Clinical Study Report Appendix 16.1.1

Drug Substance	Breztri PT010
Study Code	D5985C00007

Appendix 16.1.1
Protocol and Protocol Amendments

VERSION OF PROTOCOL OR PROTOCOL AMENDMENT

Global Document Name	Version No	Version Date
First final version of the protocol prior to any amendments	1.0	08 December 2022

Clinical Study Protocol	
Study Intervention	Breztri PT010
Study Code	D5985C00007
Version	1.0
Date	08Dec2022

A Randomized, Double-blind, Single Dose, 2-way Crossover Study to Assess Bronchospasm Potentially Induced by the Hydrofluoroolefin (HFO) Metered Dose Inhaler (MDI) Propellant as Compared with the Hydrofluoroalkane (HFA) MDI Propellant in Participants with Asthma, Well Controlled or Partially Controlled on Short-acting beta$_2$-agonists (SABA) with or without Low-Dose Inhaled Corticosteroids (ICS)

A multicenter, 2-way crossover, phase IIIb, double-blind study to assess bronchospasm potentially induced by HFO MDI as compared with HFA MDI in participants with asthma, well controlled or partially controlled, on SABA with or without low-dose ICS

Sponsor Name: AstraZeneca AB

Legal Registered Address: AstraZeneca AB, 151 85 Södertälje, Sweden

Manufacturer: AstraZeneca AB, 151 85 Södertälje, Sweden

Regulatory Agency Identifier Number(s)

Registry	**ID**
IND	118313

This protocol has been subject to a peer review according to AstraZeneca Standard procedures. The protocol is publicly registered and the results are disclosed and/or published according to the AstraZeneca Global Standard - Bioethics and in compliance with prevailing laws and regulations.

Version Scope: Global

Brief Title: A study to assess bronchospasm potentially induced by HFO MDI as compared with HFA MDI in participants with well controlled or partially controlled asthma

Study Phase: Phase IIIb

Study Clinical Lead Name and Contact Information will be provided separately.

Study Clinical Lead is responsible for the clinical integrity of the study (for example, the study physician or scientist).

Coordinating Investigator

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LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
ACQ	Asthma Control Questionnaire
ADE	Adverse device effect
AE	Adverse event
AUC	Area under the curve
$AUC_{0\text{-}15\ min}$	Area under the curve from 0 to 15 minutes
BGF	Budesonide, glycopyrronium, and formoterol fumarate
CFR	Code of Federal Regulations
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
COVID-19	Coronavirus disease 2019
CRO	Contract research organisation
CSR	Clinical study report
DPI	Dry powder inhaler
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EU	European Union
FEV_1	Forced expiratory volume in 1 second
GCP	Good Clinical Practice
GINA	Global Initiative for Asthma
GWP	Global warming potential
HBS	Human biological sample(s)
HFA	Hydrofluoroalkane
HFO	Hydrofluoroolefin
IATA	International Air Transport Association
IB	Investigator's Brochure
ICE	Intercurrent event
ICF	Informed consent form
ICH	International Council for Harmonisation
ICS	Inhaled corticosteroid
IMP	Investigational medicinal product
IND	Investigational New Drug
IRB	Institutional review board

Abbreviation or special term	Explanation
IRT	Interactive Response Technology
LABA	Long-acting beta$_2$-agonist
MDI	Metered dose inhaler
NI	Non-inferiority
NIMP	Non-investigational medicinal product
RTSM	Randomisation and Trial Supply Management
SADE	Serious adverse device effect
SAE	Serious adverse event
SABA	Short-acting beta$_2$-agonists
SAP	Statistical Analysis Plan
SoA	Schedule of activities
USADE	Unanticipated serious adverse device effect

1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Randomized, Double-Blind, Single Dose, 2-way Crossover Study to Assess Bronchospasm Potentially Induced by the Hydrofluoroolefin (HFO) Metered Dose Inhaler (MDI) Propellant as Compared with the Hydrofluoroalkane (HFA) MDI Propellant in Participants with Asthma, Well Controlled or Partially Controlled on Short-acting beta$_2$-agonists (SABA) with or without Low-Dose Inhaled Corticosteroids (ICS)

Brief Title: A study to assess bronchospasm potentially induced by HFO MDI as compared with HFA MDI in participants with well controlled or partially controlled asthma

Regulatory Agency Identifier Number(s):

Registry	ID
IND	118313

Rationale:

The current HFA (HFA-134a) propellant in AstraZeneca's MDI type treatment is known to have a relatively high global warming potential (GWP) compared to some new alternative propellants, and contributes substantially to AstraZeneca's carbon footprint. In order to address this issue, AstraZeneca is evaluating an MDI reformulated with HFO (HFO-1234ze) propellant, which has a near zero GWP and will allow patients to continue to use MDI type treatments, while contributing to AstraZeneca's sustainability efforts. As part of the clinical development program for gaining regulatory approval for budesonide/glycopyrronium (glycopyrrolate)/formoterol fumarate (BGF) MDI HFO and for supportting other potential products, this study is being conducted to assess if HFO MDI induces a potential change in forced expiratory volume in 1 second (FEV_1) as compared to HFA MDI in participants with well controlled or partially controlled asthma, as primarily evaluated by change from baseline in FEV_1 $AUC_{0\text{-}15\ min}$ post-dose.

Objectives, Endpoints:

Objectives	Endpoints	Strategy for ICEs
Primary		
• To assess the potential change in FEV_1 induced by HFO MDI as compared with HFA MDI in participants with asthma	• Change from baseline in FEV_1 $AUC_{0\text{-}15\ min}$ post-dose	• Principal stratum estimand - An ICE that occurs will be considered an important protocol deviation and data from that participant

		will be excluded in the primary analysis.
Secondary		
• To assess the potential of bronchospasm induced by HFO MDI as compared with HFA MDI in participants with asthma	• Cumulative incidence of bronchospasm* events	• NA
• To assess the safety and tolerability of HFO MDI as compared with HFA MDI in participants with asthma	• Safety and tolerability will be evaluated in terms of AEs	• NA

*An event of bronchospasm is defined as a reduction in FEV_1 of > 15% from baseline (i.e., the FEV_1 value obtained within 30 minutes prior to study intervention administration) at 5 or 15 minutes post-dose with associated symptoms of wheezing, shortness of breath, or cough.
Abbreviations: AE = adverse event; $AUC_{0\text{-}15\ min}$ = area under curve from 0 to 15 minutes; FEV_1 = forced expiratory volume in 1 second; HFA = hydrofluoroalkane; HFO = hydrofluoroolefin; ICE = intercurrent event; MDI = metered dose inhaler; NA = not applicable.

