CLINICAL STUDY PROTOCOL

Primary Study Intervention(s)	Salbutamol
Other Study Intervention(s)	Not Applicable
Study Identifier	220735
EU CT Number	2023-509001-76-00
Approval Date	28 Nov 2024
Title	A randomized, double-blind, parallel group, multi-center study to evaluate the long-term safety of salbutamol rescue medication when administered via metered dose inhalers containing the propellant HFA-152a or reference HFA-134a
Compound Number/Name	AH3365 (Salbutamol)
Brief Title	A study to assess and compare safety and tolerability of 3 months treatment with salbutamol administered via MDI containing propellant HFA-152a or HFA-134a in participants ≥18 years of age with asthma
Sponsor	GlaxoSmithKline Research & Development Limited 980 Great West Road, Brentford, Middlesex, TW8 9GS, UK
Sponsor signatory	Oscar Della Pasqua MD, PhD Executive Director Clinical Pharmacology Modelling and Simulation

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

Based on TMF-14732712 Protocol v2.0.

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Protocol Amendment 2 Investigator Agreement

I agree:

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

Hence, I:

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

Study identifier	220735
Approval date	28 Nov 2024
Title	A randomized, double-blind, parallel group, multi-center study to evaluate the long-term safety of salbutamol rescue medication when administered via metered dose inhalers containing the propellant HFA-152a as compared to reference HFA-134a
Investigator name	
Signature	
Date of signature (DD Month YYYY)	

Protocol Amendment Summary Of Changes Table

DOCUMENT HISTORY	
Document	**Date of Issue**
Amendment 2	28 Nov 2024
Amendment 1	13 May 2024
Original Protocol	07 December 2023

Type of Protocol Amendment	Numbering	Type of changes
Global	Amendment 2	New changes for all

Amendment 2 (28 Nov 2024)

Overall rationale for the current Amendment:

The objective of this amendment is to expand the eligible adult asthmatic population, inclusive of subjects on as-needed SABA therapy, as well as those on ICS/LABA/LAMA (plus as-needed SABA) therapy. Additionally, the demonstration of airway reversibility during screening is amended to allow for the use of historic reversibility (when present) in as-needed SABA and ICS subjects, and only the characterization of reversibility in ICS/LABA and ICS/LABA/LAMA subjects. It is estimated that up to 80% of current asthmatics do not exhibit significant reversibility and that the presence of a negative bronchodilator reversibility test still warrants additional asthma diagnostic testing. Moreover, response to asthma controller treatment (for example, maintenance medicines containing an ICS) can confirm a positive diagnosis and airflow variability. Reversibility will still be assessed in all subjects during the screening period and documented in the patient listings. Subjects will not be uncontrolled and will continue to receive their background daily maintenance therapy (for those on daily ICS, ICS/LABA, or ICS/LABA/LAMA) during the study. This would allow for the inclusion of a broader population that is more representative of global clinical practice standards. Other updates are detailed in the Summary of Changes.

LIST OF MAIN CHANGES IN THE PROTOCOL AND THEIR RATIONALE:

Section # and title	Description of change	Brief rationale
Section 1.3 Schedule of Activities	Return of eDiary row added Updated footnote ‘a, m ,n’ Added footnote ‘o’	To clarify the collection of data.
Section 5.1 Inclusion criteria	Updated inclusion criteria	To update the reversibility criteria
Section 5.1 Exclusion criteria	Updated exclusion criteria	To update the exacerbation and reversibility criteria
Section 5.5 Screen failures	Reversibility wording updated.	To update the reversibility criteria
Section 6.1.1 Medical devices	Added text that states the MDI is used to administer study intervention	To better reflect the use of the MDI.
Section 6.7.Treatment of overdose	To update the overdose treatment	To clarify the overdose criteria.
Section 8 Study Assessments and procedures	Updated the wording on assessment of schedule	To indicate order is not mandatory
Section 8.3.4.1 Pre-Bronchodilator FEV1	Updated the wording on screening period.	To update the reversibility criteria
Section 8.3.4.2 Reversibility testing	Updated the text regarding Reversibility	To update the reversibility criteria
Section 1.1.1 Electrocardiograms		
Section 8.4.4 Regulatory reporting requirements for SAEs	Added ‘electronic pregnancy‘ report’ to Table 5	
Section 8.4.7 Medical Devices Deficiencies	Added ‘to administer’	To better reflect the use of the MDI
Section 9.4 Interim Analyses	Not required	To update the section as per EMA regulatory recommendation
Section 10.6.1 Definition of medical device AE and ADE	Removed ”investigational”	To better reflect the use of the MDI

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ACQ	Asthma Control Questionnaire
ADE	Adverse device effect
AE(s)	Adverse event(s)
ALT	Alanine transaminase
AST	Aspartate transaminase
ATC	Anatomical Therapeutic Chemical code
AxMP	Auxiliary medicinal product
BMI	Body mass index
CA	Competent authority
CFC	Chlorofluorocarbon
CFR	Code of Federal Regulations
CI	Confidence intervals
CIOMS	Council for International Organizations of Medical Sciences
Cmax	Maximum concentration of the drug in the body
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	Coronavirus disease 2019
CPK	Creatine phosphokinase
CRF	Case report form
CSR	Clinical study report
ECG	Electrocardiogram
eCRF	Electronic case report form
ED	Emergency Department
eDiary	Electronic diary

Abbreviation	Definition
eGFR	Estimated glomerular filtration rate
EMA	European Medical Agency
FEV1	Forced expiratory volume in 1 second
FSFV	First subject first visit
FSH	Follicle stimulating hormone
GC	Gas chromatography
GCP	Good Clinical Practice
GINA	Global Initiative for Asthma
GSK	GlaxoSmithKline
GWP	Global warming potential
HBsAg	Hepatitis B surface antigen
hCG	Human chorionic gonadotropin
HCV	Hepatitis C virus
HFA	Hydrofluoroalkane
HFA-134a	1,1,1,2-tetrafluoroethane
HFA-152a	1,1-difluoroethane
HIV	Human immunodeficiency virus
HR	Heart rate
HRT	Hormonal replacement therapy
IB	Investigator's Brochure
ICE	Intercurrent event
ICF	Informed consent form
ICH	International Council for Harmonization
ICMJE	International Committee of Medical Journal Editors

Abbreviation	Definition
ICS	Inhaled corticosteroid
ICSR	Individual case safety reports
IDFU	Investigational directions for use
IEC	Independent ethics committee
IgG	Immunoglobulin G
IMP	Investigational medicinal product
INR	International normalized ratio
IRB	Institutional review board
ITT	Intention to treat population
IVRS/IWRS	Interactive voice/web response system
LABA	Long-acting bronchodilator
LAMA	Long-acting muscarinic antagonist
LSLV	Last Subject Last Visit
MDI	Metered dose inhaler
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial Infarction
MOA	Monoamine oxidase inhibitor
MRT	Mean residence time
PFT	Pulmonary function testing
PI	Personal information
PK	Pharmacokinetic(s)
QTc	Corrected QT interval
QTcF	QT interval corrected using Fridericia's formula
QTL	Quality tolerance limit

Abbreviation	Definition
RR	Respiratory rate
SABAs	Short-Acting β2-Adrenoreceptor Agonists
SADE	Serious adverse device effect
SAE(s)	Serious adverse event(s)
SAP	Statistical Analysis Plan
SmPC	Summary of product characteristics
SoA	Schedule of activities
SPO2	Saturation of peripheral oxygen
SRT	Safety Review Team
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
USADE	Unanticipated serious adverse device effect
VS	Vital Signs
WOCBP	Woman of childbearing potential
WONCBP	Woman of nonchildbearing potential

Term	Definition
Adverse Drug Reaction	An adverse event where a causal relationship between a medicinal product and the adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out. a. In the context of a clinical trial, an ADR can be serious or non-serious. Serious ADRs may be subject to expedited reporting if they are considered unexpected (see SUSAR definition). b. For marketed products, ADRs are subject to expedited reporting within the country where they are authorized.

Term	Definition
Auxiliary Medicinal Product (AxMP)	Medicinal products used in the context of a clinical trial but not as investigational medicinal products, such as medicinal products used for background treatment, challenge agents, rescue medication, or used to assess end-points in a clinical trial. Auxiliary medicinal products should not include concomitant medications, that is medications unrelated to the clinical trial and not relevant for the design of the clinical trial.
a. 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 Labeling of the medicinal product. Safety reporting with regard to auxiliary medicinal products shall be made in accordance with Chapter 3 of Title IX of Directive 2001/83/EC.
b. Unauthorized AxMP	a. Medicinal product not authorized in accordance with Regulation (EC) No 726/2004. Safety reporting for unauthorized auxiliary medicinal products 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 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.

Term	Definition
	In an open-label study, no blind is used. Both the investigator and the participant know the identity of the intervention assigned. 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.
Challenge agents	A product given to trial participants to produce a physiological response that is necessary before the pharmacological action of the IMP can be assessed.
Co-administered (concomitant) products	A product given to clinical trial participants as required in the protocol as part of their standard care for a condition which 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).
Eligible	Qualified for enrollment into the study based upon strict adherence to inclusion/exclusion criteria.
Essential documents	Documents which individually and collectively permit evaluation of the conduct of a study and the quality of the data produced.
Intervention Number	A number identifying an intervention to a participant, according to intervention allocation.

Term	Definition
Investigational Product	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.
Medicinal products used to assess end-points	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.
Participant	Term used throughout the protocol to denote an individual who has been contacted to participate or who participates in the clinical study as a recipient of the study intervention (vaccine(s)/product(s)/control). Synonym: subject
Participant Number	A unique identification number assigned to each participant who consents to participate in the study.
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.
Randomization	Process of random attribution of intervention to participants to reduce selection bias.
Rescue medication	Medicines 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 patient, or to manage an emergency situation.

Term	Definition
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 completion date	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).
Study intervention	Term used throughout the clinical study to denote a set of investigational product(s) or marketed product(s) or placebo intended to be administered to a participant. Note: “Study intervention” and “study treatment” are used interchangeably unless otherwise specified.
Study monitor	An individual assigned by the sponsor and responsible for assuring proper conduct of clinical studies at 1 or more investigational sites.
SUSAR	Suspected Unexpected Serious Adverse Reaction; 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., Investigator's Brochure for an unapproved investigational medicinal product). All adverse drug reactions (ADRs) that are both serious and unexpected are subject to expedited reporting.

1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A randomized, double-blind, parallel group, multi-center study to evaluate the long-term safety of salbutamol rescue medication when administered via metered dose inhalers containing the propellant HFA-152a or reference HFA-134a.

Brief Title: A study to assess and compare safety and tolerability of 3-months treatment with salbutamol administered via MDI containing propellant HFA-152a or HFA-134a in participants ≥18 years of age with asthma.

Rationale: Refer to Section 2.1.

Objectives, Endpoints, and Estimands: Refer to Section 3.

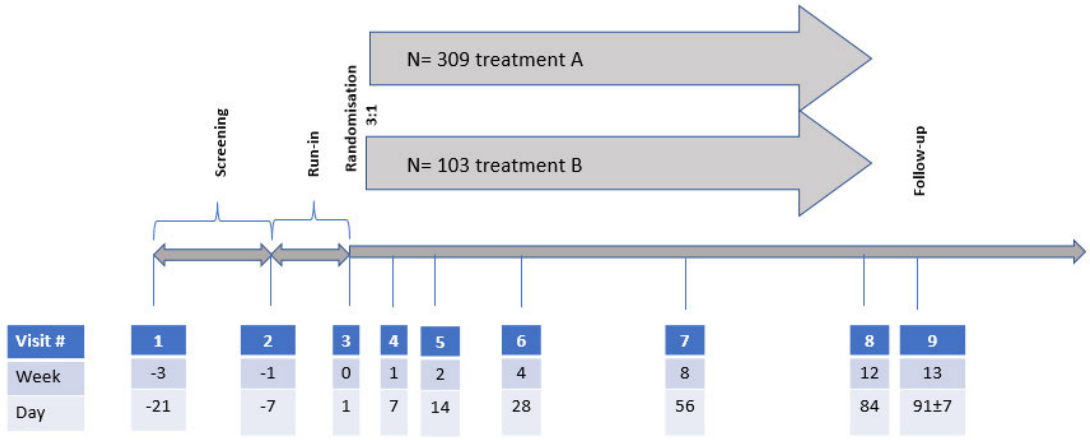
Overall Design: Refer to Section 4.1.

Number of Participants: Refer to Section 4.1 and Section 9.5

Data Monitoring/Other Committee: Refer to Section 10.1.6.

