent clinical study participation: Exposure to more than 4 new chemical entities within 12 months prior to the first dosing day or participation in a clinical study within 30 days of study start, or 5 half-lives (if known) of study drug if that is longer.

Hypersensitivity/Allergy: known or suspected hypersensitivity to either Test or Reference propellant or any of the study medication components, or history of drug or other allergy that, in the opinion of the investigator or GSK Medical Monitor, contraindicates their participation.

For female subjects only: pregnant or lactating women, where pregnancy is defined as the state of a female after conception and until termination of the gestation.

5.5. Screen failures

A screen failure occurs when a participant who has consented to participate in the clinical study is not subsequently randomized to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once. However, screen failure data will be included in the datasets and source data review will be conducted. 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

Please see Section 8.2.2 for the specific conditions for rescreening relate to pulmonary function testing (pre-bronchodilator FEV1 testing).

5.6. Criteria for temporarily delaying administration of study intervention

Not applicable.

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

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

6.1. Study intervention(s) administered

Table 3 Study intervention(s) administered

Intervention Label	Test Treatment	Reference treatment
Intervention name	HFA-152A	HFA-134A
Intervention description	Single dose, given as 8 inhalations at 20 second intervals	Single dose, given as 8 inhalations at 20 second intervals
Type	IMP	Comparator
Dose formulation	Propellant	Propellant
Unit dose strength(s)	63 µl per actuation	63 µl per actuation
Dosage level(s)	Single dose of 8 x 63 µl	Single dose of 8 x 63 µl
Route of administration	Oral inhalation	Oral inhalation
Use	Experimental	Comparator
Non-IMP	NA	NA
Authorized AxMP/Unauthorized AxMP	NA	NA
Sourcing	GSK	GSK
Packaging and labeling	Study intervention will be provided in a canister fitted with a metering valve within an actuator. Each canister will be labeled as required per country requirement.	Study intervention will be provided in a canister fitted with a metering valve within an actuator. Each canister will be labeled as required per country requirement.
Current/Former name(s) or alias(es)	1,1-Difluoroethane (Zephex 152a)	1,1,1,2-Tetrafluoroethane

AxMP = Auxiliary medicinal product; IMP = Investigational medicinal product; HFA-134a = 1,1,1,2-Tetrafluoroethane (Reference); HFA-152 = 1,1-Difluoroethane (Test).

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 pMDI, which is used to administer the study intervention.
- pMDIs need to be primed before use. The priming of pMDIs 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 labelled 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 randomization schedule, order of treatment sequence assignment, will be generated using the GSK validated randomization system Randall NG. The randomization schedule is made up of randomization numbers mapped to treatment sequences. Randomization numbers are assigned in sequential order. Each participant will be assigned 1 randomization number to determine which treatment sequence will be followed. 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 TP1, 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.

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 pMDI training as described in the SoA (Section 1.3) and in study specific training manual. The study will adopt pMDI training systems CCI [redacted] CCI 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 modification

Not applicable.

6.6.1. Retreatment criteria

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 therapy

Any medication (including over-the-counter or prescription medicines, recreational drugs, vitamins, and/or herbal supplements) or other specific categories of interest that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use.
- Dates of administration including start and end dates.
- Dosage information including dose and frequency.

The GSK medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

The use of all over-the-counter medication, vitamin preparations and other food supplements, or herbal medications (e.g., St. John's wort) is not allowed from 14 days prior to admission to the clinical research centre until discharge. An exception is made for the occasional use of paracetamol/acetomenaphine which is allowed throughout the study as needed, up to 4 g/day paracetamol.

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

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 (Section 1.3) 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 Unknown
Participant achieved protocol-defined stopping criteria	Liver chemistry stopping criteria QTc stopping criteria
Physician decision	Specify
Pregnancy	
Protocol deviation	Specify
Site terminated by the Sponsor	
Study terminated by the Sponsor	
Sponsor terminated study treatment	
Withdrawal by participant	Burden of procedure Participant relocated Pursue alternative treatment Other
Other	Specify
Death	