For tertiary/exploratory objectives, see Section 3 of the protocol.

Overall Design Synopsis:

This is a phase 3b, multicentre, randomized, double-blind, single-dose crossover study comparing the safety and tolerability of HFO MDI with HFA MDI delivered in participants with well controlled or partially controlled asthma defined as an Asthma Control Questionnaire 5 (ACQ-5) score < 1.5, and on current treatment for asthma, including, low-dose inhaled corticosteroids (ICS) daily or low-dose ICS/formoterol as needed (not approved in the US), or short-acting $beta_2$-agonists (SABA) as needed, or low-dose ICS whenever SABA as needed is used.

This study will be conducted at approximately 5 sites in the US and will randomize approximately 52 adult participants to achieve 46 completers.

All participants will remain on their current treatment for asthma, including, low-dose ICS daily or low-dose ICS/formoterol as needed (not approved in the US), or SABA as needed, or low-dose ICS whenever SABA as needed is used, during the screening, treatment, and washout periods.

Note: Albuterol/salbutamol must be withheld for at least 8 hours prior to FEV_1 measurements.

CCI participants' eligibility will be verified, and whether the participant has an ACQ-5 score < 1.5 and a pre-dose FEV_1 > 60% will be assessed. Participants will remain on their current treatment for asthma, including, low-dose ICS daily or low-dose ICS/formoterol as

needed (not approved in the US), or SABA as needed, or low-dose ICS whenever SABA as needed is used, through the study.

CCI

[redacted]

[redacted]

[redacted]

Brief Summary:

The purpose of this study is to assess bronchospasm potentially induced by hydrofluoroolefin (HFO) metered dose inhaler (MDI) as compared with hydrofluoroalkane (HFA) MDI in participants with asthma, well controlled or partially controlled on treatment for asthma, including, low-dose inhaled corticosteroid (ICS) daily or low-dose ICS/formoterol as needed (not approved in the US), or short-acting beta$_2$-agonists (SABA) as needed, or low-dose ICS whenever SABA as needed is used.

Study details include:

- CCI [redacted]

Disclosure Statement: This is a 2-way crossover study with 2 treatment arms that is participant, sponsor, and investigator blinded.

Number of Participants:

It is estimated that approximately 52 participants with well controlled or partially controlled asthma will be randomized to achieve 46 completers, with 26 participants in each treatment

sequence. This assumes a 10% dropout rate.

Study Arms and Duration:

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Study treatment will be administered via MDI device as 4 inhalations:

- Treatment A: HFO propellant only MDI; 4 inhalations per dose – test formulation
- Treatment B: HFA propellant only MDI; 4 inhalations per dose – reference formulation

Participants will be randomized in a ratio of 1:1 to receive treatments in one of two possible treatment sequences: A followed by B, or B followed by A.

Data Monitoring/Other Committee: No

Statistical Methods

The null hypothesis tested in this study for the primary objective is that HFO MDI (test arm) is inferior to HFA MDI (reference arm) in terms of the change from baseline in FEV_1 $AUC_{0\text{-}15\ min}$, versus the alternative hypothesis that the test arm is non-inferior to the reference arm. The non-inferiority (NI) margin is set at –200 mL. If the lower limit of the 2-sided 95% confidence interval (CI) for the difference in the mean change from baseline of HFO MDI minus HFA MDI is > −200 mL, then NI will be demonstrated.

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The following populations are defined:

Population/Analysis set	Description
Enrolled	All participants who sign the ICF. The Enrolled Analysis Set will be used to summarise disposition.
Randomised	All enrolled participants who are randomised to one of the study treatment sequences. The Randomised Analysis Set will be used to summarise baseline characteristics.
Safety	All participants who are randomised to one of the study treatment sequences and have received any amount of the study treatment (ie, at least 1 puff). Participants will be analysed according to the actual treatment received.

Abbreviations: ICF = informed consent form.

For secondary safety endpoints and other safety assesssments, no formal statistical analyses will be performed. Descriptive summaries will be produced and any clinically relevant differences will be noted and discussed.

Demographic and baseline characteristics data will be summarised by treatment sequence. Categorical variables will be summarised using frequency and percentages, where the denominator for calculation is the underlying analysis set population unless otherwise specified. Continuous variables will be summarised with descriptive statistics using number of available observations, mean, standard deviation, median, minimum, and maximum, and quartiles where appropriate.

The primary endpoint is defined as change from baseline in FEV_1 $AUC_{0\text{-}15\ min}$ post-dose. The analysis will be performed based on the Safety Analysis Set using a Principal Stratum estimand.

Change in FEV_1 $AUC_{0\text{-}15\ min}$ post-dose will be calculated from FEV_1 change from baseline at 5 and 15 minutes post-dose using the trapezoidal rule, divided by the actual observation time from the first to the last non-missing value, for each treatment period. Baseline is the FEV_1 value obtained within 30 minutes prior to study intervention administration in each treatment period.

For the primary endpoint, a Mixed Model Repeated Measures analysis with treatment sequence, period, average baseline FEV_1, and treatment as fixed effects, and participant within sequence as the random effect will be used. Average baseline (period-specific baseline FEV_1 averaged over the treatment periods) is included to account for cross-level bias.

Adjusted mean change from baseline estimates per treatment group and corresponding 2-sided 95% CIs along with an overall estimate of the treatment difference (HFO MDI minus HFA MDI) will be presented. If the lower limit of the 2-sided 95% CI for the difference in mean change from baseline of HFO MDI minus HFA MDI is > −200 mL, the null hypothesis of

inferiority will be rejected and NI will be demonstrated.

Descriptive summaries for FEV_1 at 30 minutes pre-dose, 5 and 15 minutes post-dose, and change in FEV_1 $AUC_{0\text{-}15\ min}$ post-dose, will be reported by treatment and period.