1.2. Schema

Figure 1 Study design overview



Treatment A: HFA-152a (Experimental group)
Treatment B: HFA-134a (Reference group)

1.3. Schedule of activities (SoA)

Procedures	Screening	Run-In	Treatment						Follow-Up	Early Withdrawal
Visit	**1**	**2**	**3**	**4**	**5[b]**	**6**	**7**	**8**	**9**	
Week of Study	**-3**	**-1**	**0**	**1**	**2**	**4**	**8**	**12**	**13**	
Treatment Day[a]	**-21**	**-7**	**1**	**7**	**14**	**28**	**56**	**84**	**91 ±7[o]**	
Informed consent (paper or electronic)	x									
Inclusion and exclusion criteria[c]	x		x							
Demography	x									
FEV1[†]	x		x					x		x
FEV1 reversibility[n]	x									
Physical examination including height and weight, and BMI[d]	x		x						x	x
Medical and Medication history (includes substance of abuse usage)	x		x							
HIV, Hepatitis B and C screening	x	(x)								
Laboratory assessments (including hematology, clinical chemistry and urine dipstick)[e]	x	(x)	x	x		x	x	x	x	x
Randomization Criteria			x							

Asthma Control Questionnaire[f]	x		x					x		x
Randomization			x							
Prime and Dispense investigational product[g]			x			x	x			
Collect investigational product						x	x	x		
Study treatment			→	→	→	→	→	→		
12-lead ECG[h]	x		x	x		x	x	x	x	x
Inhaler Training[i]			x			x	x			
Vital signs (VS)[j]	x		x	x		x	x	x	x	x
Urine pregnancy test[k]	x	x	x	x		x	x	x	x	x
Electronic Diary dispensed		x								
Subject eDiary Completion		→	→	→	→	→	→	→		
eDiary reviewed		x	x	x		x	x	x		
Return of eDiary									x	
Adverse EventsAssessment[l]		x	x	x	x	x	x	x	x	x
Serious Adverse Events Assessment[l]	x	x	x	x	x	x	x	x	x	x
Concomitant Medication Review	x		x	x	x	x	x	x	x	x
Asthma Exacerbation Assessments[m]	x	x	x							

AE=adverse event; HCV=hepatitis C virus; HIV=human immunodeficiency virus; BMI=body mass index; ECG=electrocardiogram; HBsAg=hepatitis B surface antigen; HR=heart rate; MDI=metered dose inhaler; VS= Vital Signs

†FEV1: At least 3 acceptable spirometry maneuvers (from a maximum of 8 attempts) should be achieved on each occasion that spirometry assessments are performed, in accordance with ATS/ERS standards. Please see Section 5.1, inclusion criteria 3 and 5 for information on when repeat FEV1 testing can be used

a. Screening procedures may be performed between Day-21 and Day -8. A window of +/- 1 day for visits 2 & 3 , & ±2 days is allowed for visits 4 & 5 (included). A window of ±3 days is allowed for subsequent visits
b. Visit 5 will be a virtual/telephone visit
c. Inclusion/Exclusion criteria will include assessment of recent exacerbations (at screening & randomization)
d. Complete physical examinations will be conducted at screening. Symptom driven physical examinations may be conducted at discharge or any other time, per the investigator's discretion. Randomization (visit 3) clinical examination should asses for visual evidence of oral candidiasis resulting from inhaled steroid use. Participants HEIGHT will be recorded at Visit 1 only

e. Urine microscopy only in case of abnormal dipstick. Blood draws may be pre- or post-dose. If, in case of technical , transportion or sample viability issues, labs may be repeated at Visit 2. Results must be available before randomization.
f. Asthma Control Questionnaire: pre-dose on Day 1 (visit 3). Note: ACQ Question 6 at visits 3 & 8 should not include the protocol mandated 2 puffs/day ; only those required for symptom alleviation.
g. See Section 6.1.1 for instructions on priming inhaler. Salbutamol should be administered before the participant's daily maintenance ICS.
h. 12-lead ECG: ECG will be measured on Visit 1 (screening) and at predose on Visit 3 in triplicate. The 3 predose measures will be averaged for QTc interval and HR to derive one baseline value. Each individual capture of the triplicate 12-lead ECG set will be separated by 1 to 5 minutes between the first and the third ECG. Post-dose & Visit 9 safety 12-lead ECG measurements (30 minute) will be single
i. Review the instructions (including cleaning). Provide feedback as necessary until proper technique is observed before conducting the full dose using the investigational inhaler.
j. Vital Signs will include temperature, systolic and diastolic blood pressure and pulse rate
k. If positive, urine pregnancy will be followed by serum pregnancy test
l. All SAEs will be collected from the signing of the ICF until discharge. All AEs will be collected from the start of study intervention until discharge
m. In addition, participants will also be instructed to contact the site if they experience an asthma exacerbation at any point during the study
n. Reversibility is performed during screening in all subjects, regardless of background asthma medications, Subjects on SABA only or daily maintenance ICS (plus as needed SABA), will meet the reversibility inclusion if a documented historic reversibility within two years is present. If a documented history of reversibility within 2 years is not present, the screening reversibility maneuver(s) must meet the incusion criterion. Subjects on ICS/LABA or ICS/LABA/LAMA will perform a reversibility maneuver during screening only to characterize the degree of change.
o. Visit 8 and visit 9 cannot overlap

2. INTRODUCTION

2.1. Study rationale

Asthma is a chronic inflammatory disorder of the airways, which is defined by a history of respiratory symptoms of variable length and intensity together with variable airflow limitation. SABAs are a class of 'as needed' reliever medications that provide fast relief or prevention of asthma symptoms. Ventolin Evohaler (also branded as Ventolin HFA, Ventolin Inhaler, Ventolin Aerosol or similar in some countries) is a rescue inhaler, containing the active substance salbutamol sulphate (a SABA), for the prevention and treatment of bronchospasm. GSK intends to move towards the supply of a modified formulation of Ventolin Evohaler to reduce its impact on climate by replacing HFA-134a propellant with HFA-152a which is a propellant of lower GWP.

The aim of this Phase 3 study is to establish the long-term safety of the modified Ventolin Evohaler hereafter referred to as Salbutamol test MDI with HFA-152a propellant compared to the currently approved Ventolin Evohaler (hereafter referred to as Salbutamol reference MDI with HFA-134a propellant) in patients ≥18 years of age with asthma.

2.2. Background

The current propellant used in Ventolin Evohaler MDI is a potent greenhouse gas, which urgently needs to be addressed to reduce our climate impact. GSK is developing a sustainable version of its Ventolin Evohaler product using an alternative new propellant (HFA-152a) with a much lower GWP compared to the current propellant HFA-134a. The use of this lower GWP propellant will reduce the carbon footprint by a minimum of 90% compared with the currently marketed Ventolin Evohaler (HFA-134a).

2.2.1. Background information on the disease to be treated

Salbutamol sulfate is used in the management of bronchospasm and reversible airway obstruction. These symptoms arise in patients with a variety of airway diseases including asthma, chronic bronchitis, and emphysema. The predominant use of salbutamol is in asthma, which is a heterogeneous disease usually characterized by chronic airway inflammation. It is defined by a history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation [GINA, 2023].

Asthma is also usually associated with airway hyperresponsiveness to direct or indirect stimuli and with chronic airway inflammation. These features usually persist, even when symptoms are absent or lung function is normal but may normalize with treatment [GINA, 2023].

Approximately 339 million people currently suffer from asthma, and it is the most common noncommunicable disease among children [WHO, 2020]. Asthma requires medical assessment and care when it occurs on either a persistent, or intermittent but frequently recurring basis. Exacerbations of asthma are episodes characterized by a progressive increase in symptoms of shortness of breath, cough, wheezing, or chest tightness and a progressive decrease in lung function, such that they represent a change from the patient's usual status that is sufficient to require a change in treatment [GINA, 2023]. Severe exacerbations are potentially life threatening and their treatment requires close medical supervision [GINA, 2023].

Pharmacotherapy for asthma follows a stepwise process determined by symptoms and disease severity. The most common treatment options are inhaled short-and long-acting bronchodilators, corticosteroid anti-inflammatory agents, and combination products containing both bronchodilators and corticosteroids. Biological agents are also available for more severe disease in patients with eosinophilic asthma. Short-acting reliever medications such as salbutamol sulfate are a cornerstone of asthma therapy for as-needed relief of breakthrough symptoms, including worsening asthma or exacerbations [GINA, 2023].

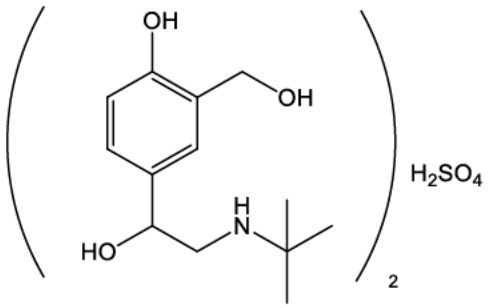
2.2.2. Background information on the product

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

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

Information on the chemical structure of salbutamol sulfate is provided in Table 1.

Table 1 Structural information for salbutamol sulfate

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

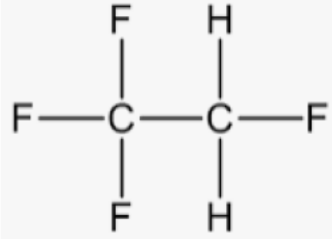
ATC=Anatomical Therapeutic Chemical code

Pharmacotherapeutic group: adrenergic, inhalants. Selective β2-adrenoreceptor agonists. ATC code: R03AC02

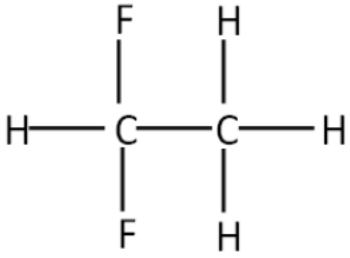
The sustainable new version of Ventolin will use propellant HFA-152a which is being investigated to replace propellant HFA-134a. The chemical structures of these 2 propellants are presented in Figure 2.

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

Propellant HFA-134a
1,1,1,2–tetrafluoroethane



Propellant HFA-152a
1,1–difluoroethane



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

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

2.2.3. Quality development

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

2.2.4. Nonclinical development

The safety profiles of salbutamol and HFA-152a have been established by studying the active component and propellant independently and, based on their chemical and physical properties, no interaction between is expected. The change in propellant from HFA-134a to HFA-152a is supported by a nonclinical toxicology program for HFA-152a conducted by the propellant manufacturer in accordance with current ICH guidelines for the technical requirements of nonclinical testing of pharmaceuticals for human use. These studies include an evaluation of safety pharmacology (respiratory [dogs, guinea-pigs] and cardiac sensitization [dogs]), acute toxicity (mice, rats, dogs), repeat dose toxicity (up to 14 days in mice, 6 months in rats, 9 months in dogs [the latter incorporating safety pharmacology parameters]), genotoxicity (in vitro Ames and in vitro/in vivo micronucleus assay), developmental and reproductive toxicity studies (rats), carcinogenicity (2-year study in rats), juvenile toxicity, and a metabolism study (rats).

In addition, data from nonclinical bridging toxicology studies (repeat dose toxicity [13 weeks in rats and dogs] and embryo fetal development [in rabbits]) that were conducted to support the change in propellant from Ventolin MDI (using propellants P11/P12) to Ventolin Evohaler (HFA-134a), the current commercial product, were shown to be similar. These data support the change to propellant HFA-152a based on the structural and toxicological similarity to HFA-134a.

2.2.5. Clinical development

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

2.2.5.1. Background information on propellant HFA-152a

In humans, a study was performed to determine the uptake, distribution, and elimination of HFA-152a during and after short-term inhalation exposure [Ernstgård, 2012]. Healthy participants were exposed to 0 ppm, 200 ppm or 1000 ppm HFA-152a for 2 hours at light exercise in an exposure chamber. Capillary blood, urine, and exhaled air were sampled up to 22 hours post-exposure and analyzed for HFA-152a. Fluoride and other potential metabolites were analyzed in urine. Symptoms of irritation and central nervous system effects were rated, and inflammatory markers were analyzed in blood. Within a few minutes of exposure to 200 ppm and 1000 ppm, HFA-152a increased rapidly in blood and reached average levels of 7.4 µM and 34.3 µM, respectively. The post-exposure decreases in blood were fast and parallel to those in exhaled air. The estimated net uptake during exposure to 1000 of 6.6 mmol (6.7%) equates to the amount exhaled post-exposure. About 20 µM 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.

In addition, a Phase 1 clinical study has investigated HFA-152a exposure in healthy male participants following inhalation [Protocol Number: Mex-HFA-152a]. The primary objective was to assess the safety and tolerability of HFA-152a following oral inhalation from an MDI. Eight male participants were administered 4 consecutive doses of 50 µL/actuation of HFA-152a from an MDI within a 6-minute timespan. Dose delivery was with a 3 second inhalation and a 10 second breath hold. Endpoints included PFT, vital signs (HR, BP, RR and SPO2), taste and clinical observations. Blood samples were collected to quantify HFA-152a via a GC headspace method. The analysis of the PFT's for each participant prior to dose delivery and 60 minutes post-delivery showed no change in FEV1. All vital signs at all time points pre and post dosing were all within the normal, expected range. Results of the organoleptic survey indicated that the taste of HFA-152a was not a clinical concern. The PK analysis performed on the HFA-152a concentration vs time profile showed rapid absorption, with all participants except 1 having their tmax at the first assayed time point. The average Cmax value was 0.69 mg/L (immediate post-exposure). The average MRT was 8.95 min. Overall HFA-152a was well tolerated, had minimal impact on taste, and was rapidly cleared from the blood. There were no AEs during the study.

2.2.5.2. Salbutamol sulfate and propellant HFA-152a MDI

At the maximum recommended daily dose of 8 inhalations of salbutamol sulfate, the exposure to HFA-152a (8x63 µL) is estimated to be 454 µg/day (6.87 µmol/day). This is well below the exposures shown to have no adverse effects in humans. The human peak blood exposure (Cmax) of HFA-152a from the salbutamol HFA-152a propellant MDI for 8 actuations of 63 µL (delivering a total dose of 800 µg of salbutamol) is estimated to be 1.739 mg/L (26.2 µmol/L). This represents acute and transient exposure to HFA-152a, whereas, following extended exposure 1000 ppm of HFA-152a for 2 hours in an exposure chamber resulted in average concentrations of 34.3 µmol/L, which was well tolerated, had minimal impact on taste, and was rapidly cleared from the blood.

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

Additionally, in GSK Study 219430, single 800 µg doses of Salbutamol MDI formulated with propellant HFA-152a were administered to 27 healthy volunteers. In this study, the exposure to salbutamol in terms of Cmax, AUC(0-30min), AUC(0-t), and AUC(0-inf) was observed to be higher for salbutamol HFA-152a MDI (Test Formulation) compared with salbutamol HFA-134a MDI (Reference Formulation). However, the extent (AUC[0-inf] 21.09 ng*h/mL) and rate (Cmax 2.36 ng/mL) of exposure were within the range of exposures observed in historical studies where the salbutamol MDI formulated with HFA-134a was administered. As such, any systemic effects due to salbutamol exposure observed in the current study are expected to be similar for both the HFA-152a and HFA-134a formulations.