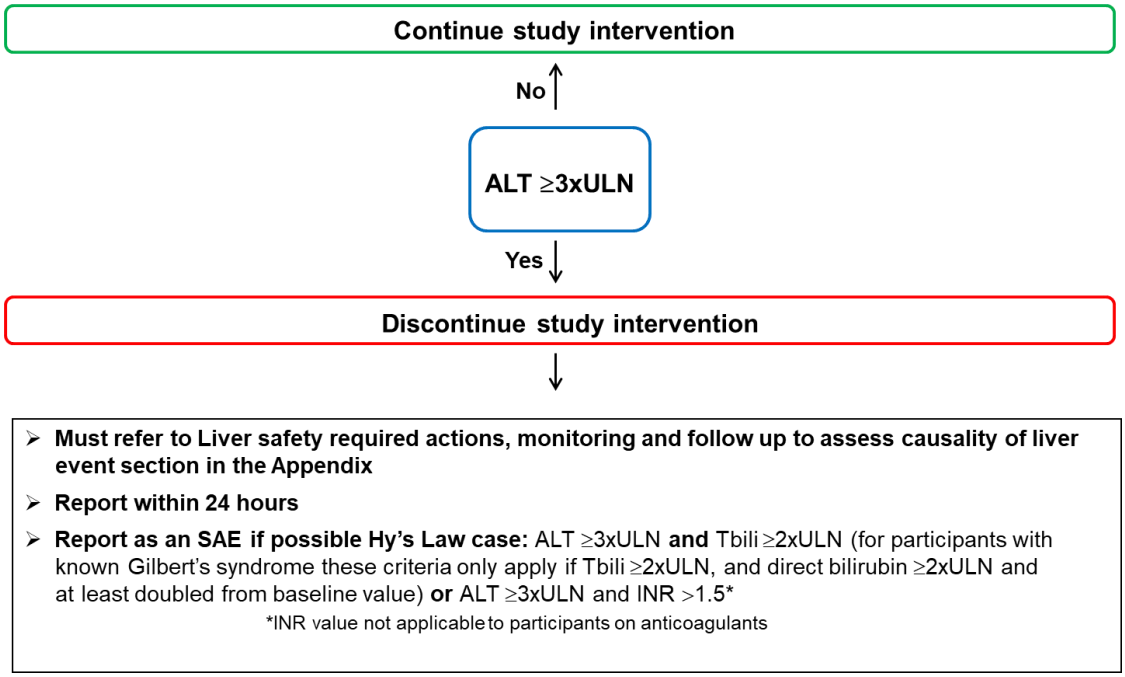
7.1.1. Liver event stopping criteria

Liver event stopping criteria with increased monitoring and follow-up assessments have been designed to assure participant safety and evaluate liver event etiology.

Discontinuation of study intervention for abnormal liver tests is required when:

- A participant meets one of the conditions outlined in the algorithm or
- In the presence of abnormal liver chemistry not meeting protocol-specified stopping rules, if the investigator believes it is in the best interest of the participant.

Figure 2 Liver event study intervention stopping criteria algorithm



ALT = Alanine transaminase; INR = International normalized ratio; SAE = Serious adverse event; ULN = Upper limit of normal, Tbili = Total bilirubin.

Refer to Section 10.6.1 for required liver safety actions, monitoring and follow-up to assess causality of liver event.

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

7.2. Participant discontinuation/withdrawal from the clinical 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.

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

At the time of withdrawing from the study, if possible, an ED visit should be conducted, as shown in the SoA. See SoA (Section 1.3) for data to be collected at the time of study withdrawal and follow-up and for any further evaluations that need to be completed.

All data and samples collected up to and including the date of withdrawal of/last contact with the participant will be available for 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 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 Unknown
Participant achieved protocol-defined stopping criteria	Liver chemistry stopping criteria QTc stopping criteria
Physician decision	Specify
Pregnancy	
Protocol deviation	Specify
Site terminated by the Sponsor	
Study terminated by the Sponsor	
Sponsor terminated study treatment	
Withdrawal by participant	Burden of procedure Participant relocated Pursue alternative treatment Other
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, (Section 1.3) 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 or withholding certain therapies prior to spirometry) 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 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 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 assessments

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

8.2.1. Inhaler training

Participants' proficiency in the use of pMDI's will be reviewed by the investigator or site team. Inhaler proficiency will be assessed as per 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.

8.2.2. Spirometry

Spirometry will be conducted at screening, Day-1 and during the study intervention period as detailed in the SoA (Section 1.3). Spirometry will be performed at the study site to assess FEV1.

To enroll in this study, participants must demonstrate a baseline FEV1 ≥60% of predicted at screening and at Day-1. Spirometry assessments will be performed in accordance with the American Thoracic Society/European Respiratory Society (ATS/ERS) standards. GLI 2012 equations will be used to determine predicted values. Spirometry should be obtained using the spirometry equipment that is calibrated and maintained in accordance with the manufacturers guidance and meets ATS and ERS guidelines.

FEV1 at Screening

Participants who are unable to perform the pre-bronchodilator FEV1 maneuvers at Visit 1 can, at the discretion of the investigator, attend the clinic once more after Visit 1 to attempt to perform the pre-bronchodilator FEV1 maneuvers again. This must be within 7 days of Visit 1.

Participants who provide a technically sound pre-bronchodilator FEV1 at Visit 1 which is not within the FEV1 inclusion limits cannot make another attempt and cannot be re-screened. - Should the participant successfully meet these requirements and all other criteria are met, the participant may enter the run-in period. - Should the participant not successfully meet the requirements of Inclusion Criterion 9 at the second attempt then they will not be considered eligible for further study participation.

Spirometry equipment will be provided to all sites by a third-party vendor; the same third party vendor will also centrally analyze the spirometry data from this study. Details on performing the spirometry assessments, including information on the equipment provided and its use as well as specific instructions on performing the spirometry maneuvers, will be provided in separate documentation.