The secondary endpoint is defined as cumulative incidence of bronchospasm events. The analysis will be performed based on the Safety Analysis Set. McNemar's test for the bronchospasm event rate analysis will be applied given the crossover design. For each treatment, the proportion of participants who experience an event along with the 2-sided 95% CI (if applicable) will be reported. The difference in proportions along with the 2-sided 95% CI (if applicable) will also be reported.

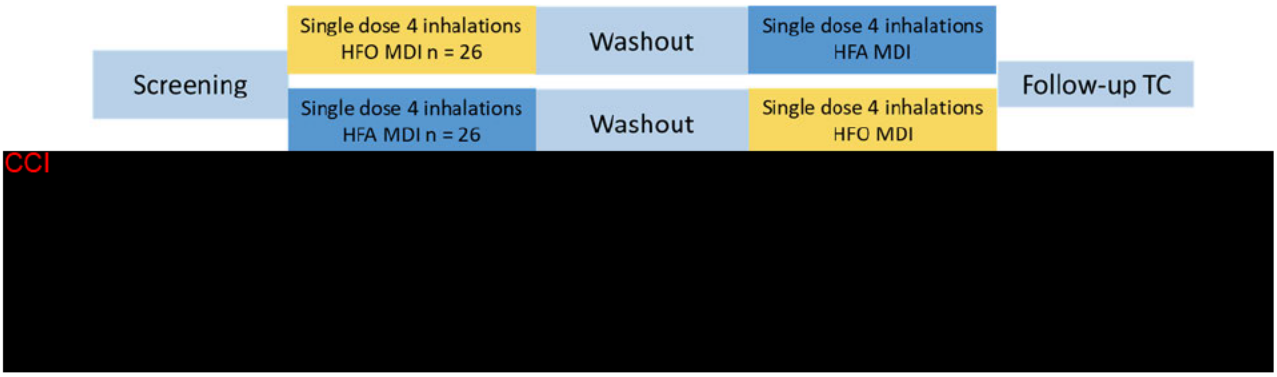
The number and rate of adverse events will be summarised for each treatment in the Safety Analysis Set.

CCI [redacted]

No interim analysis is planned for this study.

1.2 Schema

Figure 1 Study Design



CCI [redacted]

Study participants will be randomised to 2 treatment sequences (n = 26 per sequence) with the following treatment schemes:

- AB - TP1 (single dose – 4 inhalations HFO MDI) followed by TP2 (single dose – 4 inhalations HFA MDI)
- BA - TP1 (single dose – 4 inhalations HFA MDI) followed by TP2 (single dose – 4 inhalations HFO MDI).

Abbreviations: DPI = dry powder inhaler; HFA = hydrofluoroalkane; HFO = hydrofluoroolefin; ICS = inhaled corticosteroid; MDI = metered dose inhaler; TC = telephone contact; TP = treatment period.

1.3 Schedule of Activities

Table 1 Schedule of Activities

CCI								Details in protocol section or appendix
Informed consent [d]	X							Section 5.1
Inclusion/exclusion criteria	X	X						Sections 5.1 and 5.2
Verify continued eligibility				X	X			Sections 5.1 and 5.2
ACQ-5	X [e]							Section 7.3.1
Randomisation		X						Section 6.3
Routine clinical procedures								
Demographics and medical/surgical history	X							Sections 5.1, 5.2, and 7.1.1
Prior/concomitant medication review	X	X		X	X	X	X	Section 6.9
Spirometry [f]	X	X [g]		X [g]	X	X		Section 7.3.2
Routine safety measurements								
AE	X	X		X	X	X	X	Section 7.4 and Appendix B
Pregnancy testing [h]	X	X		X				Sections 5.1 and 7.3.3.1
FSH [h]	X							Section 7.3.3.1
(Local) Clinical laboratory tests (blood and urine)	X							Section 7.1.6
Physical examination	X	X [i]		X [i]		X		Section 7.1.3

Table 1 Schedule of Activities

CCI [redacted]								Details in protocol section or appendix
Height and weight	X							Section 7.1.2
Vital signs	X	X [i]		X [i]		X		Section 7.1.4
12-lead ECG	X							Section 7.1.5
Study intervention administration								
Inhalation technique verification	X	X		X				Section 6
Administer blinded study intervention in clinic		X		X				Sections 4.1 and 6

[a] All participants should remain on their current treatment for asthma through the study, including, low-dose ICS daily or low-dose ICS/formoterol as needed (not approved in the US), or SABA as needed, or low-dose ICS whenever SABA as needed is used.

[b] Assessments done at unscheduled visits are at the discretion of the Investigator.

[c] CCI [redacted] sites should call participants 1 to 2 days before each scheduled in-clinic visit to remind them of the upcoming visit and related restrictions/requirements, including withholding morning dose of asthma medications on the day of on-site study visit.

[d] ICF could be signed up to 7 days prior to CCI [redacted]

[e] Whether the participant has an ACQ-5 score < 1.5 and a pre-dose FEV_1 > 60% will be assessed at CCI [redacted] for study participation.

[f] Albuterol/salbutamol must be withheld for at least 8 hours prior to FEV_1 measurements. All LABAs, formoterol included and combinations there-of, must be withheld for 48 hours prior to spirometry.

[g] Pre-dose spirometry will be performed at 30 minutes prior to dosing and post-dose spirometry will be performed at 5, 15, and 30 minutes after dosing. During both Treatment Periods, if FEV_1 drops > 15% from baseline, measurements should be repeated at Investigator's discretion until FEV_1 values are within 10% of baseline performed that day.

[h] A serum pregnancy test CCI [redacted] and urine pregnancy tests at following visits will be performed for women of childbearing potential. A serum FSH test will be conducted at CCI [redacted] only, for women who have been amenorrhoeic for 12 months without an alternative medical cause, to confirm postmenopausal status.

[i] Assessments will be performed prior to dosing. Brief physical examinations will be performed at CCI [redacted]

Abbreviations: ACQ-5 = Asthma Control Questionnaire 5; AE = adverse event; ECG = electrocardiogram; FEV_1 = forced expiratory volume in 1 second; FSH = follicle-stimulating hormone; ICF = informed consent form; ICS = inhaled corticosteroid; LABA = long-acting $beta_2$-agonist; TC = telephone contact; WD = withdrawal.