2.3. Benefit/risk assessment

More detailed information about the known and expected benefits and risks and reasonably expected AEs of salbutamol delivered via MDI containing propellant 134a may be found in the patient information, package insert, SmPC. A risk assessment has been presented in Section 2.3.1

2.3.1. Risk assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Participants will be instructed to administer a minimum of 200 µg up to a maximum of 800 µg of salbutamol daily. There is a potential risk that the HFA-152a propellant delivers a higher effective dose of salbutamol compared to the reference Ventolin Evohaler. Based on nonclinical and clinical studies conducted with HFA-152a, and information from the SmPC of Ventolin Evohaler (salbutamol sulfate containing propellant HFA-134a), the safety concerns following salbutamol dosing at the levels employed in this study include hypokalemia, hyperglycemia, and cardiovascular effects (including tachycardia and, in rare cases, cardiac arrythmias).	Hypokalemia: β-adrenergic agonist medicines may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects. The decrease in serum potassium is usually transient, not requiring supplementation. Hyperglycemia: β-adrenergic agonist medicines may produce a transient rise in serum glucose which is not expected to be clinically significant with inhalational administration. However, large doses of intravenous salbutamol have been reported to aggravate pre-existing diabetes mellitus and ketoacidosis. Cardiovascular effects: β-adrenergic agonist medicines may produce clinically significant cardiovascular effects in some patients such as changes in pulse rate or blood pressure. In addition, β-agonists have been reported to produce ECG changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression. The clinical relevance of these findings is unknown	The study will be conducted with participation of patients with asthma. They will be carefully screened against the inclusion and exclusion criteria (including asthma control status, overall cardiac health, vital signs, ECG interval values, and lab safety values [including serum potassium and glucose levels]) with further ECG assessment and lab PD/safety assessments at study visits.
Study Intervention(s)		
There are no specific risks associated with the study design.		
Study Procedures		
Risk of HFA-152 test inhaler being less efficacious in alleviating asthma symptoms	Participants will be instructed to administer salbutamol once daily regardless of symptoms, and additional inhalations as needed for the relief of asthma symptoms. If the test inhaler with HFA-152a is less efficacious, participants may need to administer more doses than expected to alleviate asthma symptoms.	Participants will be provided with clear instructions to seek medical care if they are not able to achieve adequate relief of symptoms using their inhaler device. In addition, study site will be made aware via automatic alert if participants report using (≥)8 actuations (≥800 µg of salbutamol) for 2 or more days in a row as entered via their eDiary.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		Increasing use of short-acting bronchodilators, in particular beta-2 agonists to relieve symptoms may indicate deterioration of asthma control. In this case patients should be advised to seek medical advice and contact the site as soon as feasible. Appropriateness of the patient to continue in the study will be assessed as per the discretion of the investigator and in conjunction with the sponsor where necessary.

2.3.2. Benefit assessment

Ventolin Evohaler (salbutamol) with HFA-134a propellant is approved for the treatment and prevention of bronchospasm as well as the prevention exercised induced bronchospasm. Participants in this study will contribute to the process of developing a formulation of Ventolin that contributes less greenhouse gas emissions.

In this study, benefit considerations for a participant may include:

- Participants in this study will be required to attend study visits approximately every 4 weeks and they may benefit from additional monitoring of their standard asthma care and the additional assurance this may bring.
- Participants may benefit from information about their general health status through medical evaluations/assessments associated with this study (i.e., physical examinations and blood testing [hematology and biochemistry data]).

2.3.3. Overall benefit-risk conclusion

Taking into account the measures taken to minimize risk to participants in this study and the well-established safety profile of the active substance, the potential risks identified in association with salbutamol sulfate suspension in propellant HFA-152a (Test) or HFA-134a (Reference) are justified by the anticipated benefits to all ongoing and future programs with HFA-152a as a propellant as well as the anticipated environmental and societal benefits of introducing a new propellant (HFA-152a) with greatly reduced GWP compared to the current propellant HFA-134.

3. OBJECTIVES, ENDPOINTS AND ESTIMANDS

Table 2 Objectives and Endpoints

Objective(s)	Endpoint(s)
Primary	
To assess the safety and tolerability of 3 months treatment with a formulation of salbutamol administered via MDI containing propellant test HFA-152a or reference HFA-134a in participants ≥18 years of age with asthma	• Incidence of AEs
Secondary	
Safety	
• To assess the safety and tolerability of salbutamol test (HFA-152a MDI) or reference (HFA-134a MDI) in participants ≥18 years of age with asthma.	• Incidence of SAEs • Minimum serum potassium • Absolute values for serum potassium at each assessed visit • Change from baseline for serum potassium at each assessed visit. • Absolute values for clinical laboratory assessments at each assessed visit. • Change from baseline for clinical laboratory assessments at each assessed visit. • Absolute values for vital signs parameters (systolic blood pressure, diastolic blood pressure, pulse rate) at each assessed visit • Change from baseline for vital signs parameters (systolic blood pressure, diastolic blood pressure, pulse rate) at each assessed visit. • Absolute values for 12 Lead ECGs in QTc and heart rate at each assessed visit • Change from baseline for 12 Lead ECGs in QTc and heart rate at each assessed visit.
Efficacy	
• To assess ACQ-6 score and FEV1 in salbutamol test (HFA-152a MDI) or reference (HFA-134a MDI) in participants ≥18 years of age with asthma.	• Change from baseline for ACQ-6 score at each assessed visit. • Change from baseline for pre-bronchodilator FEV1 at each assessed visit

3.1. Estimands

3.1.1. The Primary Estimand

The primary clinical question of interest is to assess the incidence of AEs in asthma participants (≥18 years of age) up to 3 months on-treatment period for salbutamol test (HFA-152a MDI) and reference (HFA-134a MDI) treatment groups after administration at a minimum of 2x100 µg once daily and as needed for symptoms not to exceed 800 µg daily.

The primary estimand is described by the following attributes:

- The population should include male and female participants aged ≥18 years with asthma.
- The primary endpoint is incidence of AEs throughout the 3 months treatment period.
- The treatment condition is salbutamol minimum of 2x100 µg once daily and as needed for symptoms not to exceed 800 µg daily for the test (HFA-152a MDI) and reference (HFA-134a MDI) treatment groups.
- The intercurrent event (ICE) and estimand strategy are as follows:
  - Study treatment discontinuation due to any reason (While on-treatment strategy). Interest lies in group of participants from first dose to end dose of test (HFA-152a MDI) or reference (HFA-134a MDI) treatment groups including 7 days follow up period.
- The population level summary to be estimated is:
  - Counts and percentages for incidence of AEs in the on-treatment (3 months) period for test (HFA-152a MDI) and reference (HFA-134a MDI) treatment groups.
- Rationale for primary estimand: The primary clinical question of interest is whether taking investigational product adversely affects patients in targeted population while they are taking the product. Therefore, the AEs will be captured for on-treatment (3 months) from first dose to last dose in treatments with additional 7 days follow up period.

3.1.2. Estimands for supporting secondary safety and efficacy objectives.

The secondary safety clinical question of interest is to assess the safety and tolerability profile of salbutamol test (HFA-152a MDI) and reference (HFA-134a MDI) treatment groups in asthma participants (≥18 years of age)

The estimands for supporting secondary safety objectives are same as primary estimand except for the attributes of the endpoints and population-level summary measures as detailed below:
The estimand attributes for the secondary safety objectives are as follow:

- The population is male and female participants aged ≥18 years with asthma.
- The secondary endpoints are:

  Safety endpoints-

  - Incidence of SAEs
  - Minimum serum potassium
  - Absolute values for serum potassium at each assessed visit.

- Change from baseline for serum potassium at each assessed visit.
- Absolute values for clinical laboratory assessments at each assessed visit.
- Change from baseline for clinical laboratory assessments at each assessed visit.
- Absolute values for vital signs parameters (systolic blood pressure, diastolic blood pressure, pulse rate) at each assessed visit.
- Change from baseline for vital signs parameters (systolic blood pressure, diastolic blood pressure, pulse rate) at each assessed visit.
- Absolute values for 12 lead ECGs in QTc and heart rate at each assessed visit.
- Change from baseline for 12 Lead ECGs in QTc and heart rate at each assessed visit.

Efficacy endpoints-

- Change from baseline for ACQ-6 score at each assessed visit.
- Change from baseline for pre-bronchodilator FEV1 at each assessed visit.

- The treatment condition is salbutamol minimum of 2x100 µg once daily and as needed for symptoms not to exceed 800 µg daily for the test (HFA-152a MDI) and reference (HFA-134a MDI) treatment groups.
- The intercurrent (ICE) strategy for secondary objectives follows the primary estimand strategy.
- The population level summary to be estimated are:

Safety endpoints-

- Counts and percentages for incidence of SAEs in on treatment (3 months) period for test (HFA-152a MDI) and reference (HFA-134a MDI) treatment groups.
- Mean difference in serum potassium between test (HFA-152a MDI vs reference (HFA-134a MDI) treatment groups and its associated 95% CI in on treatment period.
- Mean of absolute values for clinical laboratory assessments including serum potassium, vital signs (systolic blood pressure, diastolic blood pressure, pulse rate), and 12 lead ECG parameters (QTc and heart rate) in on-treatment period.
- Mean of change from baseline values for clinical laboratory assessments including serum potassium, vital signs (systolic blood pressure, diastolic blood pressure, pulse rate), and 12 lead ECG parameters (QTc and heart rate) in on-treatment period.

Efficacy endpoints-

- Mean of change from baseline values for ACQ-6 at each assessment on-treatment period.
- Mean of change from baseline values for pre-bronchodilator FEV1 at each assessment on-treatment period.

- Rationale for estimands supporting secondary safety objectives: The clinical question of interest for secondary objectives is whether taking investigational product can adversely affects patients in targeted population while they are taking the product. Therefore, the secondary endpoints will be captured for on-treatment period from first dose to last dose in treatments with additional 7 days follow up period.

3.1.3. Supplementary estimands for supporting safety objectives:

Supplementary estimands will address additional safety clinical questions of interest by evaluating the safety and tolerability profile of salbutamol test (HFA-152a MDI) and reference (HFA-134a MDI) treatment groups in asthma participants (≥18 years of age) for overall follow-up period (including any post-treatment follow-up).

The estimand attributes for the supplementary estimands are as follows:

- The population is male and female participants with asthma aged ≥18 years.
- The endpoints are AEs, SAEs, serum potassium, clinical laboratory assessment, vital signs, and ECGs data are specifically defined in Section 3.1.1 (for primary estimands) and Section 3.1.2 (for secondary estimands).
- The treatment condition is salbutamol minimum of 2x100 µg once daily and as needed for symptoms not to exceed 800 µg daily for the test (HFA-152a MDI) and reference (HFA-134a MDI) treatment groups.
- The intercurrent (ICE) strategy for the supplementary analyses are as follows:
  - Study treatment discontinuation due to any reason (treatment policy strategy). Interest lies in the group of participants irrespective of whether they discontinued study treatment.
  - The population level summary to be estimated are defined above in Section 3.1.1 (for primary estimands) and Section 3.1.2 (for secondary estimands).
- Rationale for supplementary estimands: Treatment policy approach will facilitate analysis efforts to whereby analyzing participant safety data provided from regularly scheduled assessments even after they discontinue the investigational product, thereby providing a transparent and complete analysis of all safety events recorded during follow-up.

AE and SAEs may also be presented in the post-treatment period alone with further details specified in the SAP and output specifications documents.

4. STUDY DESIGN

4.1. Overall design

This will be a multicenter, randomized, double-blind, parallel group study. Participants meeting all the inclusion criteria and none of the exclusion criteria during the screening visit (Visit 1) will enter the study open-label run-in period where they will be asked to switch from their current rescue inhaler to the salbutamol HFA-134a MDI. During this run-in period, subjects will be instructed to self-administer this reliever inhaler at a dosage of 2x100 µg actuations once daily ± as required for symptom relief (up to maximum 800 µg daily). Subjects will continue their daily maintenance therapy throughout the run-in period. The run-in period will also enable participants to develop familiarity with the eDiary procedures and data entry. Baseline safety evaluations and baseline measures of asthma status will also be performed at screening. At the end of the run-in period, the start of Week 0 (Visit 3) subjects meeting randomization criteria will stop using the salbutamol HFA-134a MDI and will be randomly assigned to continue receiving the salbutamol HFA-134a MDI or new test salbutamol HFA-152a MDI. Subjects will be instructed to self-administer their assigned rescue inhalers 2x100 µg once daily ± as required for symptoms (up to maximum 800 µg daily). Subjects will continue their regular daily maintenance therapy throughout the study (see Section 5.1 Inclusion Criteria).

Approximately 412 participants recruited globally will be randomly assigned with 3:1 ratio in the study, 309 participants in salbutamol test (HFA-152a MDI) treatment group to achieve 300 participants and 103 participants in salbutamol reference (HFA-134a MDI) treatment group to achieve 100 participants for the primary analysis.

The Experimental group will receive a Salbutamol MDI inhaler containing HFA-152a propellant, to be taken at a dosage of 2x100 µg actuations once daily + as needed up to maximum 800 µg) for symptom relief. The Reference group will receive a currently marketed product, a Salbutamol MDI inhaler containing HFA-134a propellant, to be taken at dosage of 2x100 µg actuations once daily + prn for symptom relief (up to maximum 800 µg).

Subjects will attend 5 on-treatment visits at Visits 3,4,6,7, and 8 (Weeks 0, 1, 4, 8, and 12 respectively). Visit 5 at Week 2 will be a virtual/telephonic visit. Subjects will receive enough treatment for 3 months of dosing over the course of the study. To ensure adequate exposure to the intervention, subjects will be instructed to use the inhaler once daily, as well as on an as needed basis (up to maximum 800 µg), according to their asthma symptoms in the same manner as their current rescue inhaler.

A follow-up visit will be performed 1 week after completion of the 12-week treatment period. A subject will be considered to have completed the study upon completion of all assessments and procedures up to and including the follow-up visit.

The total duration of the study for each participant will be approximately 13 weeks plus a screening visit.

4.2. Scientific rationale for study design

4.2.1. Participant input into design

Not applicable.

4.3. Justification for dose

In order to account for the variability of rescue medication use in mild-moderate asthmatics, participants will be instructed to use their rescue medication as needed, up to the recommended maximum dose (8x actuations) daily. As participants with milder disease may not use rescue medication each day, participants are instructed to use a minimum dose of 2x100 µg to achieve a minimum exposure to the study intervention.

The minimum daily dose of 200 mcg is low compared to the overall therapeutic range of salbutamol commonly used in clinical practice. This, coupled with the extensive history of salbutamol use in obstructive lung disease, means the required dose is considered a low risk compared with the benefit of conducting the proposed study to determine the safety profile of the new pressurized MDI formulation.

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 last scheduled procedure shown in the SoA.