Refer to the Spirometry Manual for detailed information on spirometry during the Treatment Periods 1 and 2

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

8.3. Safety assessments

AEs, SAEs and other safety reporting including pregnancy will be captured as per GSK standard procedure.

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

8.3.1. Physical examination

A complete physical examination will include, at a minimum, assessments of the CV, respiratory, gastrointestinal (including liver and spleen), dermatologic, and neurological systems. Height and weight will also be measured and recorded.

8.3.2. Vital signs

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

- Screening, Day -1, and post-dose TP2 (or early discontinuation) will be conducted via single 12-lead ECG(s) as outlined in the SoA (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.
- All ECGs will be performed in single assessment. In case of any QT abnormalities ECGs will be repeated in triplicate. See Section 7.1.2 for QTc withdrawal criteria and any additional QTc readings that may be necessary.
- 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. Clinical safety laboratory tests

- See Section 10.2 for the list of clinical safety laboratory tests to be performed in accordance with lab 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 or within 1 day after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.
  - In the absence of a diagnosis, abnormal laboratory findings assessments or other abnormal results the investigator considers clinically significant will be recorded as an AE or SAE, if they meet the definition of an AE or SAE (see Section 10.3.1 and Section 10.3.2).
  - If clinically significant values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified, and the sponsor notified.
  - If laboratory values from non-protocol-specified laboratory tests performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (e.g., SAE or AE), then the results must be recorded.

8.3.5. Pregnancy testing

Refer to Section 5.1 Inclusion Criteria for pregnancy testing entry criteria.

- A urine or blood pregnancy test must be performed for all female participants before the administration of the first dose of study intervention. Pregnancy testing must be done even if the participant is menstruating at the time of the study visit. The study intervention may only be administered if the pregnancy test is negative.
- Pregnancy testing (urine or serum as required by local regulations) should be conducted at specific timepoints as per the SoA (Section 1.3) during the study intervention period.
- Pregnancy testing (urine or serum as required by local regulations) should be conducted at the end of relevant systemic exposure.
- Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the participant's participation in the clinical study.
- See Section 8.4.6 for the information on study continuation for participants who become pregnant during the study.

8.3.6. Asthma Control Questionnaire

The ACQ-6 measures 6 attributes of asthma control [Juniper, 1999]. Six attributes are measured with a patient-completed questionnaire, and the questions are designed to be self-completed by the participant. Participants will complete the ACQ at specified study visits. The 6 questions (concerning nocturnal awakening, waking in the morning, activity limitation, shortness of breath, wheeze and rescue medication use) enquire about the frequency and/or severity of symptoms over the previous week. The response options for all these questions consist of a 0 (no impairment/limitation) to 6 (total impairment/ limitation) scale. The recall period is the past week.

The questionnaire should be completed before any procedures are performed on the participant to avoid influencing the participant's response. To avoid biasing responses, the participants should not be told the results of diagnostic tests prior to completing the questionnaire and it is recommended that the questionnaire be administered at the same time of day during each visit (as applicable) using the provided electronic device (unless otherwise specified). Adequate time must be allowed to complete all items on the questionnaires; the questionnaires must be reviewed for completeness and, if necessary, the participant must be encouraged to complete any missing assessments or items.

8.4. Adverse events, serious adverse events, and other safety reporting

For definitions relating to safety information see Section 10.3.

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

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

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

All SAEs will be collected from the signing of the ICF until final discharge from the study at the time points specified in the SoA (Section 1.3).

All AEs will be collected from the start of study intervention until final discharge from the study at the time points specified in the SoA (Section 1.3).

AEs assessed as related to study participation (e.g., study intervention, protocol-mandated procedures, invasive tests, or change in existing therapy) will be collected from the time a participant consents to participate in the study.

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 per the local country requirements. If the investigator considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

See Section 8.4.9 for contact information.

8.4.2. Method of detecting AEs and SAEs

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

8.4.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Section 10.3.5.5 and Section 10.7.4.4.

8.4.4. AESIs

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 Section 8.4.1 for reporting timeframes.
- For SAEs, the investigator must always provide an assessment of causality at the time of the initial report, as defined in the Section 10.3.5.6.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file it along with the investigational directions for use or package insert and will notify the IRB/IEC, if appropriate according to local requirements.

Table 4 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/electronic pregnancy report	24 hours*	paper pregnancy follow-up report/electronic pregnancy report

AE = Adverse event; SAE = Serious adverse event.
* 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 participants will be collected after the start of study intervention and until 30 days after the last study intervention.
- If a pregnancy is reported, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the female participant's pregnancy.
- Any 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 participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the sponsor. See Table 4 for reporting timeframes.

- Any poststudy pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.4.4. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will be withdrawn from the study.