2 INTRODUCTION

The sponsor, AstraZeneca, has developed orally inhaled drug products containing budesonide (an inhaled corticosteroid; ICS), glycopyrronium (a long-acting muscarinic antagonist), and formoterol fumarate (a long-acting beta$_2$-agonist) (BGF metered dose inhaler [MDI]) for the treatment of asthma. These drug products are formulated as a suspension with micronized active pharmaceutical ingredients and Co-Suspension™ Delivery Technology in MDIs. The Co-Suspension Delivery Technology of spray-dried porous particles comprised of the phospholipid 1,2-distearoyl-sn-glycero-3-phosphocholine and calcium chloride suspended in a hydrofluoroalkane (HFA) propellant. Hydrofluoroolefin (HFO) has been identified by sponsor as a novel propellant potentially suitable for replacement of HFA-134a in the BGF MDI HFA product for the purpose of lowering global warming potential (GWP).

The test and reference formulation used in this study is an MDI with a desiccated flow path containing HFA or HFO propellant only.

2.1 Study Rationale

The current HFA (HFA-134a) propellant in AstraZeneca's MDI type treatments is known to have a relatively high GWP compared to some new alternative propellants, and contributes substantially to AstraZeneca's carbon footprint. In order to address this issue, AstraZeneca is evaluating an MDI reformulated with a next generation propellant HFO (HFO-1234ze), which has a near zero GWP and will allow patients to continue to use MDI type treatments, while contributing to AstraZeneca's sustainability efforts.

As part of the clinical development program for gaining regulatory approval for BGF MDI HFO for the treatment of asthma and chronic obstructive pulmonary disease (COPD), and for supporting other potential products, this study is being conducted to assess if HFO MDI induces a potential change in FEV_1 as compared to HFA MDI in participants with well controlled or partially controlled asthma, as primarily evaluated by change from baseline in forced expiratory volume in 1 second (FEV_1) area under curve from 0 to 15 minutes ($AUC_{0\text{-}15\ min}$) post-dose .

2.2 Background

Asthma is a heterogeneous disease that is characterized by chronic airway inflammation and bronchial hyperreactivity. 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 obstruction [Global Initiative for Asthma (GINA) Guidance 2022].

The long-term goals of asthma management are risk reduction and symptom control. The aim is to reduce the patient burden and risk of asthma-related death, exacerbations, airway damage, and medication side effects. The patient's own goals regarding their asthma and its

treatment should also be identified [GINA 2022]. This concept encompasses 2 components: (1) patient's recent clinical status and current disease impact which includes assessment of symptoms, night awakenings, use of rescue medication, and lung function and (2) patient assessment for future risk of exacerbations, decline in lung function, or treatment-related side effects.

AstraZeneca has developed MDI products with HFA for the treatment of asthma. Their formulations are generally comprised of a therapeutic material, a propellant, co-solvents, and surfactants. The HFA MDI products are formulated with HFA-134a propellant, a liquefied compressed gas, in which the active pharmaceutical ingredients are suspended. HFA-134a is a common propellant in pharmaceutical MDI products that provides the force to generate an aerosol to deliver a product inhalation or dose. More information on the HFA MDI drug product is provided in the BGF MDI Investigator's Brochure (IB).

The current HFA (HFA-134a) propellant in AstraZeneca's MDI type treatments is known to have a relatively high GWP compared to some alternative propellants, and contributes substantially to AstraZeneca's carbon footprint. HFO-1234ze, which is available for industrial uses such as refrigeration, has been further purified by the manufacturer through fractional distillation to provide a propellant of suitable grade for clinical studies. HFO-1234ze has a near-zero GWP and very low photochemical reactivity. In addition, it has very similar physical properties to HFA-134a, which are expected to have comparable performance of the HFA MDI product. The sponsor has identified HFO-1234ze as a novel propellant potentially suitable for replacement of HFA-134a in the BGF MDI HFA product.

Study D5985C00001 assessed the safety and tolerability of a combination of BGF when administered as single doses in 3 different propellant formulations: BGF MDI HFO, BGF MDI hydrofluorocarbon, and BGF MDI HFA in 47 healthy volunteers. The combination of BGF when administered as single doses in 3 different propellant formulations demonstrated a similar and acceptable safety profile among 3 formulations and was well tolerated in healthy volunteers. The development of BGF MDI HFO products including non-clinical toxicology results and study D5985C00001 results is specified in IB Section 3.2.3, Section 5.2.5, and Appendix A.

To further support HFO-1234ze regulatory applications, this study will assess the safety and tolerability of HFO-1234ze (HFO MDI; propellant only) compared with HFA-134a (HFA MDI; propellant only) delivered in participants with well controlled or partially controlled on treatment for asthma, including, low-dose ICS daily or low-dose ICS/formoterol as needed (not approved in the US), or short-acting beta$_2$-agonists (SABA) as needed, or low-dose ICS whenever SABA as needed is used, defined as an Asthma Control Questionnaire 5 (ACQ-5) score < 1.5.

2.3 Benefit/Risk Assessment

More detailed information about the known and expected benefits and potential risks of HFO MDI and HFA MDI may be found in the IB.

2.3.1 Risk Assessment

Table 2 Risk Assessment

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
Study intervention		
Safety (ie, risk of bronchospasm)	Study intervention is a pMDI containing HFA or HFO propellant only.	Participants will be well controlled or partially controlled on treatments for asthma, including, low-dose ICS daily or low-dose ICS/formoterol as needed (not approved in the US), or SABA as needed, or low-dose ICS whenever SABA as needed is used.
Study procedures		
Risk of bronchospasm	Handling of bronchospasm events by site staff in case such event happens	Sites will be equipped with well trained site staff to deal with bronchospasm events. Sites will also provide appropriate medications for bronchospasm treatment. In the event of a bronchospasm, participants could be discharged should FEV_1 values be within 10% of the baseline FEV_1 performed that day, or at investigator discretion.
Trial integrity	Improper blinding leading to bias	Participants should not be able to distinguish the propellants by colour or smell since they are similar. There are few participants and only 2 products that need to be blinded.
Study population		
Safety	1. Asthma stability is related to seasonality. 2. Excessive hyperreactivity may happen because some patients that are perceived as having mild	1. For inclusion criteria, participants with asthma ACQ-5 score < 1.5 will be enrolled, which is also an indication of the stability of asthma.