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

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:

- Participant must be ≥18 years of age at the time of signing the informed consent or written informed consent is obtained from each study participant's legal guardian. **INC#1**
- Asthma for ≥ 6 months, defined as:
- Documented history of asthma, as defined by GINA [GINA, 2023]

- Receiving one of the following asthma treatments, at a stable dose (applicable to daily ICS, ICS/LABA, and ICS/LABA/LAMA), for at least 12 weeks prior to the screening visit, with treatment that is anticipated to remain stable for the duration of the study:
  - SABA used as needed for asthma symptoms
  - Daily maintenance low to medium dose ICS (low to medium dose ICS defined as 100-500 µg/day fluticasone propionate or equivalent as defined in the 2023 GINA guidelines [GINA, 2023], plus SABA, which is anticipated to remain stable for the duration of the study.
  - Daily maintenance low to medium dose ICS/LABA (low to medium dose ICS defined as 100-500 µg/day fluticasone propionate or equivalent as defined in the GINA guidelines [GINA, 2023] plus SABA, which is anticipated to remain stable for the duration of the study.
  - Daily maintenance ICS/LABA/LAMA (low to medium dose ICS defined as 100-500 µg/day fluticasone propionate or equivalent as defined in the GINA guidelines [GINA, 2023] plus SABA, which is anticipated to remain stable for the duration of the study.
  - Subjects who utilize combination budesonide/formoterol as reliever therapy, whether or not this is in addition to a SABA – are not eligible for screening.
  - Subjects who utilize ICS/SABA combination therapy as reliever therapy, in addition to low to medium dose ICS or ICS/LABA as maintenance, are only eligible if they agree to discontinue their ICS/SABA inhaler for the duration of the study (screening through follow-up). **INC#2**
- Severity of disease:
- Baseline pre-bronchodilator FEV_1 ≥60% of predicted at screening.
  - Participants who are unable to perform the pre-bronchodilator FEV_1 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 FEV_1 maneuvers again, as well as perform the post-bronchodilator FEV1 maneuvers for the assessment of reversibility (see Inclusion Criterion 5). This must be within the screening period.
  - Should the participant successfully meet the requirements of Inclusion Criterion 3 at the second attempt then, provided that Inclusion Criterion 5 is met and all eligibility criteria assessed at Visit 1 are met, the participant may enter the run-in period.
  - Should the participant not successfully meet the requirements of Inclusion Criterion 3 at the second attempt then they will not be considered eligible for further study participation.
  - Refer to Section 8.3.4 for further information on pulmonary function testing. **INC#3**

- Asthma Control Status
- ACQ-6 score <1.5 at screening
- Asthma that has remained stable with no severe exacerbations in the last 6 months. Severe exacerbation defined as:
    - Deterioration of asthma-requiring the use of systemic corticosteroids (tablets, suspension or injection), for at least 3 days,

OR

    - An inpatient hospitalization or ED visit because of asthma, requiring systemic corticosteroids. **INC#4**
- Evidence of reversibility of disease:

Airway reversibility is defined as ≥12% and ≥200 mL increase in FEV_1 within 20 to 60 minutes following up to 4 inhalations of albuterol/salbutamol aerosol.

Subjects on as-needed SABA only, or daily maintenance ICS (plus as needed SABA):

- With a documented history of reversibility (as defined above) within 2 years will meet this inclusion criterion. Pre- and post-bronchodilator measurements will still be collected at screening to characterize the degree of reversibility.
- Who do not have a documented history of reversibility within the past 2 years will need to demonstrate reversibility during the screening period.
    - SABA should be withheld for ≥6 hours
    - If the subject does not meet the above reversibility definition at Visit 1 then the reversibility assessment may be repeated once during the screening period.
    - Subjects who fail 2 attempts at reversibility testing cannot make another attempt but may be rescreened.

Subjects on daily maintenance ICS/LABA or ICS/LABA/LAMA:

- Do not need to demonstrate reversibility in accordance with the above definition during the screening period. A reversibility maneuver will be performed to characterize the degree of post-bronchodilator change.
    - SABA should be withheld for ≥6 hours
    - LABA- and LAMA-containing medications should be withheld for ≥24 hours for the characterization of post-bronchodilator change.
    - Refer to Section 8.3.4 for further information on pulmonary function testing. **INC#5**
- Subjects should be able to withhold SABA for ≥6 hours and LABA-/LAMA-containing medications for ≥24 hours for the purposes of performing spirometry. **INC#6**
- Short acting beta-2-agonist use:

- All subjects must be able to replace their current rescue inhalers with the marketed Ventolin HFA-134a formulation at Visit 2 for the run-in period and Visit 3 for use as directed for the duration of the study. The use of a spacer device with MDI or nebulized albuterol/salbutamol will not be allowed during the study with the exception of their use during reversibility at screening. **INC#7**
- Participants who are current non-smokers, who have not used any tobacco or vaping products within 12 months of the start of the study, and with a total pack year history of ≤10 pack years. **INC#8**
- Participant should demonstrate ability to use Salbutamol Test MDI device in a satisfactory and repeatable manner, as judged visually by the investigator or designee. **INC#9**
- Serum potassium and blood glucose values within ranges considered not clinically significant by the investigator. **INC#10**
- Male and female patients are eligible to participate.

a. Female participants:

- A female participant is eligible to participate if she is not pregnant or breastfeeding, and 1 of the following conditions applies:
  - Is a WONCBP as defined in [Section 10.4.1.1 Contraceptive and Barrier Guidance],

OR

  - Is a WOCBP and using a contraceptive method that is highly effective, with a failure rate of <1%, as described in Section 10.4.1.1 during the study intervention period and for at least 48 hours after the last dose of study intervention. The investigator should evaluate the potential for contraceptive method failure (e.g., noncompliance, recently initiated) in relationship to the first dose of study intervention.
- A WOCBP must have a negative highly sensitive pregnancy test at the screening visit and the randomization visit, before the first dose of study intervention. See Section 8.3.8, Pregnancy Testing
  - [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.]
- Additional requirements for pregnancy testing during and after study intervention are in Section 8.3.8.
- 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#11**
- Adult participants capable of giving signed informed consent (written or digital) which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

For participants not capable of signed informed consent, a legally acceptable representative must be available to help the study site personnel ensure follow-up and support the participant to attended assessment days according to the SoA (i.e., must be able to comply with study procedures and use of study intervention as directed). **INC#12**

- Subjects must be able to comply with all the study requirements including clinic visit schedules and completion of eDiary. **INC#13**

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. **EXC#1**

  NOTE: Life-threatening asthma is defined as an asthma episode that required intubation/non-invasive positive pressure ventilation and/or was associated with hypercapnia, respiratory arrest or hypoxic seizures within the last 5 years.

- Other significant pulmonary diseases to include (but not limited to): pneumothorax, pulmonary fibrotic disease, bronchopulmonary dysplasia, chronic bronchitis, emphysema, chronic obstructive pulmonary disease, tuberculosis or other respiratory abnormalities other than asthma. **EXC#2**

- Respiratory Infection: Culture-documented or suspected bacterial or viral infection of the upper or lower respiratory tract, sinus or middle ear that is not resolved within 4 weeks of screening that led to a change in asthma management,

  OR

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

  OR

  the participant's ability to participate in the study. **EXC#3**

- Asthma Exacerbation: Any severe asthma exacerbation within 6 months prior to screening. **EXC#4**

- Participants must have had no more than 1 severe exacerbation during the 12 months prior to screening. **EXC#5**

  NOTE: Any 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.

- Other concurrent diseases/abnormalities: A participant has any clinically significant or uncontrolled condition or disease state that, in the opinion of the investigator, would put the safety of the participant at risk through study participation or would

confound the interpretation of the study results if the condition/disease exacerbated during the study. (e.g., stroke or MI within 3 months, uncontrolled hypertension, congestive heart failure). EXC#7

- Current or chronic history of liver disease or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones). **EXC#8**
- Biologic/immunosuppressive therapies 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#10**
- Participants undergoing de-sensitization therapy. **EXC#11**
- Current use of cholinesterase inhibitor medication (e.g., for myasthenia gravis). **EXC#12**
- Any other prescription or over the counter medication which would significantly affect the course of asthma, or interact with sympathomimetic amines, such as: anticonvulsants (barbiturates, hydantoins, carbamazepine); antidepressants; beta-adrenergic blockers; phenothiazines; MOA inhibitors. **EXC#13**

  NOTE: If a subject is established on a stable dose of a concomitant medication, that has no known capacity for interactions with their existing asthma medication and that is also not known to affect asthma symptoms, then this should not be reason to exclude subject. This would be as per investigator discretion and take into account usual considerations such as drug interactions.
- Administration of systemic, oral, or depot corticosteroids within 12 weeks of Visit 2

  NOTE: Subjects taking medicines known to either lower potassium levels (such as thiazide diuretics, loop diuretics) or raise potassium levels (such as ACE inhibitors, aldosterone antagonists) may continue to take these medications, at the discretion of the investigator, if these remain at a stable dose. **EXC#14**
- Drug Allergy: Known or suspected hypersensitivity to the components of the study drugs (e.g., salbutamol sulphate, HFA-134a, HFA-152a, oleic acid etc.). **EXC#15**
- 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#16**
- Participants with a known or suspected history of alcohol or drug abuse. **EXC#17**
- A participant will not be eligible if he/she or his/her or legal representative has any infirmity, disability, or geographic location which seems likely (in the opinion of the investigator) to impair compliance with any aspect of this study protocol or scheduled visits to the study center and non-compliance with study medication or procedures (i.e., completion of eDiary). **EXC#18**
- Twelve-Lead ECG abnormality: Significant abnormality in the 12-lead ECG performed at screening. **EXC#19**
- QTc >450 msec or QTc > 480 msec in participants with bundle branch block. **EXC#20**

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.

- Alanine transaminase (ALT) >2x upper limit of normal (ULN). **EXC#21**
- Total bilirubin >1.5xULN; for participants with Gilbert's syndrome can be included with total bilirubin >1.5xULN as long as direct bilirubin is ≤1.5xULN. **EXC#22**
- Cirrhosis or current unstable liver or biliary disease per investigator assessment defined by the presence of ascites, encephalopathy, coagulopathy, hypoalbuminemia, esophageal or gastric varices, or persistent jaundice. **EXC#23**

  Note: Stable non-cirrhotic chronic liver disease (including Gilbert's syndrome, asymptomatic gallstones, and chronic stable hepatitis B [in whom hepatitis D (HDV) has been excluded] or C) is acceptable if the participant otherwise meets entry criteria.

5.3. Randomization (Baseline) Criteria

After the screening visit and run-in period, participants meeting any of the following criteria on Visit 3 must not be randomized:

1. The participant experienced more than 2 consecutive days in which ≥8 inhalations/day of salbutamol rescue medication were used.
2. Participants who experience a severe exacerbation since the screening visit (refer to Section 5.2 for 'severe exacerbation' definition).
3. Clinical asthma worsening which in the opinion of the investigator requires additional asthma treatment.
4. Clinically significant abnormal laboratory tests during Visit 1 or 2, which are still abnormal upon repeat analysis and are not believed to be due to disease(s) present. 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.
5. Changes in asthma maintenance medication (excluding albuterol/salbutamol inhalation aerosol provided at Visit 1) occurring between Visits 1 and 3.
6. ACQ-6 score ≥1.5 at randomization visit.
7. Pre-bronchodilator FEV1 <60% of predicted at randomization visit.

8. 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.
9. Clinical visual evidence of oral candidiasis at the Randomization Visit (Visit 3)
10 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.
11 QTc >450 msec or QTc > 480 msec in participants with bundle branch block.

5.4. Lifestyle considerations

5.4.1. Meals and dietary restrictions

None.

5.4.2. Caffeine, alcohol, and tobacco

Use of tobacco products will not be allowed from 12 months prior to screening until after the final follow-up visit.

5.4.3. Other restrictions

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

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 5.1 for the specific conditions for rescreening relate to pulmonary function testsing . Subjects who previously screen failed due to reversibility testing may be rescreened.

5.6. Criteria for temporarily delaying administration of study intervention

Not Applicable.

6. STUDY INTERVENTIONS AND CONCOMITANT THERAPY

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

6.1. Study interventions administered

Table 3 Study Interventions Administered

Intervention Label	Experimental MDI	Reference Marketed MDI
Intervention Name	Salbutamol HFA-152a MDI	Salbutamol HFA-134a MDI
Intervention Description	100 µg (ex-valve) at 30-second intervals per actuation	100 µg (ex-valve) at 30-second intervals per actuation
Type	Investigational Product	Comparator
Dose Formulation	Salbutamol sulfate HFA-152a suspension	Salbutamol sulfate HFA-134a suspension
Unit Dose Strength(s)	100 µg (ex-valve)	100 µg (ex-valve)
Route of Administration	Inhalation	Inhalation
Use	Experimental	Active Comparator
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.

6.1.1. Medical devices

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

- Of note, MDIs need to be primed before use. Refer to the Pharmacy Manual for full instructions for use.

6.2. Preparation, handling, storage, and accountability

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

Intervention Label	Experimental MDI
Study using IVRS/IWR	All participants will be centrally assigned to randomized study intervention using an IVRS/IWRS. Before the study is initiated, the telephone number and call-in directions for the IVRS and/or the log-in information and directions for the IWRS will be provided to each site. Study intervention will be dispensed at the study visits as summarized in the SoA. Returned study intervention should not be re-dispensed to the participants.

6.4. Blinding, masking

Type of Study	
Blinding of laboratory testing	The laboratory in charge of sample testing will be blinded to the study intervention assignment. Codes will be used to link the participant and study to each sample. There will be no link between the study intervention groups and the identity of the participant.
Emergency unblinding	This is a double-blind study in which participants investigators/outcomes assessors, and investigational site staff. are blinded to the study interventions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participants' intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator may, at the investigator's discretion, contact GSK to discuss the situation prior to unblinding a participant's intervention assignment unless this could delay emergency treatment for the participant. If a participant's intervention assignment is unblinded, GSK must be notified within 24 hours of this occurrence. The date and reason for the unblinding must be recorded in the eCRF. If the investigator is unable to access RAMOS they can contact the GSK helpdesk based on the information provided in the pharmacy manual. A physician other than the investigator (e.g., an emergency room physician) or participant/participant's caregiver or family member may also request emergency access to the participant's study intervention information as per participant card.