8.4.7. CV and death events

For any CV events detailed in Section 10.3 and all deaths, whether or not they are considered SAEs, specific CV and Death sections of the eCRF will be required to be completed. These sections include questions regarding CV (including sudden cardiac death) and non-CV death.

The CV eCRFs are presented as queries in response to reporting of certain CV MedDRA terms. The CV information should be recorded in the specific CV section of the eCRF within one week of receipt of a CV Event data query prompting its completion.

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 1 week of when the death is reported.

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

Not applicable.

8.4.9. Contact information for reporting SAEs, and pregnancies

Table 5 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 OAX37649@gsk.com; facsimile number: +44(0) 20 81814780

GSK = GlaxoSmithKline; SAE = Serious adverse event.

8.4.10. Participant card

Not applicable.

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.

If the site(s) uses non-sponsor medical devices, i.e., medical devices not provided by GSK, then the investigators are obligated to report any device deficiencies to the legal manufacturer of the devices directly.

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. If email 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 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

PK is not evaluated in this study

8.6. Pharmacodynamics

PD is not evaluated in this study.

8.7. Genetics

Genetics are not evaluated in this study.

8.8. Biomarkers

Biomarkers are not evaluated in this study.

8.9. Immunogenicity assessments

Immunogenicity is not evaluated in this study.

8.10. Health economics or medical resource utilization and health economics

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

8.11. Participant experience questionnaire

A questionnaire will be provided to participants following completion of all study periods (EoS), or at the Early Withdrawal visit where applicable. The questions will evaluate participant experience with the HFA-152a (Test) and HFA-134a (Reference) inhalers.

9. STATISTICAL CONSIDERATIONS

The SAP 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 SAP will be reported in the Section "Changes in Planned Analysis" in the CSR.

9.1. Statistical hypotheses

The primary objective of the study is to evaluate the potential for bronchoconstriction in pMDIs containing HFA-152a (Test) and HFA-134a (Reference) propellants in participants aged 18 to 45 with mild asthma. This is a non-inferiority study designed to test whether pMDIs containing HFA-152a (Test) propellant is not worse than HFA-134a (Reference) propellant. The primary endpoint of the study is percentage change from baseline in FEV1 (at 15 mins) after administration of a single dose of pMDIs. The study is designed to determine whether the lower limit of two-sided 95% confidence interval (CI) of the adjusted mean difference between Test and Reference propellants for the primary endpoint, greater than a predefined non-inferiority margin of -10%. Hence, the null and alternative hypotheses are as follows:

Null Hypothesis (H0):

$\mu_T - \mu_R \leq -10\%$

Alternative Hypothesis (H1):

$\mu_T - \mu_R > -10\%$

Where μT represents the mean change from baseline in the HFA-152a (Test) propellant and μR represents the mean change from baseline in the HFA-134a (Reference) propellant.

Here, the null hypothesis (H0) states that the adjusted mean difference between HFA-152a (Test) and HFA-134a (Reference) propellants falls below the non-inferiority margin of -10%. The alternative hypothesis (H1) states that the adjusted mean difference between HFA-152a (Test) and HFA-134a (Reference) propellants does not fall below the non-inferiority margin of -10%.

The non-inferiority margin for the study has been decided based on insights from a previous study [Salvadori, 2023], ensuring it reflects a predefined threshold below which the Test propellant is considered clinically non-inferior to the Reference propellant.

9.1.1. Multiplicity Adjustment

No multiplicity adjustments will be applied for this study.

9.2. Analysis sets

Table 6 Analysis sets

Analysis Set	Definition/Criteria	Main analyses in scope
Screened	• All participants who were screened for eligibility.	• Study population
Enrolled	• All participants who entered the study (who were randomized or received study intervention or underwent a post screening study procedure). • Note screening failures (who never passed screening even if rescreened) and participants screened but never enrolled into the study (Met eligibility but not needed) are excluded from the Enrolled analysis set as they did not enter the study.	• Study Population
FAS	• All randomized participants who received at least a single dose period of study intervention • Data will be reported according to the randomized study intervention.	• Study Population
Safety	• Participants who received study intervention	• Safety
FCAS	• All participants who were able to adhere to the dose of study intervention as prescribed and completed the study	• Estimand for Primary and Secondary endpoints

FAS = Full Analysis Set; FCAS = Fully compliant analysis set.

9.3. Statistical analyses

9.3.1. General considerations

Calculations will be based on the actual sampling times recorded during the study.

The Primary and secondary endpoint 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, CV_b 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 primary and secondary endpoints.

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

9.3.2. Primary endpoint analyses

9.3.2.1. Definition of endpoints

The definitions of parameters are described in Table 7.