Table 2 Risk Assessment

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
	asthma can actually react with a dramatic decline in FEV_1. Sometimes this issue could not be recognized prior.	2. Participants will be well controlled or partially controlled on treatments for asthma, including, low-dose ICS daily or low-dose ICS/formoterol as needed (not approved in the US), or SABA as needed, or low-dose ICS whenever SABA as needed is used.
Medical device		
N/A	N/A	N/A

Abbreviations: ACQ-5 = Asthma Control Questionnaire 5; FEV_1 = forced expiratory volume in 1 second; HFA = hydrofluoroalkane; HFO = hydrofluoroolefin; ICS = inhaled corticosteroid; N/A = not applicable; pMDI = pressurized metered dose inhaler; SABA = short-acting $beta_2$-agonists.

2.3.2 Hydrofluoroolefin

Hydrofluoroolefin was negative in a battery of genotoxicity tests. It was also very well tolerated in a series of single and repeat-dose inhalation studies of 3 months (mouse), 6 months (rat), and 9 months (dog). Refer to the IB for more details on non-clinical studies with HFO.

2.3.3 Risk Assessment for COVID-19 Pandemic

AstraZeneca is committed to supporting the safety and well-being of the study participants, investigators, and site staff. All local regulations and site requirements are being applied in the countries that are affected by the coronavirus disease 2019 (COVID-19) pandemic. A benefit/risk assessment has been determined to be positive for the participants that are planned to be enrolled in the proposed clinical trial. As the COVID-19 situation evolves, investigators must use their best judgment to minimize risk to participants during the conduct of the study.

Measures to mitigate the additional risks caused by COVID-19 are:

- This study is going to start enrolling only when the sponsor and contract research organization (CRO) in collaboration deem it is safe to start the study. In addition, the study will not start until the local confinement measures or other safety restrictions linked to the COVID-19 pandemic are lifted by the local authorities.
- Current national laws and local recommendations for prevention of pandemic will be strictly adhered to.

- Participants will be closely monitored for any signs and symptoms of COVID-19, including fever, dry cough, dyspnea, sore throat, and fatigue throughout the study. Once clinical signs of infection are reported by participants, the investigator needs to determine whether samples can be collected, and safety data can be recorded on site. If not, adverse events (AEs) and concomitant medications will be obtained via phone calls. Daily body temperature measurements during outpatient visits will be implemented.
- The investigator will not dose participants upon identification of any signs of COVID-19 infection.
- The probability of virus transmission will be controlled as much as possible by:
  - Advising the participant to adhere to local requirements for reduction of the public exposure while ambulatory.
  - If applicable, all participants will be contacted by phone 1 day prior to every visit for assessing COVID-19 symptoms and signs and are asked not to attend the site in case of suspected reports. In addition, participants are asked for any contact with a person who has tested positive for severe acute respiratory syndrome coronavirus 2. If applicable, participants will be referred to the local health care system for further follow-up and treatment.
  - Physical distancing and person-to-person contact restrictions will be applied during site visits.
  - Where physical distancing is not possible, personal protective equipment will be used by participants (surgical face masks, gloves) and staff (for example, but not limited to masks, gloves, protectors, medical suits) if deemed appropriate by the investigator and site staff and guided by local requirements.
  - Logistical improvements of the site and structural measures of the study site building will be implemented to further improve physical distancing.

2.3.4 Benefit Assessment

No direct benefit for individuals in this study is expected. Indirect benefits include assisting with clinical development of MDI products with a lower GWP.

2.3.5 Overall Benefit/Risk Conclusion

Considering the measures taken to minimize risk to participants participating in this study, the potential risks identified in association with HFO MDI are justified by the anticipated indirect benefits that may be afforded with regard to a reduced carbon footprint of MDI products.

3 OBJECTIVES AND ENDPOINTS

Table 3 Objectives and Endpoints

Objectives	Endpoints	Strategy for ICEs
Primary		
• To assess the potential change in FEV_1 induced by HFO MDI as compared with HFA MDI in participants with asthma	• Change from baseline in FEV_1 $AUC_{0\text{-}15\ min}$ post-dose	• Principal stratum estimand - An ICE that occurs will be considered an important protocol deviation and data from that participant will be excluded in the primary analysis.
Secondary		
• To assess the potential of bronchospasm induced by HFO MDI as compared with HFA MDI in participants with asthma	• Cumulative incidence of bronchospasm* events	• NA
• To assess the safety and tolerability of HFO MDI as compared with HFA MDI in participants with asthma	• Safety and tolerability will be evaluated in terms of AEs	• NA
CCI [redacted]		
[redacted]	[redacted]	[redacted]

*An event of bronchospasm is defined as a reduction in FEV_1 of > 15% from baseline (ie, the FEV_1 value obtained within 30 minutes prior to study intervention administration) at 5 or 15 minutes post-dose with associated symptoms of wheezing, shortness of breath, or cough.

Abbreviations: AE = adverse event; $AUC_{0\text{-}15\ min}$ = area under curve from 0 to 15 minutes; FEV_1 = forced expiratory volume in 1 second; HFA = hydrofluoroalkane; HFO = hydrofluoroolefin; ICE = intercurrent event; MDI = metered dose inhaler; NA = not applicable.

4 STUDY DESIGN

4.1 Overall Design

This is a phase 3b, multicentre, randomized, double-blind, single-dose crossover study comparing the safety and tolerability of HFO MDI with HFA MDI delivered in participants with well controlled or partially controlled asthma defined as an ACQ-5 score < 1.5. Eligible participants are at least 18 years of age and no older than 45 years of age and are required to have asthma as defined by GINA guidelines (GINA 2022). Participants are required to be well controlled or partially controlled on their current treatment for asthma, including, low-dose ICS daily or low-dose ICS/formoterol as needed (not approved in the US), or SABA as needed, or low-dose ICS whenever SABA as needed is used. The primary objective is to assess the potential change in FEV_1 induced by HFO MDI as compared with HFA MDI in participants with asthma.

This study will be conducted at approximately 5 sites in the US and will randomize approximately 52 adult participants to achieve 46 completers.

CCI [redacted]

Single dose study treatment will be administered via MDI device as 4 inhalations:

- Treatment A: HFO propellant only MDI; 4 inhalations per dose – test formulation
- Treatment B: HFA propellant only MDI; 4 inhalations per dose – reference formulation

Participants will be randomized in a ratio of 1:1 to receive treatments in one of two possible treatment sequences: A followed by B, or B followed by A.