A participant may continue in the study if that participant's intervention assignment is unblinded. The primary reason for discontinuation (the event or condition which led to the unblinding) will be recorded in the eCRF.

GSK's Global Safety staff may unblind the intervention assignment for any participant with an SAE. If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the participant's intervention assignment, may be sent to investigators in accordance with local regulations and/or GSK policy.

6.5. Study intervention compliance

When participants are dosed at the site, they will be asked to self-administer a dose (2x actuations) under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents.

When participants self-administer study intervention(s) at home, an eDiary system will be used. Participants will be asked/prompted to record the number of MDI actuations each day. Investigator and site staff are encouraged to remind participants of daily dosing and completion of the eDiary.

In order to adhere to study intervention, participants will be required to perform pre-dose MDI training as described in the SoA and in study specific training manual.

6.6. Dose modification

In this study a minimum fixed dose level will be administered through the MDI device. Subjects will be instructed take a minimum of 2x100 µg once daily (morning, prior to maintenance ICS) and as needed for symptoms, but not to exceed 800 µg daily.

Dose modifications will not be applicable.

6.7. Treatment of overdose

An overdose is any dose of study intervention given to a participant that, in the opinion of the investigator, exceeds the maximum labeled daily dose (800 µg) for salbutamol could impact patient safety.

These should be recorded by the Investigator on the AE/SAE eCRF pages. In the event of an overdose of study treatment, the Investigator should use clinical judgment in managing the overdose and ensuring the patient is able to access appropriate medical care if required. The investigator may opt to contact the GSK medical monitor. GSK is not recommending specific treatment guidelines for overdose and toxicity management. The Investigator is advised to refer to the relevant document(s) for detailed information regarding warnings, precautions, contraindications, adverse events, and other significant data pertaining to the study drug being used in this study. Such documents may include, but not be limited to, the Prescribing Information or equivalent document provided by GSK.

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

Permitted asthma medications

Temporary changes in asthma and other medications are permitted for the treatment of moderate asthma exacerbations, at the Investigator's/treating physician's discretion. Asthma exacerbations should be treated in line with national and international recommendations and local medical standards.

Asthma medications permitted on a temporary basis to treat a moderate asthma exacerbation include, but are not limited to, the following:

- An increase in maintenance inhaler i.e., ICS, dose:
- Systemic corticosteroids (tablets, suspension or injection) for no more than7 days.
- An Investigator-advised change in SABA use (i.e., routinely scheduled versus as needed use)

The Medical Monitor may be contacted for additional guidance.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of study intervention

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

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

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

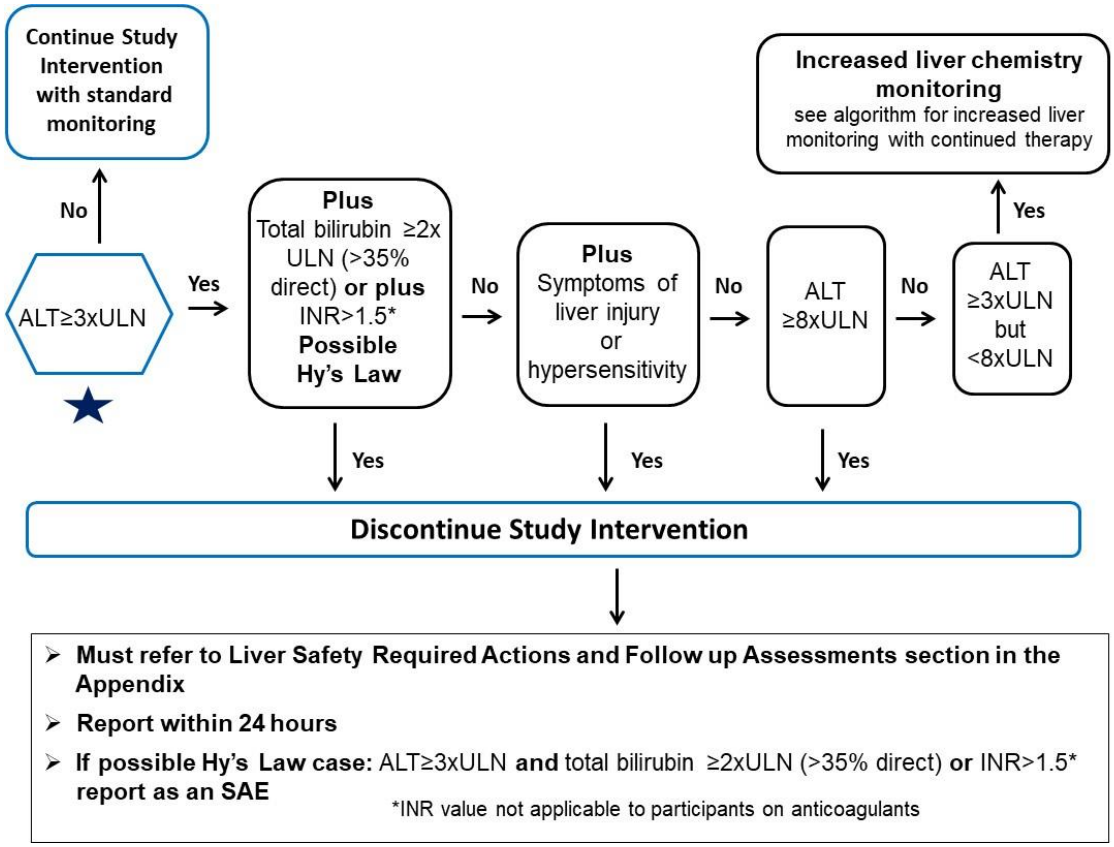
Reasons	Additional items/Sub-reasons
AE	
Lost to follow-up	Participant Relocated Participant was Incarcerated Other Unknown
Participant Reached Protocol-Defined Stopping Criteria	Liver chemistry stopping criteria QTc Stopping criteria
Physician Decision	Specify
Pregnancy	
Progressive Disease	Specify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

7.1.1. Liver chemistry stopping criteria

Discontinuation of study intervention and any further treatments for abnormal liver tests is required by the investigator when a participant meets 1 of the conditions outlined in Figure 3 or in the presence of abnormal liver chemistries not meeting protocol-specified stopping rules if the investigator believes that it is in best interest of the participant.

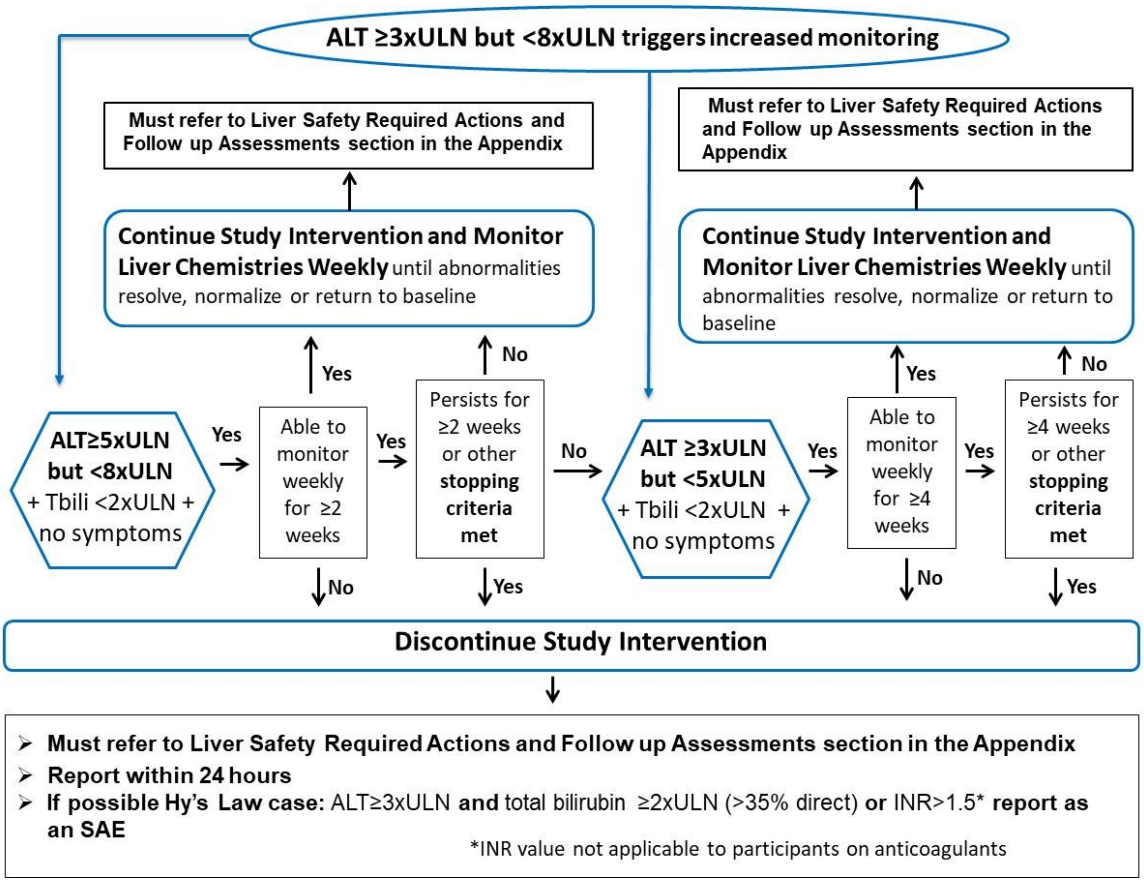
Study intervention will be discontinued for a participant if liver chemistry stopping criteria are met.

Figure 3 Phase 3-4 Liver Chemistry Stopping Criteria and Increased Monitoring Algorithm



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

Figure 4 Phase 3-4 Liver Chemistry Increased Monitoring Algorithm with Continued Study Intervention for Participants with ALT ≥3xULN but <8xULN



Abbreviations: ALT = alanine transaminase; Tbili = total bilirubin; INR = international normalized ratio; SAE = serious adverse event; ULN = upper limit of normal, Tbili = Total bilirubin.

Refer to Section 10.5 for required liver safety actions and follow-up Assessments.

7.1.2. QTc Stopping criteria

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

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

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

7.2. Participant discontinuation/withdrawal from the study

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

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

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

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

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

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

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

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

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

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

Participants who are withdrawn from the study because of AEs/SAEs must be clearly distinguished from participants who are withdrawn for other reasons. Investigator will follow participants who are withdrawn from the study due to an AE/SAE until the event is resolved (see Section 10.3.5.5).

7.3. Lost to follow-up

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

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study.

- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls, and if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, the participant will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA (Section 1.3). Protocol waivers or exemptions are not allowed.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. Participants 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 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.
- 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.
- If assessments are scheduled for the same nominal time, then it is recommended, if possible, that the assessments should occur in the following order:
    - Twelve-lead ECG
    - Vital signs
    - Blood draws

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/vaccination history

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

8.2. Efficacy and/or immunogenicity assessments

Efficacy will be evaluated as a secondary objective using endpoints described in Table 2. Planned timepoints for all efficacy assessments are provided in the SoA (see Section 1.3). Immunogenicity will be evaluated in this study.

8.3. Safety assessments

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

8.3.1. Physical examinations

- A complete physical examination will include, at a minimum, assessments of the Skin, Cardiovascular, Respiratory, Gastrointestinal, and abdominal (liver and spleen) systems BMI will also be measured and recorded.
- A brief physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).
- Investigators should pay special attention to clinical signs related to previous serious illnesses.
- Any unfavorable clinically significant change from baseline will be recorded as an adverse event in the CRF and source data.

8.3.2. Vital signs

- Vital signs will be measured at screening and at during each study Visit.
- Vital signs will be measured in a supine position after 5 minutes rest and will include temperature, systolic and diastolic blood pressure, and pulse rate. The measurement may be repeated if out of range.
- 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. Diary Assessments

Eligible subjects will be issued with an eDiary at Visit 2 for daily use throughout the study. CCI [redacted] CCI [redacted] Information on the device and its use are documented in the third-party vendor manual. Subjects will be instructed on how to use the device in order to record results for the following in the eDiary each day from Visit 2 onwards:

- The number of inhalations of rescue albuterol/salbutamol used during the day and night for relief of asthma symptoms.

For safety, the following alert, indicative of possible worsening asthma, will be programmed into the eDiary with instructions for the participant to contact the investigator (either by telephone and/or by visiting the study clinic) if any of the alert criteria are met:

- ≥ Eight puffs /day of albuterol/salbutamol use on 2 consecutive days.

Sites will also be notified if participants report via the eDiary that they are using ≥ 8 puffs /day of albuterol/salbutamol use on 2 consecutive days.

In addition, participants will also be instructed to contact the site if they experience an exacerbation at any point during the study.

8.3.4. Pulmonary Function Test

8.3.4.1. Pre-Bronchodilator FEV1

Spirometry will be performed at the study site to assess FEV1. To enroll in this study, participants must demonstrate a baseline pre-bronchodilator FEV_1 ≥60% of predicted at screening.
At least 3 acceptable spirometry maneuvers (from a maximum of 8 attempts) should be achieved on each occasion that spirometry assessments are performed, in accordance with the American Thoracic Society/European Respiratory Society (ATS/ERS) standards [Graham, 2019]. The highest of 3 technically acceptable measurements will be recorded at each visit.

At Visits 1, 3 and 8 (and the Early Withdrawal Visit, if applicable), participants should withhold short-acting beta-2-agonists (SABAs) for ≥6 hours and long-acting beta agonists and/or long-acting-muscarinic-antagonists for ≥24 hours prior to the clinic visit (termed 'trough' FEV1)

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.

FEV1 and Screening

- Participants who are unable to perform the pre-bronchodilator FEV_1 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 FEV_1 maneuvers again, as well as perform the post-bronchodilator FEV1 maneuvers for the assessment/characterization of reversibility. This must be within the screening period.
- Participants must meet Inclusion Criteria 3 and 5 to be eligible for the study.
- Should the participant successfully meet the requirements of Inclusion Criterion 3 at the second attempt then, provided that Inclusion Criterion 5 is met and all eligibility criteria assessed at Visit 1 are met, the participant may enter the run-in period.
- Should the participant not successfully meet the requirements of Inclusion Criterion 3 at the second attempt then they will not be considered eligible for further study participation.