Table 7 Definition of endpoints

Parameter	Description
Percentage change from baseline in FEV1 (at 15 mins post dose) (primary)	Percentage change from baseline in FEV1 (at 15 mins) after administration of a single dose (8 puffs) of pMDIs containing HFA-152a (Test) and HFA-134a (Reference) propellants
FEV1 AUC0-15min (secondary)	Area under the FEV1-time curve from time zero to 15 minutes after administration of a single dose(8 puffs) of pMDIs containing HFA-152a (Test) and HFA-134a (Reference) propellants
Percentage change from baseline in FEV1 (at 5, 60 and 180 mins post dose) (secondary)	Percentage changes from baseline in FEV1 (at timepoints 5, 60 and 180 minutes) after administration of a single dose (8 puffs) of pMDIs containing HFA-152a (Test) and HFA-134a (Reference) propellants
Participants with a Percentage change from baseline in FEV1 <-15% (at timepoints pre-dose,5, 15, 60 and 180 minutes) (secondary)	Participants with a Percentage change from baseline in FEV1 <-15% (at timepoints 5, 15, 60 and 180 minutes) after administration of a single dose (8 puffs) of pMDIs containing HFA-152a (Test) and HFA-134a (Reference) propellants

FEV1 = Forced expiratory volume in 1 second; FEV1 AUC0-15 mins = Area under the forced expiratory volume in 1 second-time curve from zero to 15 minutes; pMDI = Pressurized metered dose inhalers.

9.3.2.2. Main analytical approach

The primary endpoint is percentage change from baseline in FEV1 (at 15 mins post-dose). The primary analysis will evaluate the primary estimand in the FCAS analysis set. In cases where reliable estimation of FEV1 is not possible due to last nonreportable measurable data, the corresponding data will be treated as missing data. Missing data will be handled under the assumption that it is missing at random (MAR).

The primary endpoint will be analysed using mixed effect model approach with the percent change from baseline in FEV1 as the response variable. The model will include fixed effect for FEV1 at baseline, period, treatment group, timepoint, and interaction terms for treatment group and timepoint, FEV1 at baseline and period, FEV1 at baseline and timepoint. Participants will be included as random effects. The point estimates of adjusted mean difference and their associated 95% CI will be provided for pMDIs containing HFA-152a (Test) and HFA-134a (Reference) propellants.

Non-inferiority will be demonstrated if the lower limit of the 95% confidence interval for the difference in percentage change from Baseline in FEV1 between the pMDIs containing HFA-152a (Test) and HFA-134a (Reference) propellants exceeds -10%.

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

9.3.3. Secondary endpoints analyses

The secondary endpoints are as follows:

- FEV1 AUC0-15min after administration of a single dose of pMDIs
- Percentage changes from baseline in FEV1 (at timepoints5, 60 and 180 minutes) after administration of a single dose of pMDIs
- Participants with a percentage change from baseline in FEV1 <-15% (at timepoints 5, 15, 60 and 180 minutes) after administration of a single dose of pMDIs

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

The key secondary endpoint, FEV1 AUC0-15min, will be analyzed using mixed effect model approach with fixed effect period, treatment group and participants as random effects. The point estimates of mean difference and their associated 95% CI will be provided for of pMDIs containing HFA-152a (Test) and HFA-134a (Reference) propellants.

The secondary endpoint, percentage change from baseline in FEV1 at the timepoints 5, 60, and 180 minutes post-dose, will be analysed using the same mixed effects model as the primary analysis. Point estimates of adjusted mean differences and their associated 95% confidence intervals at these timepoints will be extracted from the primary analysis model results.

The endpoint, proportion of participants with a Percentage change from baseline in FEV1 <-15% (at timepoints 5, 15, 60 and 180 minutes) after administration of a single dose of pMDIs containing HFA-152a (Test) and HFA-134a (Reference) propellants, will be summarized descriptively.

More details will be described in the SAP.

9.3.4. Safety Analysis

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

Safety and tolerability will be assessed through AEs and 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.

9.3.4.1. 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.

9.3.4.2. 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.

9.3.4.3. 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.

9.3.5. Participant experience questionnaire

The experience questionnaire relating to participant feedback for the HFA-152a (Test) and HFA-134a (Reference) inhalers will be summarized descriptively. More details will be described in the SAP.

9.4. Interim analyses

No interim analysis will be performed for this study.

9.5. Sample size determination

A minimum of 16 participants (approximately n = 18 enrolled to account for potential ICEs) will be randomly assigned with 8 randomized to each treatment sequence.

The sample size for the primary endpoint was calculated using the 'Non-Inferiority Tests for the Difference Between Two Means in a 2x2 Crossover Design' module within PASS 19 software (Table 8). It was based on an assumption of no difference in percentage change from baseline in FEV1 between the pMDIs containing HFA-152a (Test) and HFA-134a (Reference) propellants, with a non-inferiority margin set at -10%, within-participant variability (Sw) of 8% (conservative approach, as the previous crossover study showed only 4% Sw), 90% power, and a one-sided alpha of 2.5% (total alpha = 5%).

Design assumptions were informed by a previous cross-over study conducted on HFA-152a. A 10% reduction in change in baseline FEV1 at 15 minutes was considered to be a clinically relevant and aligned to the NI margin pre-specified in the prior study. Primary endpoint results reported on percentage change in baseline FEV1 were reported to be 1.86% (95% CI -0.48; 4.20) [Salvadori, 2023].