All participants will remain on their current treatment for asthma, including, low-dose ICS daily or low-dose ICS/formoterol as needed (not approved in the US), or SABA as needed, or low-dose ICS whenever SABA as needed is used, during the screening, treatment, and washout periods.

Note: Albuterol/salbutamol must be withheld for at least 8 hours prior to FEV_1 measurements.

CCI [redacted] participants' eligibility will be verified, and whether the participant has an ACQ-5 score < 1.5 and a pre-dose FEV_1 > 60% will be assessed. Participants will remain on their

current treatment for asthma, including, low-dose ICS daily or low-dose ICS/formoterol as needed (not approved in the US), or SABA as needed, or low-dose ICS whenever SABA as needed is used, through the study.

CCI

[redacted]

Note: An event of bronchospasm is defined as a reduction in FEV_1 of > 15% from baseline (ie, the FEV_1 value obtained within 30 minutes prior to study intervention administration) at 5 or 15 minutes post-dose with associated symptoms of wheezing, shortness of breath, or cough.

For details on study interventions given during the study, see Section 6.1. The study schematic with flow of events for all treatments, depending on the participant's assigned randomization is presented in Figure 1. The schedule of activities (SoA) displaying assessments/tasks and timepoints is presented in Table 1.

4.2 Scientific Rationale for Study Design

The primary objective is to assess the potential change in FEV_1 induced by HFO MDI as compared with HFA MDI in participants with asthma. As such, the primary endpoint is the change from baseline in FEV_1 $AUC_{0\text{-}15\ min}$ post-dose. The secondary objectives of the study are to assess the potential of bronchospasm induced by HFO MDI as compared to HFA MDI in participants with asthma, measured as the cumulative incidence of bronchospasm events, and to assess the safety and tolerability of HFO MDI as compared to HFA MDI in participants with asthma, evaluated in terms of AEs. An event of bronchospasm is defined as a reduction in FEV_1 of > 15% from baseline (ie, the FEV_1 value obtained within 30 minutes prior to study intervention administration) at 5 or 15 minutes post-dose.

The study is double blinded to minimize any bias from the participants, investigators, or sponsor that may affect study results. Participants will be randomised to prevent bias in allocation of treatments in each treatment period, with each participant serving as his/her own matched control.

This study will enroll participants with well controlled or partially controlled asthma defined by ACQ-5 score < 1.5 who are on current treatment with low-dose ICS daily or low-dose ICS/formoterol as needed (not approved in the US), or SABA as needed, or low-dose ICS whenever SABA as needed is used. As patients with asthma have hyperreactive airways and could be more prone to develop a bronchospasm as compared with patients with COPD, asthma patients were chosen for this study even though the MDI products are intended to be used in both populations. Participants in the study will be maintained on their current treatment, open-label, at study entry.. This would allow an effective assessment of potential events of bronchospasm should they be induced by HFO propellant in comparison to the HFA propellant in the study.

4.2.1 Participant and Site Input Into Design

Gathering input on study design from both investigators and aimed study population has been part of the preparations for this study and development of this Clinical Study Protocol. This aims to provide opportunities for informing study design, improving operational aspects of the study, reducing patient/site burden and retaining interest, enthusiasm, and engagement in a study. Investigator input has been provided by potential sites as part of the study feasibility evaluation. Participant input has been obtained from similar programs/studies where interviews have been held with asthma patients.

4.3 Justification for Dose

The dose of BGF MDI HFA is 2 inhalations per dose for a total of 4 inhalations per day. As there is no regulatory or company precedent for dosing in this type of study, a single dose of 4 inhalations of HFA/HFO propellant will be administered, which is the same dose as the maximum daily dose of propellant administered with BGF MDI HFA. This dose is well within the safety margin of the non-clinical exposure data.

4.4 End-of-study Definition

For the purpose of clinical trial transparency, the definition of the end of the study differs under FDA and EU regulatory requirements:

European Union requirements define study completion as the last visit of the last subject for any protocol-related activity.

Food and Drug Administration requirements defines 2 completion dates:

Primary Completion Date – the date that the final participant is examined or receives an intervention for the purposes of final collection of data for the primary outcome measure, whether the clinical study concluded according to the pre-specified protocol or was terminated. In the case of clinical studies with more than one primary outcome measure with different completion dates, this term refers to the date on which data collection is completed for all of the primary outcomes.

Study Completion Date – the date the final participant is examined or receives an intervention for purposes of final collection of data for the primary and secondary outcome measures and AEs (for example, last participant's last visit), whether the clinical study concludes according to the pre-specified protocol or is terminated.

A participant is considered to have completed the study if they have completed all phases of the study including the last scheduled treatment period shown in the SoA (Table 1).

5 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrolment 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:

Age

1 Male and female participant must be 18 to 45 years of age inclusive, at the time of signing the informed consent form (ICF).

Type of Participant and Disease Characteristics

2 Participants who have a documented history of physician-diagnosed asthma ≥ 12 months prior to Visit 1, according to GINA guidelines (GINA 2022).

3 Participants who are well controlled or partially controlled on their current treatment for asthma, including, low-dose ICS daily or low-dose ICS/formoterol as needed (not approved in the US), or SABA as needed, or low-dose ICS whenever SABA as needed is used (low-dose ICS as defined by GINA 2022 in Table 4), for 4 weeks prior to screening.