8.3.4.2. Reversibility testing

Reversibility testing will be performed on all subjects. Subjects who have previously screen-failed due to reversibility may be re-screened. To perform the reversibility assessment, 4 puffs of the provided SABA is administered (a spacer device may be used for reversibility testing, if required, but use of nebulized SABA is not allowed). Following completion of the pre-bronchodilator assessment, a second spirometry assessment is performed within 20 to 60 minutes after administration of the salbutamol/albuterol.

All reversibility evaluations should follow the recommendations of the ATS/ERS Task force: Standardization of Lung Function Testing [Graham, 2019] A pre-bronchodilator spirometry assessment should be performed after withholding their bronchodilator medication: hold ≥6 hours for short-acting β2-agonists (SABAs) and 24 hours for long-acting β2-agonists (LABA)s or long-acting-muscarinic antagonists (LAMAs).

Percent reversibility will be calculated as follows:

$$\frac{(\text{Post-bronchodilator } FEV_1 - \text{Pre-bronchodilator } FEV_1)}{\text{Pre-bronchodilator } FEV_1} \times 100$$

- The reversibility requirement for eligibility must be assessed during the screening period. Subjects on as needed SABA or daily maintenance ICS (with as needed SABA) who do not have documented evidence of reversibility within 2 years must demonstrate a ≥12% and ≥200 mL post-bronchodilator increase in FEV_1 to be eligible for the study. If this reversibility criterion is not met at Visit 1 it may be repeated once during the screening period. Should participants on as needed SABA or daily maintenance ICS (plus as needed SABA) who do not have documented evidence of reversibility within 2 years successfully demonstrate airway reversibility at the second attempt then, provided that all other eligibility criteria assessed at Visit 1 are met, the participant may enter the run-in period.
- Participants on the following background medications will meet the reversibility inclusion criterion and will only perform pre- and post-bronchodilator measurements to characterize the degree of change:
  - As needed SABA with documented evidence of reversibility within 2 years
  - Daily maintenance ICS (plus as needed SABA) with documented evidence of reversibility within 2 years
  - Daily maintenance ICS/LABA (plus as needed SABA)
  - Daily maintenance ICS/LABA/LAMA (plus as needed SABA)
- Subjects who fail 2 attempts at reversibility testing cannot make another attempt but can rescreen..

8.3.5. Asthma Control Questionnaire (ACQ)

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.

It is recommended that the questionnaire 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.

ACQ may also be issued via participants' personal devices.

8.3.6. Electrocardiograms

Twelve-lead ECGs (including HR, PR, QRS, QT, and QTcF intervals will be measured by the investigator or his/her suitably qualified designee at screening (Visit 1), Visit 3, Visit 4, Visit 6-8, Visit 9 (Follow-up) and Early Withdrawal.

In order to coincide with peak salbutamol levels, ECG measurements during treatment period should occur, where possible, 30 minutes after last dose of study medication (except for the follow-up visit).

In general, where ECG, vital sign, and safety lab measurements are scheduled for the same timepoint, ECGs should be taken first, followed by vital signs, and finally blood draws.

ECGs should be recorded after the subject has been at rest for 5 minutes.

There will be electronic capture and storage of the data by a validated method. The calculation of ECG parameters will be used to determine whether a subject meets the eligibility criteria for enrollment in the study at Visit 3.

ECGs will be interpreted at screening as normal, abnormal not clinically significant or abnormal clinically significant. At all other visits where ECGs are performed, the change from baseline will be interpreted as no change/insignificant change from baseline, significant favorable change from baseline, or significant unfavorable change from baseline.

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

8.3.7. Clinical safety laboratory tests

- See Section 10.2 for the list of clinical 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 (refer to 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.

8.3.8. Pregnancy testing

- A urine pregnancy test must be performed for all female participants of childbearing potential 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. See Section 8.4.5 for the information on study continuation for participants who become pregnant during the study.
- Pregnancy testing should be conducted during study intervention period as detailed in the SoA.
- Pregnancy testing 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 study.

8.3.9. Study stopping rules, safety monitoring OR Committee

- Participant safety will be continuously monitored by the Medical Monitor, designated Safety Lead and sponsor's internal or external committee throughout the study. Pertinent findings and conclusions are shared with the product's SRT (Safety Review Team) for review of the overall benefit-risk profile of the product.
- Safety data will be summarized and reviewed by the sponsor's internal safety review for agreement of next steps.
- In particular, data will be reviewed by the sponsor for identification of events that would potentially contribute to a requirement to (pause/stop) the study.
- If a [pausing/stopping] rule is met, a decision will be made, based on the review, as to whether enrollment in the study will be allowed to resume.

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

For definitions relating to safety information see Section 10.3

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

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

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

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

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

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

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

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

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

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

8.4.2. 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. AEs and SAEs will be captured in the eCRF.

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.

8.4.4. Regulatory reporting requirements for SAEs

- Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a study intervention under clinical investigation are met. See Section 8.4.1 for reporting timeframes.
- For SAEs, the investigator must always provide an assessment of causality at the time of the initial report, as defined in the Section 10.3.5.6
- 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 IB/IDFU documents and will notify the IRB/IEC, if appropriate according to local requirements.

Table 4 Timeframes for submitting SAE and pregnancy reports to GSK

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

SAE(s)=serious adverse events
* Timeframe allowed after receipt or awareness of the information by the investigator/site staff.
‡ Paper Adverse Events Report (in case eCRF is not working) will be dated and signed by the investigator (or designee). For each SAE, the investigator(s) must document in the medical notes that they have reviewed the SAE and have provided an assessment of causality.

8.4.5. Pregnancy

Prior to continuation of study intervention following pregnancy, the following must occur:

- The sponsor and the relevant IRB/IEC should give written approval.
- The participant should give signed informed consent.
- The investigator agrees to monitor the outcome of the pregnancy and the status of the participant and her offspring.

Female participants who become pregnant after the first study intervention dose must not receive subsequent doses of the study intervention but may continue other study procedures at the discretion of the investigator and should revert to usage of their usual reliever inhaler.

- Details of all pregnancies in female participants will be collected after the start of study intervention and up to 48 hours 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 or pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.
- The 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 discontinue study intervention or be withdrawn from the study.

8.4.6. Contact information for reporting SAEs and pregnancies

Table 5 Contact information for reporting SAEs and pregnancies

Study contact for questions regarding SAEs and pregnancies	**Study contact for reporting of stopping rules**
Contact GSK's local and/or medical contacts	If a stopping rule is met, the investigator must immediately inform GSKs Local and/or Medical contacts.
Contacts for reporting SAEs and pregnancies Available 24/24 hours and 7/7 days OAX37649@gsk.com	**Back-up study contact for escalation of stopping rules** OAX37649@gsk.com OR facsimile number +44(0) 20 81814780.

8.4.7. Medical device deficiencies

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

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

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

8.4.7.1. Time Period for Detecting Medical Device Deficiencies

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

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

8.4.7.2. 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.

8.4.7.3. Prompt Reporting of Device Deficiencies to the Sponsor

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

8.4.7.4. 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

Pharmacokinetics will not be evaluated in this study.

8.6. Pharmacodynamics

Pharmacodynamics will not be evaluated in this study.

8.7. Genetics

Genetic markers will not be evaluated in this study.

8.8. Biomarkers

Biomarker evaluations will not be performed 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.

9. STATISTICAL CONSIDERATIONS

Full details of all data handling conventions and statistical analyses conducted for this study will be provided in the SAP.

9.1. Statistical hypothesis

The nature of the study is purely descriptive therefore, no formal hypothesis testing will be performed for the primary and secondary endpoints.

9.1.1. Multiplicity Adjustment

No multiplicity adjustment will be performed for the primary and secondary endpoints.

9.2. Analysis sets

Analysis Set	Definition / Criteria	Analyses Evaluated
Screened	• All participants who were screened for eligibility.	Study Population
Enrolled	• All participants who screen passed and entered the study. • 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
Intent to Treat	• All participants who were randomly assigned to study treatment in the study. • The screened, enrolled and randomized populations must be nested, i.e., the enrolled population must be a subset of the screened population, the randomized population must be a subset of the enrolled population.	Study Population and secondary efficacy objective
Safety	• All randomized participants who take at least at least 1 puff/actuation of study treatment. Participants will be analyzed according to treatment they actually received	Estimands primary and secondary safety objectives

9.3. Statistical analyses

The study 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 primary and secondary endpoints.

9.3.1. General considerations/definitions

This study aims to estimate the counts and percentages of participants who received at least 1 puff/actuation of salbutomol test (HFA-152a MDI) or reference (HFA-134a MDI) treatment group. Continuous data descriptively summarized by means of the number of observations, the arithmetic mean, median, standard deviation, minimum, maximum as appropriate. Discrete data will be summarized by counts and percentages as appropriate.

9.3.2. Primary analysis

The primary analysis will estimate the primary estimands and are described in the Section 3.1.1 using safety analysis set.

9.3.2.1. Definition of Main Analytical Approach

All reported on-treatment AEs will be coded using the standard GSK dictionary, (MedDRA) and grouped by body system and preferred terms.

The incidence of adverse events will be estimated by counts and percentages in test (HFA-152a MDI) and reference (HFA-134a MDI) treatment groups for "on-treatment" period (if AEs occurs between treatment start date and treatment end date + including 7 follow-up days).

Counts and percentages for participants with at least 1 AEs for test (HFA-152a MDI) and reference (HFA-134a MDI) treatment group will be presented.

Risk difference between test (HFA-152a MDI) and reference (HFA-134a MDI) treatment group for participants with at least 1 AEs will be computed by counts and percentages along with 95% CI using Wald method.

9.3.2.2. Sensitivity analysis

No sensitivity analysis will be performed for the primary endpoint.

9.3.3. Secondary endpoint(s) analyses

All analyses of safety data will be performed using safety analysis set.

Safety endpoints-

Adverse Event analysis:

All reported AEs and SAEs will be coded using the standard GSK dictionary, (MedDRA) and grouped by body system and preferred terms.

While on strategy (as described in Section 3.1.2) for the ICE of study treatment discontinuation due to any reason will be used for summarizing the on-treatment period SAEs.

Counts and percentages will be presented for incidence of AEs and SAEs by system organ class and preferred terms.

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. Data will be tabulated and reported by absolute grade for Grades 3 and higher and shift tables, as appropriate.

Summary of the common (≥3% incidence) adverse events by system organ class and preferred term will also be analyzed.

Listings for all AEs and SAEs will also be produced.

Poisson regression analysis may be explored for assessing the impact of different average daily doses on bronchoconstriction, hoarseness, and cough AEs and common (≥3% incidence) AEs between test (HFA-152a MDI) and reference (HFA-134a MDI) treatment group treatment, considering baseline ACQ-6 score, baseline pre-bronchodilator trough FEV1, age, reversibility and average daily dose as covariates and duration of exposure as off set.

Detailed analysis will be described in Statistical Analysis Plan.

Serum potassium assessment:

Minimum, absolute values and change from baseline at each assessed visit for serum potassium will be listed and summarized by descriptive statistics (mean, median, standard deviation, minimum and maximum).

Minimum of serum potassium will be analyzed using a general linear model with treatment, average daily dose and baseline serum potassium as covariates (fixed effect) including interaction effect for treatment by average daily dose. Point estimate of mean difference in serum potassium between test (HFA-152a MDI vs reference (HFA-134a MDI) treatment group and its associated 95% CI will be produced.

Clinical laboratory assessments:

Absolute values and change from baseline each assessed visit for clinical laboratory assessments parameters detailed in Section 10.2. Appendix listed and presented descriptively using mean, median, standard deviation, minimum and maximum by treatment group. A summary of all data outside the reference range of the clinical laboratory will be provided.

Vital signs assessments and 12 lead ECG:

Absolute values and change from baseline at each assessed visit in vital signs (SBP, DBP and pulse rate) will be listed and presented descriptively using mean, median, standard deviation, minimum and maximum by treatment groups.

Absolute and change from baseline at each assessed visit in 12 lead ECG parameters (QTc and heart rate) will be listed and presented descriptively using mean, median, standard deviation, minimum and maximum by treatment groups.

While on-treatment strategy (as described in Section 3) for the ICE of study treatment discontinuation due to any reason will be used to present the on-treatment period serum potassium, clinical laboratory assessment data, vital signs, and ECGs data.

Supplementary estimand analysis:

A supplementary estimand (as described in Section 3.1.3) using treatment policy strategy for the ICE of study treatment discontinuation due to any reason will be considered to evaluate AEs, SAEs, serum potassium, clinical laboratory assessment, vital signs, and ECGs data for salbutamol test (HFA-152a MDI) and reference (HFA-134a MDI) treatment groups in overall follow-up period (including any post-treatment follow-up). The supplementary estimand will be estimated using the safety analysis set. AEs and SAEs data will be analyzed by counts and percentages. Descriptive statistics of absolute values and change from baseline at each assessed visit will be presented for serum potassium, clinical laboratory assessment, vital signs, and ECGs data in salbutamol test (HFA-152a MDI) and reference (HFA-134a MDI) treatment groups.

Efficacy endpoints-

Asthma Control Questionnaire (ACQ-6) and Pre-Bronchodilator Forced Expiratory Volume in 1 second (FEV1)

Absolute and change from baseline at each assessed visit for Asthma Control Questionnaire (ACQ) and pre-bronchodilator Forced Expiratory Volume in 1 second (FEV1) will be summarized using ITT analysis set. Mixed effect linear model analysis will be used to analyse the change from baseline in pre- bronchodilator FEV1 at Visit 8 (Week 12) including baseline pre-bronchodilator FEV1, treatment, age, sex, reversibility and maintenance therapy (ICS, ICS/SABA, ICS/LABA/LAMA) as fixed effect covariates for the calculation of point estimates and 95% confidence intervals of salbutamol test (HFA-152a MDI) and reference (HFA-134a MDI) treatment groups.

Mixed effect linear model analysis will be used to analyse the change from baseline in ACQ-6 score at Visit 8 (Week 12) including baseline ACQ-6 score, treatment, age, sex, reversibility and maintenance therapy (ICS, ICS/SABA, ICS/LABA/LAMA) as fixed effect covariates for the calculation of point estimates and 95% confidence intervals of salbutamol test (HFA-152a MDI) and salbutamol reference (HFA-134a MDI) treatment groups.