Table 8 Total Sample Size and Expected 95% Confidence Intervals for Different Assumed Differences (T-R) and Within-Participant Variability

Assumed Difference (T-R)	Sw (Within-Participant Variability)	Total Sample Size	Expected 95% CI
0	7%	14	(-0.0519, 0.0519)
0	8%	16	(-0.0554, 0.0554)
0	9%	20	(-0.0558, 0.0558)
0.019	7%	10	(-0.0424, 0.0804)
0.019	8%	12	(-0.0450, 0.0830)
0.019	9%	16	(-0.0434, 0.0814)

CI = Confidence interval; Sw = within-participant variability.

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 Council for International Organizations of Medical Sciences international ethical guidelines.
  - Applicable ICH GCP guidelines.
  - Applicable laws and regulations.
- The protocol, protocol amendments, ICF, IB, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following, as applicable:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations.

10.1.2. Financial disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the 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 sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB/IEC or study center.
- Sample testing will be done in accordance with the recorded consent of the individual participant.
- Blood and/or urine samples collected for this study will be analyzed and then destroyed after the results are reported. There will be no extended storage period for any biological samples.
- The medical record must include a statement that informed consent was obtained before the participant was enrolled in the study and the date the 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 collection of information about the baby may be obtained from the participant and/or their partner as per local regulations.

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

10.1.4. Recruitment strategy

Due to the nature of the study, participants will be recruited from the site's database of asthmatic patients and / or through local advertising / referrals from health care professionals. A media kit may be developed and used in local outreach efforts.

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 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.
- GSK has a global, internal policy that requires all GSK staff and complementary workers to report data incidents or breaches immediately, using dedicated tools. Clear procedures are defined for assessing and investigating data breaches to identify and to take appropriate remediation steps, to contain and to mitigate any risks for individuals resulting from a breach, in compliance with applicable laws.

10.1.6. Committees structure

A SRT is in place for each GSK product. It comprises a global cross-functional team responsible for the ongoing assessment of benefit-risk for a product. The SRT contribute to the continual assessment of incoming new efficacy and safety information.

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 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 6 months of primary/study completion date (pediatric population) and within 12 months of primary/ study completion date (adult population). 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 layperson summary of results with the study participants, as appropriate. The full study report will be made available upon request, after decision on marketing authorization by regulatory authorities.
- Where required by regulation, the names of the sponsor signatory and investigator signatory will be made public.
- 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. Data will be shared with researchers in a non-identifying way, and appropriate measures will be taken to protect PI; these measures will comply with data protection and privacy laws that apply.

10.1.8. Data quality assurance

- All participant data relating to the study will be recorded on printed or eCRFs 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 QTL Report 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 non-compliance 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 a minimum period of 15 years from the issue of the final CSR/ equivalent summary, or in accordance with Applicable Law, whichever is longer. 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. In the event of a conflict between this Protocol and the fully executed clinical study agreement, the protocol shall prevail with respect to records retention.

10.1.9. Source documents

- For this study there will not be source data recorded directly into the eCRF (i.e., no prior written or electronic record of data is available).
- 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 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, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or temporary suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.11. Publication policy

GSK seeks to publish medically or scientifically significant results in searchable peer-reviewed scientific literature within 18 months from LSLV. We follow International Committee of Medical Journal Editors standards for authorship and use Good Publications practices to guide our publications.

10.2. Appendix 2: Clinical laboratory tests

- The 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 safety laboratory report.
- The addresses of the clinical laboratories in charge of the testing can be found in the "List of Clinical Laboratories and Key Vendors".

Table 9 Protocol-required safety laboratory tests

Laboratory Tests	Parameters	
Hematology	• Platelet count	
	• RBC count	
	RBC indices	• MCV • MCH • %Reticulocytes
	Absolute WBC count with differential:	• Neutrophils • Lymphocytes • Monocytes • Eosinophils • Basophils
	• **Hemoglobin**	
	• **Hematocrit**	
Clinical chemistry[1]	• BUN/Urea • Potassium • Creatinine* • Sodium • Calcium • Glucose fasting • CPK	• AST/SGOT • ALT/SGPT • Alkaline phosphatase • Total bilirubin • Direct bilirubin • Total protein
Routine urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, [bilirubin, urobilinogen, nitrite, leukocyte esterase] by dipstick • Microscopic examination. Please note, this will only be performed if there is an abnormality in accordance with Clinical Laboratory standard procedures.	
Pregnancy testing	• Highly sensitive serum or urine hCG pregnancy test [2]	
Other tests conducted at screening/prior to treatment	• FSH and estradiol • 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, 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	

ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; BUN = Blood urea nitrogen; CPK = Creatine phosphokinase; eGFR = Estimated glomerular filtration rate; FSH = Follicle stimulating hormone; HBsAg = Hepatitis B surface antigen; hCG = Human chorionic gonadotropin; HCV = Hepatitis C virus; HIV = Human immunodeficiency virus ;IEC = International ethics committee; INR = International normalized ratio; IRB = Institutional review board; MCV = Mean corpuscular volume; MCH = Mean corpuscular hemoglobin; RBC = Red blood cell; SARS-CoV-2 = Severe acute respiratory syndrome coronavirus 2; SGOT = Serum glutamic-oxaloacetic transaminase; SGPT = Serum glutamic-pyruvic transaminase; ULN = Upper limit of normal; WBC = White blood cell.