4 ACQ-5 total score < 1.5 at CCI

5 A pre-bronchodilator FEV_1 > 60% predicted normal value at CCI

6 Demonstrate acceptable MDI administration technique.

Sex and Contraceptive/Barrier Requirements

7 Females must be not of childbearing potential, or should be using a form of highly effective birth control as defined below:

- Female participants: Women not of childbearing potential are defined as women who are either permanently sterilised (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy), or who are postmenopausal. Women included in this study will be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatment and follicle-stimulating hormone levels in the postmenopausal range.
- Female participants of childbearing potential must use one highly effective form of birth control. A highly effective method of contraception is defined as one that can achieve a failure rate of less than 1% per year when used consistently and correctly. At enrolment, women of childbearing potential who are sexually active with a non-sterilised male partner should be stable on their chosen method of highly effective birth control, as defined below, and willing to remain on the birth control until at least 14 days after last dose of study intervention. Cessation of contraception after this point should be discussed with a responsible physician. Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method are not acceptable methods of contraception. Female condom and male condom should not be used together. All women of childbearing potential must have a negative serum pregnancy test result [redacted]
- Highly effective birth control methods are listed below:
  - Total sexual abstinence is an acceptable method provided it is the usual lifestyle of the participant (defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments). Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of exposure to study intervention, and withdrawal are not acceptable methods of contraception.
  - Contraceptive subdermal implant
  - Intrauterine device or intrauterine system
  - Oral contraceptive (combined or progesterone only)
  - Injectable progestogen
  - Contraceptive vaginal ring
  - Percutaneous contraceptive patches
  - Male partner sterilisation with documentation of azoospermia prior to the female participant's entry into the study, and this male is the sole partner for that participant. The documentation on male sterility can come from the site

personnel's review of participant's medical records, medical examination and/or semen analysis or medical history interview provided by her or her partner.

- Bilateral tubal ligation

Informed Consent

8 Capable of giving signed informed consent as described in Appendix A which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

5.2 Exclusion Criteria

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

Medical Conditions

1 Life-threatening asthma defined as a history of significant asthma episode(s) requiring intubation associated with hypercapnia, respiratory arrest, hypoxic seizures, or asthma related syncopal episode(s).

2 Current smokers, former smokers with > 10 pack-years history, or former smokers who stopped smoking < 6 months prior to Visit 1 (including all forms of tobacco, e-cigarettes or other vaping devices, and marijuana).

3 Historical or current evidence of a clinically significant disease including, but not limited to: cardiovascular, hepatic, renal, hematological, neurological, endocrine, gastrointestinal, or pulmonary (e.g., active tuberculosis, bronchiectasis, pulmonary eosinophilic syndromes, COPD, and uncontrolled severe asthma). Significant is defined as any disease that, in the opinion of the investigator, would put the safety of the participant at risk through participation, or that could affect the safety/tolerability analysis.

4 Any respiratory infection or asthma exacerbation treated with systemic corticosteroids and/or additional ICS treatment in the 8 weeks prior to Visit 1 and throughout the screening period.

5 Hospitalization for asthma within 1 year prior to Visit 1.

6 Admission to intensive care unit or mechanical ventilation due to asthma exacerbation.

7 Known history of drug or alcohol abuse within 12 months of Visit 1.

Prior/Concomitant Therapy

8 Do not meet the stable dosing period prior to Visit 1 (see Table 5) or unable to abstain from protocol-defined prohibited medications during screening and treatment periods (see Table 6 and Table 7).

9 Receipt of COVID-19 vaccine (regardless of vaccine delivery platform, e.g., vector, lipid nanoparticle) ≤ 7 days prior to Visit 1 (from last vaccination or booster dose).

Prior/Concurrent Clinical Study Experience

10 Participation in another clinical study with an investigational product administered within 30 days or 5 half-lives (whichever is longer).

11 Participants with a known hypersensitivity to HFO or HFA or any of the excipients of the product.

12 Previously randomised into a study with an HFO-containing MDI.

Diagnostic Assessments

13 Any clinically relevant abnormal findings in physical examination, clinical chemistry, hematology, urinalysis, vital signs, or electrocardiogram (ECG), which in the opinion of the investigator, may put the participant at risk because of his/her participation in the study.

Note: Participants with ECG QT interval corrected for heart rate using Fridericia's formula (QTcF) > 480 msec will be excluded. Participants with high degree atrioventricular block II or III, or with sinus node dysfunction with clinically significant pauses who are not treated with pacemaker will also be excluded.

Other Exclusions

14 Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site).

15 Judgment by the investigator that the participant should not participate in the study if the participant is unlikely to comply with study procedures, restrictions, and requirements.

16 Previous enrolment or randomisation in the present study.

17 For women only – currently pregnant (confirmed with positive pregnancy test), breast feeding, or planned pregnancy during the study or women of childbearing potential not using acceptable contraception measures.

18 Study investigators, sub-investigators, coordinators, and their employees or immediate family members.

5.3 Lifestyle Considerations

5.3.1 Caffeine, Alcohol, and Tobacco

- During each dosing session, participants will abstain from ingesting caffeine- or xanthine-containing products (eg, coffee, tea, cola drinks, and chocolate) for 6 hours before and for the duration of each in-clinic study visit.
- Use of tobacco products or vaping will not be allowed from 6 months prior to Visit 1 until after the final follow-up visit.

- Participants will abstain from consuming any intoxicants (eg, alcohol) within 24 hours before spirometry testing.

5.3.2 Activity

Participants will abstain from strenuous exercise for 24 hours before each spirometry testing and each blood collection for clinical laboratory tests. Participants may participate in light recreational activities during studies (eg, watching television, reading).

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious AE (SAE).

Rescreening is allowed for screen failure reason(s) that are transient (including, but not limited to, pre-defined time period requirements, respiratory tract infection not treated with systemic corticosteroids, equipment/procedure failure, required study documentation, or unforeseen personal reasons).

Participants may not be rescreened due to failure to meet the study requirements of pre-bronchodilator FEV_1 (including stability) during the screening period.

Participants on SABA alone therapy who have failed screening due to an ACQ-5 score >1.5 could be rescreened if they have subsequently received treatment with low-dose ICS for a period of 4 weeks as prescribed by their treating physician (i.e. healthcare provider). If they failed screening for a second time, they must be considered screen-failures.

Albuterol/salbutamol must be withheld for at least 8 hours prior to FEV_1 measurements. If repeat spirometry failed, then participant must be screen-failed.

Only one rescreening is allowed in the study. Rescreened participants should be assigned the same participant number as for the initial screening. Rescreened participants will sign a new ICF. All procedures required for the screening periods, starting CCI should be repeated. Rescreening should be documented so that its effect on the study results, if any, can be assessed.

For all participants who are screen failures, an AE assessment and highly sensitive urine pregnancy test (for women of childbearing potential) must be performed within 7 days of the screen failure date.

5.5 Criteria for Temporarily Delaying Enrolment/Randomisation/Administration of Study Intervention

Should there be an emergency situation (eg, COVID-19 pandemic), a risk assessment will be performed to determine if temporary delaying of enrolment/randomisation/administration of study intervention is allowed.