9.4. Interim analyses

Not applicable

9.5. Sample size determination

The sample size with primary interest in the test (HFA-152a MDI) treatment group is determined based on the calculation of the probability of observing an adverse event (AE). Table 6 and Table 7 provide the probabilities of observing various numbers of Adverse Events (AEs) based on a series of theoretical risks of an event occurring in a given participants of 300 in salbutamol test (HFA-152a MDI) treatment group and 100 in salbutamol reference (HFA-134a MDI) treatment group during a study of 3 months duration.

For an example, for a theoretical risk of an AE of 1 out of 100 for sample size of 300 in salbutamol test (HFA-152a MDI) treatment group, we would have a greater than 95.09% chance of observing at least one participant having the AE, and for a theoretical risk of an AE of 3 out of 100 for sample size of 100 in salbutamol reference (HFA-134a MDI) treatment group, we would have a greater than 95.24% chance of observing at least 1 participant having the AE.

Table 6 Probabilities of observing a given number of participants experiencing an adverse event or more (k) for given theoretical risks in a study for a sample size of 300 participants in salbutamol HFA-152a MDI (Test).

	Theoretical Risk of an Event*				
K	**0.01**	**0.02**	**0.03**	**0.04**	**0.05**
1	95%	100%	100%	100%	100%
2	80%	98%	100%	100%	100%
3	58%	94%	99%	100%	100%
4	35%	85%	98%	100%	100%
5	18%	72%	95%	99%	100%
6	8%	56%	89%	98%	100%
7	3%	39%	80%	96%	99%
8	1%	26%	68%	92%	98%
9	<1%	15%	55%	85%	97%
10	<1%	8%	41%	76%	94%

*Theoretical risk of an event occurring in a given participants in a study of 3 months duration.

Table 7 Probabilities of observing a given number of participants experiencing an adverse event or more (k) for given theoretical risks in a study for a sample size of 100 participants in salbutamol HFA-134a MDI (Reference)

	Theoretical Risk of an Event*				
K	**0.01**	**0.02**	**0.03**	**0.04**	**0.05**
1	63%	87%	95%	98%	99%
2	26%	60%	81%	91%	96%
3	8%	32%	58%	77%	88%
4	2%	14%	35%	57%	74%
5	<1%	5%	18%	37%	56%
6	<1%	2%	8%	21%	38%
7	<1%	<1%	3%	11%	23%
8	<1%	<1%	1%	5%	13%
9	<1%	<1%	<1%	2%	6%
10	<1%	<1%	<1%	<1%	3%

*Theoretical risk of an event occurring in a given participants in a study of 3 months duration.

For a given or assumed sample size of 400, the description of precision estimates, risk difference and 95% CI (calculated by Wald method) has been presented using different scenarios in Section 10.8 , Appendix 8.

Approximately 412 participants will be randomly assigned with 3:1 ratio in the study, 309 participants in salbutamol test (HFA-152a MDI) treatment group to achieve 300 participants and 103 participants in salbutamol reference (HFA-134a MDI) treatment group to achieve 100 participants for the primary analysis. A smaller reference group for HFA-134a has been proposed because the primary estimand is a descriptive characterization of AE incidence in each group, and both salbutamol and the propellant HFA-134a have been on the market for several decades. Salbutamol has a well-established safety profile, supported clinical trial data and over 50 years of on-the-market data. Clinical trials have previously observed common AEs with greater occurrence than placebo such as throat irritation, upper respiratory inflammation, viral respiratory infections, cough, and musculoskeletal pain in Ventolin HFA arm occurring at 5-10% frequency. [FDA, 2021]

In addition, HFA-134a is considered biologically inert. This is supported by several studies which show that HFA-134a is not metabolized or retained in the body, but is exhaled out rapidly after exposure [Gunnare, 2007; Pike, 1995; Shin, 2015]. Given this evidence and the extensive history of salbutamol usage, a sample size of 100 participants in the salbutamol HFA-134a treatment arm is considered appropriate for the evaluation of adverse events.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1. Regulatory and ethical considerations

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

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

10.1.2. Financial disclosure

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

10.1.3. Informed consent process

- The investigator or the investigator's representative will explain the nature of the study, including the risks and benefits, to the participants and answer all questions regarding the study.
- Potential participants must be informed that their participation is voluntary. They will be required to physically or digitally sign a statement of informed consent that meets the local regulations, ICH guidelines, privacy, and data protection requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that physical or digital informed consent was obtained before the participant was enrolled in the study and the date the physical or digital consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be reconsented to the most current version of the ICF(s) during their participation in the study.
- A physical or digital copy of the ICF(s) must be provided to the participant.
- In case of unexpected pregnancy, participant must be informed that personal information 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 be needed to be obtained or notification given as per local regulation to the partner before collecting their personal information such as last menstrual period and year of birth, or personal information such as date of birth as sex of their baby as part of safety follow-up.
- Stored samples will be coded throughout the sample storage and analysis process and will not be labeled with personal identifiers. Participants may withdraw their consent/assent for their samples to be stored for research.

10.1.4. Recruitment strategy

Participants will be identified for potential recruitment using clinical database, and IEC/IRB-approved advertisements through appropriate channels, prior to consenting to take part in this study.

10.1.5. Data protection

- Participants will be assigned a unique identifier by the investigator. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- GSK will ensure protection of the personal data of the investigator and site staff which is collected within the framework of and for the purpose of the study.
- The participantmust be informed that their personalstudy-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 participantthat their data will be used as described in the informed consent.
- The participantmust be informed that theirmedical 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, third parties working on behalf of GSK, and/or institutions working with GSK for the purposes of this study are contractually bound to protect participant coded data. GSK will protect participant coded data and will only share it as described in the ICF.

- 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 of 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 Clinical Study Register in compliance with applicable regulations/GSK policy. GSK will aim to register protocols summaries prior to study start and target results summaries submission within 12 months of primary/ study completion date. Where external regulations require earlier disclosure, GSK will follow those timelines.
- Where required by regulation, summaries will also be posted on applicable national or regional clinical study registers.
- Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the study report, and provided reasonable access to statistical tables, figures, and relevant reports. GSK will also provide the investigator with the full summary of the study results, including a summary of trial results understandable to laypersons. The investigator is encouraged to share the plain language summary with the study participants, as appropriate. The full study report will be made available upon request, after decision on marketing authorization by regulatory authorities.
- 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 electronic CRFs unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- Guidance on completion of eCRFs will be provided in eCRF completion guidelines.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source documents.
- QTLs will be predefined in the Veeva Vault System to identify systematic issues that can impact participant safety and/or reliability of study results. These predefined parameters will be monitored during the study, and important deviations from the QTLs and remedial actions taken will be summarized in the CSR.
- Monitoring details describing strategy, including definition of study critical data items and processes (e.g., risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan.
- The sponsor or designee is responsible for the data management of this study, including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (e.g., contract research organizations).
- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 15 years from the issue of the final CSR/ equivalent summary unless local regulations or institutional policies require a different retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.
- When copies of source documents are shared externally for review by a central reader mechanism (e.g., endpoint adjudication committee; expert reader), documents are stored by the external body for 25 years.

10.1.9. Source documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the eCRF/eDiaries (and/or decentralized trial platforms) or entered in the eCRF/eDiaries (and/or decentralized trial platforms) are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

- Definition of what constitutes source data and its origin can be found in e.g., source data acknowledgment or monitoring guidelines.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The sponsor or designee will perform monitoring to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements**.**

10.1.10. Study and site start and closure

Start of study and first act of recruitment

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

Study/Site Termination

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

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

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

For study termination:

- Discontinuation of further study intervention development

For site termination:

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

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

10.1.11. Publication policy

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

10.2. Appendix 2: Clinical laboratory tests

- The tests detailed in Table 8 will be performed at Q Squared Solution LLC.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.
- Investigators must document their review of each laboratory safety report.

Table 8 Protocol-required safety laboratory tests

Laboratory Tests	Parameters	
Hematology	• Platelet count	
	• Red blood cell (RBC) count	
	• RBC indices	○ Mean corpuscular volume (MCV) ○ Mean corpuscular hemoglobin (MCH) ○ %Reticulocytes
	• WBC count with differential:	○ Neutrophils ○ Lymphocytes ○ Monocytes ○ Eosinophils ○ Basophils
	• Hemoglobin	
	• Hematocrit	
Clinical chemistry[1]	• Blood urea nitrogen (BUN)/Urea • Potassium • Creatinine* • Sodium • Calcium • Glucose [non-fasting] • Creatine phosphokinase (CPK)	○ Aspartate aminotransferase (AST)/serum glutamic-oxaloacetic transaminase (SGOT) ○ Alanine aminotransferase (ALT)/serum glutamic-pyruvic transaminase (SGPT) ○ Alkaline phosphatase[1] ○ Total bilirubin ○ Direct bilirubin

Laboratory Tests	Parameters
Routine urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, [bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick • Microscopic examination (if blood or protein is abnormal) o Epithelial cells o Red Blood cells o WBC o Casts o Crystals o Culture (if positive: specify pathogen)
Pregnancy testing	• Highly sensitive [urine and/or serum] human chorionic gonadotropin (hCG) pregnancy test (as needed for WOCBP)
Other screening tests (as appropriate only)	• Follicle stimulating hormone and estradiol (as needed in WONCBP only) • [Serum or urine] • [Serology [(HIV antibody 4th generation test, HBsAg, and HCV antibody)] [or specify other tests] [if applicable]

* To assess the kidney function, use the estimated glomerular filtration rate (eGFR) 2021 calculator (CKD-Epi creatinine equation). eGFR (based on CKD-Epi) will be measured at all time points when creatinine is measured. Different eGFR equations may be used in specific geographies.

1. If alkaline phosphatase is elevated, consider fractionating

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

10.3.1. Definition of AE

AE definition
• An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of a study intervention, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention.
Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease).

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New condition detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected intervention-intervention interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.
- Significant failure of an expected pharmacologic or biological action.
- Events that occur as a result of protocol-mandated procedures (i.e., invasive procedures, modification of participant's previous therapeutic regimen.

Events NOT Meeting the AE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital, admission for routine examination).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen. Pre-existing diseases will be recorded in the medical history section of the eCRF.
- Hospitalization for elective treatment of a pre-existing condition (known or diagnosed before signing the informed consent) that did not worsen from baseline.

10.3.2. Definition of SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed:

a. Results in death

b. Is life threatening

The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

• In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AE. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. • Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
d. Results in persistent or significant disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect in the offspring of a study participant
f. Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy).
g. Is a suspected transmission of any infectious agent via an authorized medicinal product.
h. Other situations: • Possible Hy's Law case: ALT ≥ 3x ULN AND total bilirubin ≥ 2x ULN (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 bronchospasm, 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: • Myocardial infarction/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 AE, SAE and pregnancies

10.3.5.1. AE and SAE recording

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

10.3.5.2. Assessment of intensity

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

- Mild:
  A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- Moderate:
  A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
- Severe:
  A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

10.3.5.3. Assessment of causality

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

10.3.5.4. 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, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up.

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

Follow-up during the study

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

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

Follow-up of pregnancies

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

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

Furthermore, the investigator must report any SAE occurring as a result of a poststudy pregnancy that is considered by the investigator to be reasonably related to the study intervention, to GSK as described in the Section 10.3.5.7.

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

When additional SAE or pregnancy information is received after write access to the participant's eCRF is removed, new or updated information should be recorded on the appropriate paper report, with all changes signed and dated by the investigator. The updated report should be sent to the Study contact for reporting SAEs (refer to Section 8.4.3).

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 non-IMP they will report these events to GSK or to the concerned competent authority via the national spontaneous reporting system. These will be classified as spontaneous ICSRs.
- Contacts for SAE reporting can be found in Section 8.4.6.

SAE Reporting to GSK via Paper Data Collection Tool

- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE data collection tool within the designated reporting timeframes.
- Contacts for SAE reporting can be found in Section 8.4.6.

10.4. Appendix 4: Contraceptive and barrier guidance

10.4.1. Definitions

10.4.1.1. Woman of Childbearing Potential (WOCBP)

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

- Adolescents of childbearing potential: Tanner stage ≥2 (post-thelarche) irrespective of the occurrence of menarche or following menarche.
- From the time of menarche until becoming postmenopausal unless permanently sterile (see below)

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

10.4.1.2. Woman of Nonchildbearing Potential (WONCBP)

Women in the following categories are considered WONCBP:

- Premenarchal: Tanner stage 1 (prepubertal)
- Permanently sterile due to one of the following procedures:

a. Documented hysterectomy

b. Documented bilateral salpingectomy

c. Documented bilateral oophorectomy

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

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

- Postmenopausal female

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

- A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with more than 1 FSH measurement is required.
- Females on HRT and whose menopausal status is in doubt must discontinue HRT to allow confirmation of postmenopausal status before study enrolment.

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 48 hours post-dose of last study intervention.

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

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

Sexual abstinence
Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

a. Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies.
b. Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly.
c. [Male condoms must be used in addition to hormonal contraception]. If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action.