1 Details of liver event stopping criteria and required actions and follow-up are given in Section 7.1.1 Liver event stopping criteria and Section 10.6 Liver safety requirements and 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 24 hours (excluding studies of hepatic impairment or cirrhosis).

2 Local serum testing will be done at screening and urine testing thereafter.

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

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

Events meeting the AE definition
an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • Events that occur as a result of protocol-mandated procedures (i.e., invasive procedures, modification of participant's previous therapeutic regimen).
Events <u>NOT</u> meeting the AE definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless 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

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed:
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 (for participants with known Gilbert's syndrome these criteria only apply if total bilirubin ≥2xULN, and direct bilirubin ≥2xULN and at least doubled from baseline value) or INR >1.5 must be reported as SAE. • Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. – Examples of such events include invasive or malignant cancers, intensive treatment for allergic bronchoconstriction, blood dyscrasias, convulsions, or development of intervention dependency or intervention abuse.

10.3.3. Definition of CV events

CV definition:
Investigators will be required to fill out the specific CV event page of the eCRF for the following AEs and SAEs: • MI/unstable angina. • Congestive heart failure. • Arrhythmias. • Valvulopathy. • Pulmonary hypertension. • Cerebrovascular events/stroke and transient ischemic attack. • Peripheral arterial thromboembolism. • Deep venous thrombosis/pulmonary embolism. • Revascularization.

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 AEs, SAEs, 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 identifier, 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 deficiencyreported 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 study intervention 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 IB and/or product information, for marketed products.
- The investigator must review and provide an assessment of causality for each AE/SAE and document this in the medical notes There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to GSK.
- The investigator may change their opinion of causality in light of follow-up information and send a 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.
- 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.

Follow-up of pregnancies

Pregnant participants will be followed to determine the outcome of the pregnancy. At the end of the pregnancy, whether full-term or premature, information on the status of the mother and child will be forwarded to GSK using the paper pregnancy follow-up report/electronic pregnancy 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 (see Section 8.4.3).

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 product that is not part of the study design, they will report these events to GSK or to the concerned CA via the national spontaneous reporting system. These will be classified as spontaneous ICSRs.

- Contacts for SAE reporting can be found in Section 8.4.9.

SAE reporting to GSK via paper data collection tool

- Email 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, 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. 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. WONCBP

Women in the following categories are considered WONCBP:

- Premenarchal: Tanner stage 1 (prepubertal).
- Permanently sterile due to one of the following procedures:
  - Documented hysterectomy.
  - Documented bilateral salpingectomy.
  - Documented bilateral oophorectomy.

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

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

- Postmenopausal female.

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

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

10.4.2. Contraception guidance

Female participants of childbearing potential with fertile male partners must use one of the following contraceptive methods from at least 4 weeks prior to first study intervention until 30 days post-dose of last study intervention.

Contraceptives[a] allowed during the clinical 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].
• IUD.
• IUS[c].
• Bilateral tubal occlusion/ligation.
• Azoospermic partner (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. (e.g., medical assessment of the surgical success for vasectomy). If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days. Note: Documentation for a male partner can come from medical history interview with the participant.
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 clinical study and the preferred and usual lifestyle of the participant.

CTFG = Clinical Trial Facilitation Group; IUD = Intrauterine device; IUS = Intrauterine hormone-releasing system; LAM = Lactational amenorrhea method; WOCBP = Woman of childbearing potential.

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 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 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 requirements and guidelines

10.6.1. Liver safety: required actions, monitoring, and follow-up to assess causality of liver event

Liver event increased monitoring criteria	
ALT absolute	ALT ≥3xULN. If ALT ≥3xULN AND total bilirubin[1],[2] ≥2xULN (for participants with known Gilbert's syndrome these criteria only apply if total bilirubin ≥2xULN, and direct bilirubin ≥2xULN and at least doubled from baseline value) or ALT ≥3xULN AND INR >1.5, report as an SAE.
Required actions, monitoring and follow-up to assess causality of liver event	