Note: Periodic abstinence (calendar, sympto-thermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception. Male condom and female condom should not be used together (due to risk of failure from friction)

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

Phase 3-4 Liver Chemistry Stopping and Increased Monitoring Criteria are designed to assure participant safety and evaluate liver event etiology

Phase 3/4 Liver Chemistry Stopping criteria and Required Follow-up Assessments

Liver Chemistry Stopping Criteria	
ALT-absolute	ALT ≥8xULN
ALT Increase	ALT ≥5xULN but <8xULN persists for ≥2 weeks ALT ≥3xULN but <5xULN persists for ≥4 weeks
Bilirubin[1, 2]	ALT ≥3xULN and total bilirubin ≥2xULN (>35% direct bilirubin)
INR[2]	ALT ≥3xULN and INR>1.5
Cannot Monitor	ALT ≥5xULN but <8xULN and cannot be monitored weekly for ≥2 weeks ALT ≥3xULN but <5xULN and cannot be monitored weekly for ≥4 weeks
Symptomatic[3]	ALT ≥3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity
Required Actions, Monitoring and Follow-up Assessments	
Actions	**Follow-Up Assessments**
• Immediately discontinue study intervention • Report the event to GSK within 24 hours • Complete the liver event form and complete an SAE data collection tool if the event also meets the criteria for an SAE2 • Perform follow-up assessments as described in the Follow-up Assessment column. • Monitor the participant until liver chemistries resolve, stabilize, or return to within baseline (see MONITORING below) **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 assessments within 24 hours	• Viral hepatitis serology4 • Obtain INR and recheck with each liver chemistry assessment until the aminotransferases values show downward trend • Obtain blood sample for pharmacokinetic (PK) analysis, within 72 hours after last dose5 • Obtain a serum creatine phosphokinase (CPK), lactate dehydrogenase (LDH), gamma glutamyl transferase [GGT], glutamate dehydrogenase [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 liver event form

Liver Chemistry Stopping Criteria	
• Monitor participant twice weekly until liver chemistries resolve, stabilize or return to within baseline • A specialist or hepatology consultation is recommended For all other stopping criteria (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 assessments within 24-72 hours • Monitor participant weekly until liver chemistries resolve, stabilize or return to within baseline **RESTART/RECHALLENGE** • Not applicable	• 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: • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG) or gamma globulins. • Serum acetaminophen adduct assay should be conducted (where available) to assess potential acetaminophen contribution to liver injury unless acetaminophen use is very unlikely in the preceding week (e.g., where the participant has been resident in the clinical unit throughout) • Liver imaging (ultrasound, magnetic resonance, or computed tomography) to evaluate liver disease; complete Liver Imaging form • Liver biopsy may be considered and discussed with local specialist if available, for instance: o In participants when serology raises the possibility of autoimmune hepatitis (AIH) o In participants when suspected DILI progresses or fails to resolve on withdrawal of study intervention o In participants with acute or chronic atypical presentation: • If liver biopsy conducted complete liver biopsy form

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study intervention for that participant if ALT≥3xULN and total bilirubin ≥2xULN. 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 bilirubin ≥2xULN (>35% direct bilirubin) 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. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia)
4. Includes: hepatitis A Immunoglobulin M (IgM) antibody; HBsAg and HBcAb; hepatitis C RNA; cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, heterophile antibody or monospot testing); and hepatitis E IgM antibody. [Le Gal , 2005]
5. Record the date/time of the PK blood sample draw and the date/time of the last dose of study intervention prior to the PK blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the participant's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the respective manual.

Phase 3/4 Liver Chemistry Increased Monitoring Criteria with Continued Study Intervention

Liver Chemistry Increased Monitoring Criteria and Actions with Continued Study Intervention	
Criteria	**Actions**
ALT ≥5xULN and <8xULN and total bilirubin <2xULN or INR≤1.5 without symptoms believed to be related to liver injury or hypersensitivity, and who can be monitored weekly for 2 weeks. OR ALT ≥3xULN and <5xULN and total bilirubin <2xULN or INR≤1.5 without symptoms believed to be related to liver injury or hypersensitivity, and who can be monitored weekly for 4 weeks.	• Notify the GSK medical monitor within 24 hours of learning of the abnormality to discuss participant safety. • Participant must return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, total bilirubin and INR) until they resolve, stabilize or return to within baseline. • If at any time participant meets the liver chemistry stopping criteria, proceed as described above. • If ALT decreases from ALT ≥5xULN and <8xULN to ≥3xULN but <5xULN, (total bilirubin <2xULN and INR ≤1.5) continue to monitor liver chemistries weekly. • If, after 4 weeks of monitoring, ALT <3xULN and total bilirubin <2xULN and INR ≤1.5, monitor participants twice monthly until liver chemistries resolve or return to within baseline.

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

- The definitions and procedures detailed in this appendix are in accordance with ISO 14155 and the European Medical Device Regulation (MDR) 2017/745 for clinical device research (if applicable).
- Both the investigator and the sponsor will comply with all local reporting requirements for medical devices.
- The detection and documentation procedures described in this protocol apply to all sponsor medical devices provided for use in the study. See Section 6.1.1 for the list of sponsor medical devices**.**

10.6.1. Definition of medical device AE and ADE

Medical device AE and ADE definition
• A medical device AE is any untoward medical occurrence, in a clinical study participant, users, or other persons, temporally associated with the use of study intervention whether or not considered related to the 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 amedical 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 amedical device. This definition includes any AE resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the medical device as well as any event resulting from use error or from intentional misuse of the medical device.

10.6.2. 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).

10.6.3. Definition of device deficiency

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

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

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

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

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

10.6.4.2. Assessment of intensity

Refer to Section 10.3.5.2

10.6.4.3. Assessment of causality

Refer to Section 10.3.5.3

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

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

10.6.5. Reporting of medical device SAEs

Medical Device SAE Reporting to GSK via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to GSK will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken offline to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken offline, then the site can report this information on a paper SAE form or to the medical monitor by telephone.

- If the site during the course of the study or poststudy becomes aware of any serious, nonserious AEs, pregnancy exposure, related to any GSK device they will report these events to GSK or to the concerned competent authority via the national spontaneous reporting system. These will be classified as spontaneous ICSRs.
- Contacts for SAE reporting can be found in Section 8.4.6.

Medical Device SAE Reporting to GSK via Paper Data Collection Tool

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

10.6.6. Reporting of SADEs

SADE Reporting to GSK

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

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

10.6.7. Reporting of medical device deficiencies for associated person

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

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

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

10.7. Appendix 7 : Country-specific requirements

FRENCH-SPECIFIC REQUIREMENTS

This appendix includes all applicable requirements of French Public Health Code / specific local GSK requirements and identifies, item per item, the mandatory modifications or additional information to the study protocol.

- **Concerning the "SELECTION OF STUDY POPULATION AND WITHDRAWAL CRITERIA"**

A subject will be eligible for inclusion in this study if he /she is either affiliated to or beneficiary of a social security category (French Public Health Code L.1124-1).

It is the investigator's responsibility to ensure and to document (in the source document - subject notes) that the subject is affiliated to or beneficiary of a social security category.

Subjects will be compensated for the inconvenience of participating in the study. The amount of compensation is stated in the ICF. Subjects not completing the study for whatever reason could be compensated generally on a pro rata basis.

Concerning the "STUDY GOVERNANCE CONSIDERATIONS"

- **In section "Regulatory and Ethical Considerations, including the Informed Consent Process" of study protocol**

  a. Concerning the **process for informing the subject**, the following text is added:

  French Patient Informed Consent is a document which summarizes the main features of the study and allows collection of the subject written consent. It also contains a reference to the single scientific and ethical regulatory authorization.

b. Concerning the **management of the Patient ICFs**, the following text is added:

French Patient Informed Consent Form is in duplicate.

The first page of the Patient ICF is given to the investigator. The copy is kept by the patient.

- **NOTIFICATION TO THE HOSPITAL DIRECTOR**

In accordance with Article R.1123-69 of the French Public Health Code, the Hospital Director is informed of the commitment to the trial in her/his establishment. The Hospital Director is supplied with the protocol and any information needed for the financial disposition, the name of the investigator(s), the number of sites involved in his establishment and the estimated time schedule of the trial.

- **INFORMATION TO THE HOSPITAL PHARMACIST**

In accordance with Article R.1123-70 of the French Public Health Code, the Hospital Pharmacist is informed of the commitment to the trial in her/his establishment. The Pharmacist is supplied with a copy of the protocol (which allows her/him to dispense the drug(s) of the trial according to the trial methodology), all information concerning the product(s) of the trial (e.g., included in the IB), the name of the investigator(s), the number of sites involved in her/his establishment and the estimated time schedule of the trial.

- **ETHNIC ORIGIN**

In accordance with the data privacy regulation, the ethnic origin, as any personal data, can only be collected if the collection of this data is strictly necessary and relevant for the purpose of the study.

- **TESTING OF BIOLOGICAL SAMPLES**

In accordance with the French Public Health Code – article L1211-2, a biological sample without identified purpose at the time of the sample and subject's preliminary information is not authorized.

Concerning the "DATA MANAGEMENT" the following text is added:

Within the framework of this clinical trial, data regarding the identity of the investigators and/or co-investigators and/or the pharmacists if applicable, involved in this clinical trial, and data regarding the subjects recruited in this clinical trial (subject number, treatment number, subjects status with respect to the clinical trial, dates of visit, medical data) will be collected and computerized in GSK data bases by GSK or on its behalf, for reasons of follow up, clinical trial management and using the results of said clinical trial. According to the data privacy regulation, each of these people aforesaid has a right of access, correction, and opposition on their own data through GSK (Clinical Operations Department).

Concerning Data Privacy

In accordance with the applicable data privacy regulation, personal data are processed in a manner that ensures appropriate security, including protection against unauthorized or unlawful processing and against accidental loss, destruction or damage, using appropriate technical or organizational measures. The processing is whether deemed to be compliant with 1 of the methodology of reference (MR-001) or has been the subject of a request for authorization to the CNIL. The Investigator has, regarding the processing data related to her/him, a right of access, of rectification, erasure and of opposition with GSK in accordance with the legal provisions.

Additional inclusion criterion for participants in France: A participant is eligible to be included in the study only if they are either affiliated to or a beneficiary of a social security category.

INVESTIGATIONAL PRODUCT ACCOUNTABILITY, RECONCILIATION, AND DESTRUCTION

In specific situations where institutional practices dictate that the site disposes of and/or destroys IP prior to allowing the "monitor' to verify and document IP accountability, the following applies:

"*During the conduct of the Study, IP will be destroyed by the Institution prior to a GSK* ***"monitor"*** *conducting final investigational product accountability. Institution agrees that such destruction will comply with Institution's investigational product accountability procedures and will provide GSK with investigational product accountability logs and supporting documentation to verify adherence to 'Bonnes Pratiques Cliniques' (decision dated on the 24th of November 2006).*

10.8. Appendix 8: Sensitivity table of sample size based on risk difference between Test (HFA-152a MDI) and Reference treatment (HFA-134a MDI) for participants with at least one AEs, Precision criteria (HW) and 95%CI

N1	N2	P1 (%)	P2 (%)	[P1-P2] (%)	Half-width (HW) (%)	Lower Limit of 95% CI	Upper Limit of 95% CI
300	100	35	32	3	10.62	-7.6	13.6
300	100	37	32	5	10.65	-5.7	15.7
300	100	39	32	7	10.68	-3.7	17.7
300	100	42	32	10	10.72	-0.7	20.7
300	100	69	66	3	10.66	-7.7	13.7
300	100	71	66	5	10.61	-5.6	15.6
300	100	73	66	7	10.56	-3.6	17.6
300	100	76	66	10	10.47	-0.5	20.5

N1 = Number of participants in HFA-152a MDI treatment; N2 = Number of participants in HFA-134a MDI treatment; P1 = Percentage of participants for at least one AEs in HFA-152a MDI treatment; P2 = Percentage of participants for at least one AEs in HFA-134a MDI treatment group.

Note: A total sample size of 400 (as described in Section 9.5), and percentage of participants for at least one AEs in reference (HFA-134a MDI) treatment group (P2) 32%, the half width of the 95% CI for observed risk difference (P1-P2) 10 % between test (HFA-152a MDI) and reference groups (HFA-134a MDI) is estimated to be within 10.72% of point estimate for risk difference. For an example, if the observed risk difference (P1-P2) 10% and P2=32%, the upper limit of the 95% CI for observed risk difference will be 20.7 the lower limit will be 0.7.

10.9. Appendix 9: Protocol amendment history

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

CCI [redacted]

CCI [redacted]

CCI [redacted]
CCI [redacted]
CCI [redacted]
CCI [redacted]
CCI [redacted]
CCI [redacted]
CCI [redacted] Other updates are detailed in the Summary of Changes.

Summary of changes table of previous amendments: {Delete this table if this is the first amendment.}

Section # and title	Description of change	Brief rationale
Multiple	Referral to adolescent patients aged 12 and above updated to adults aged ≥18 years. In addition, all text relating to pediatric or adolescent considerations has been removed.	To reflect available safety information for propellant HFA-152a.
Table 1 and Section 6.6	Addition of order of salbutamol dosing compared with ICS	To better inform investigators.
Section 2.2.5.2 Salbutamol sulfate and HFA-152a	Addition of information from Study 219430.	To match information in IB.
Table 3 and Section 8.2 Efficacy and/or Immunogenicity Assessments	Move of exploratory endpoint to secondary efficacy endpoints.	To address Agency feedback.
Section 4.1	Addition of duration of study for each individual participant.	To provide additional clarity.
Section 4.3	Additional text to support choice of dose in study.	To provide additional justification aligned with current label and post-marketing experience.
Section 5.1 Inclusion Criteria 5, 12,	Reframing of text.	To provide clarity on the inclusion and exclusion criteria and, where relevant, to

Section # and title	Description of change	Brief rationale
Exclusion Criterion 5, 15, 22 and 23	#22 and #23 Additional language added for participants with Gilbert's syndrome, and liver tests	ensure the text is not read as a description of the events. #22 – to use latest GSK standard text for liver safety.
Section 5.3	Addition of a new randomization criteria	To ensure patient safety relating to QTc.
Section 6.1	Change to interval duration of actuations for study intervention	To align with other study documents (e.g., Pharmacy Manual)
Section 8	Added text regarding procedures conducted as part of the participant's routine clinical management and obtained before signing of the ICF	To align with latest GSK standard protocol text.
Section 8.3.8	Added text relating to pregnancy tests	To align with latest GSK standard protocol text.
Section 8.4.5 Pregnancies	Details of collection period for pregnancies in female participants updated from 90 days to 48 hours post last dose of study treatment.	To align the time period for collecting pregnancy information for female participants with the time period for post-intervention contraception
Section 9.5 Sample Size Considerations and Section 11 References	Addition of new language to support inert status of current (reference) propellant HFA-134a.and associated literature references.	To support the 3:1 randomization allocation.
Section 10.1.3 Informed Consent	Addition of data to be collected related to baby in case of unexpected pregnancy	To align with latest GSK standard protocol text.
Section 10.1.5, 10.1.7 and 10.1.8	Addition of information relating to data protection, dissemination, and retention	To align with latest GSK standard protocol text.
Section 10.3.2 Definition of SAE	Addition of language relating to participants with Gilbert's Syndrome	To align with latest GSK standard protocol text.
Global	Correction of grammar, formatting, spelling.	To correct minor errors.

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Reason for signing: Approved	Name: PPD Role: Approver Date of signature: 28-Nov-2024 10:39:26 GMT+0000

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