Actions and monitoring	**Follow-up to assess causality of liver event**
• Immediately discontinue study intervention. • Report the event to GSK within 24 hours. • Complete the liver event form, and complete SAE data collection tool if the event also meets the criteria for an SAE[2]. • Perform liver event follow-up to assess causality of liver event. • Do not restart or rechallenge participant with study intervention. • Monitor the participant liver chemistries (see MONITORING). **MONITORING:** If ALT ≥3xULN AND total bilirubin ≥2xULN or INR >1.5 • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, total bilirubin and INR) and perform liver event follow-up to assess liver event causality within 24 hours. • Monitor participants twice weekly until liver chemistries reduce to <3xULN for	• Viral serology[3]. • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total IgG (IgG or gamma globulins). • Serum CPK and LDH, GGT, GLDH, and serum albumin. • 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 ≥3xULN AND total bilirubin ≥2xULN or INR >1.5 obtain the following in addition to the assessments listed above: • Serum acetaminophen adduct assay should be done (where available) to assess potential acetaminophen contribution to liver injury unless acetaminophen use is very unlikely in the preceding week (e.g., where the

Actions and monitoring	Follow-up to assess causality of liver event
ALT, <2xULN for total bilirubin or ≤1.5 for INR or return to or remain within baseline or normal limits. • A specialist or hepatology consultation is recommended. If ALT ≥3xULN AND total bilirubin <2xULN and INR ≤1.5: • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, total bilirubin, and INR) and perform liver event follow-up to assess liver event causality within 24-72 hours. • Monitor participants weekly until liver chemistries reduce to <3xULN for ALT or return to or remain within baseline or normal limits.	participant has been resident in the clinical unit throughout). • Liver imaging (ultrasound, magnetic resonance, or computed tomography) to evaluate liver disease, complete liver imaging forms. • Liver biopsy may be considered and discussed with local specialists if available, for instance: – In patients when serology raises the possibility of AIH. – In patients when suspected DILI progresses or fails to resolve on withdrawal of study intervention. – In patients with acute or chronic atypical presentation. • If liver biopsy is conducted, then complete liver biopsy form.

AIH = Autoimmune hepatitis; ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; CPK = Creatine phosphokinase; CRF = Case report form; DNA = Deoxyribonucleic acid; DILI = Drug-induced liver injury; GGT = Gamma glutamyl transferase; GLDH = Glutamate dehydrogenase; GSK = GlaxoSmithKline Biologicals SA; HBcAb = Hepatitis B core antibody; HBsAg = Hepatitis B surface antigen; HBV = Hepatitis B virus; HDV = Hepatitis D virus; IgG = Immunoglobulin G; IgM = Immunoglobulin M; INR = International normalized ratio; LDH = Lactate dehydrogenase; PCR = Polymerase chain reaction; RNA = Ribonucleic acid; SAE = Serious adverse event; ULN = Upper limit of normal.

1. Serum bilirubin fractionation should be performed if testing is available. Additionally, if serum bilirubin fractionation testing is unavailable, record presence of detectable urinary bilirubin on dipstick, indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT ≥3xULN and total bilirubin ≥2xULN (for participants with known Gilbert's syndrome these criteria only apply if total bilirubin ≥2xULN, and direct bilirubin 2xULN and at least doubled from baseline value) or ALT ≥3xULN and INR >1.5, which may indicate severe liver injury (possible 'Hy's Law'), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis); the INR threshold value stated will not apply to participants receiving anticoagulants.
3. Includes: Hepatitis A IgM antibody; HBsAg and HBcAb (IgM); Hepatitis C RNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody and RNA PCR test. HBV DNA quantification, and HDV antibody should be measured if participant known to be HBsAg and/or HBcAb positive prior to onset of the liver event or subsequently found to be HBsAg positive on investigation following the liver event. If hepatitis delta antibody assay cannot be performed, it can be replaced with a PCR of hepatitis D RNA virus (where needed and if this is feasible).

10.6.2. Liver safety: liver chemistry increased monitoring criteria with continued study intervention

Not applicable for this study.

10.6.3. Liver safety: study intervention restart and/or rechallenge guidelines

Not applicable for this study.

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 Medical Device Regulation (MDR) 2017/745 for clinical device research (if applicable).
- Both the investigator and the sponsor will comply with all local reporting requirements for medical devices.
- The detection and documentation procedures described in this protocol apply to all sponsor medical devices provided for use in the study. See Section 6.1.1 for the list of sponsor medical devices.

10.7.1. 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 2.3).

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 AEs and/or SAEs 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 identifier, 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 product that is not part of the study design, they will report these events to GSK or to the concerned CA via the national spontaneous reporting system. These will be classified as spontaneous ICSRs.

10.7.4.2. Assessment of intensity

See Section 10.3.5.2.

10.7.4.3. Assessment of causality

See 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 post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed form.
- The investigator will submit any updated SAE data to GSK within 24 hours of receipt of the information.

10.7.5. 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 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.

Medical device SAE reporting to GSK via paper data collection tool

- Email 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, 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 deficiency/incident is linked to an event (as defined in the protocol/program guidance) please email both forms (Event form and device incident form) to gsk-rd.complaints@gsk.com and OAX37649@gsk.com (fax +44(0)20 8181 4780) for pharma product. • 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.

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