6 STUDY INTERVENTIONS AND CONCOMITANT THERAPY

Study interventions are all pre-specified investigational medicinal products (IMPs) and non-investigational medicinal products (NIMPs), medical devices, and other interventions (eg, surgical and behavioral) intended to be administered to the study participants during the study conduct.

6.1 Study Intervention(s) Administered

Arm name	Treatment A HFO MDI	Treatment B HFA MDI
Intervention name	Pressurized inhalation propellant, HFO	Pressurized inhalation propellant, HFA
Type	Combination product	Combination product
Dose formulation	MDI	MDI
Unit dose strength(s)	Experimental (propellant only)	Reference (propellant only)
Dosage level(s)	4 inhalations, single dose	4 inhalations, single dose
Route of administration	Oral inhalation	Oral inhalation
Use	Experimental	Comparator
IMP and NIMP	IMP	IMP
Sourcing	Provided centrally by the sponsor	Provided centrally by the sponsor
Packaging and labelling	Study intervention will be provided in an MDI. Each MDI will be labelled as required per US requirement.	Study intervention will be provided in an MDI. Each MDI will be labelled as required per US requirement.

Abbreviations: HFA = hydrofluoroalkane; HFO = hydrofluoroolefin; IMP = investigational medicinal product; MDI = metered dose inhaler; NIMP = non-investigational medicinal product.

Dosing instructions and dispensing details will be provided by AstraZeneca.

The HFO MDI and HFA MDI are combination products (propellant + device).

Details of the batch numbers will be included in the Trial Master File and the final clinical study report (CSR).

Study participants will be trained on the correct inhalation technique of the MDI (supplied by AstraZeneca) and other inhalers under study. Per inclusion criteria, participants must demonstrate the proper inhalation technique and have the ability to properly use an MDI device after training.

6.1.1 Medical Devices Including Combination Products with a Device Constituent

The AstraZeneca manufactured combination products with a device constituent provided for use in this study are:

- HFO MDI
- HFA MDI

Instructions for MDIs use are provided in instructions for use.

All medical device deficiencies and device constituent deficiencies (including malfunction, use error and inadequate labelling), hereafter referred to as medical device deficiencies, shall be documented and reported by the investigator throughout the clinical investigation (see Section 7.4.11) and appropriately managed by the sponsor.

6.2 Preparation, Handling, Storage, and Accountability

The HFO MDIs and HFA MDIs will be supplied by AstraZeneca as individual participant kits.

A technical agreement or Item Requirement Schedule between the investigator and AstraZeneca will be in place to cover all pharmacy-related activities, detailing roles, and responsibilities prior to receipt of the study interventions at the clinical unit.

A release document signed by a pharmacist at the clinical unit will be placed in the appropriate section of the Trial Master File to document labelling and dispensing of the study interventions to the participant.

- The investigator or designee (eg, unblinded pharmacist) must confirm appropriate conditions (eg, temperature) have been maintained during transit for all study intervention received at the site and throughout the entire study until authorisation is provided for on-site destruction or removal of the study interventions, reflecting completion of the study. In the event of a temperature excursion detected at any time during the study, sites will follow the reporting procedures for notifying AstraZeneca (or designated party); release of study interventions for clinical use can only occur once the event has been reviewed and approval is provided by AstraZeneca (or designated party).
- Only participants enrolled in the study may receive study intervention and only authorised site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored

(manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorised site staff.

- The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
- Further guidance and information for the final disposition of unused study interventions are provided in the Pharmacy Manual.

6.3 Assignment to Study Intervention

CCI participants meeting all inclusion criteria and none of the exclusion criteria will be randomized before study intervention administration.

Single dose study treatment will be administered via MDI device as 4 inhalations:

- Treatment A: HFO propellant only MDI; 4 inhalations per dose – test formulation
- Treatment B: HFA propellant only MDI; 4 inhalations per dose – reference formulation

Participants will be randomized in a ratio of 1:1 to receive treatments in one of two possible treatment sequences: A followed by B, or B followed by A. The single-dose treatment periods will be separated by a 3 to 12-day washout period.

All participants will be centrally assigned to one of two randomized study interventions using an Interactive Response Technology (IRT) system. Before the study is initiated, the log-in information and directions for the IRT system will be provided to each site.

The IRT will provide to the investigator(s) or pharmacists the kit identification number to be allocated to the participant at the dispensing visit (as summarized in the SoA, Table 1).

Routines for this will be described in the IRT user manual that will be provided to each centre.

6.4 Blinding

This study is double blinded with regard to treatment (MDI administered with 2 different propellants [Treatment A or B]), ie, the sponsor, the investigator, all clinical staff involved in the clinical study, the participants, and the study monitor will remain blinded, unless safety concerns or a regulatory requirement necessitate unblinding.

The following personnel will have access to the randomization lists from study start:

- The AstraZeneca staff carrying out the labelling and packaging of participant specific treatments

The randomisation code should not be broken except in medical emergencies when the

appropriate management of the participant requires knowledge of the treatment randomisation.

AstraZeneca retains the right to break the code for SAEs that are unexpected and are suspected to be causally related to an investigational product and that potentially require expedited reporting to regulatory authorities. A copy of the report, identifying the participant's intervention assignment, may be sent to investigators in accordance with local regulations and/or sponsor policy. Randomisation codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual participant have been made and documented.

The IRT will be programmed with blind-breaking instructions. In case of an emergency, in which the knowledge of the specific blinded study intervention will affect the immediate management of the participant's condition (eg, antidote available), 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 a participant's intervention assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. The investigator documents and reports the action to AstraZeneca, without revealing the treatment given to participant to the AstraZeneca staff.

6.5 Study Intervention Compliance

When participants are dosed at the site, they will self-administer study intervention directly under medical supervision by the investigator or designee. The date, and time if applicable, of dose administered in the clinic will be recorded in the source documents and recorded in the electronic case report form (eCRF). The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person preparing the study intervention for administration.

A record of the number of actuations from HFO/HFA MDIs taken by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays and/or dose reductions will also be recorded in the eCRF.

6.6 Dose Modification

Not applicable.

6.6.1 Retreatment Criteria

Not applicable.

6.7 Continued Access to Study Intervention After the End of the Study

Not applicable.

6.8 Treatment of Overdose

For this study, any dose of HFO MDI or HFA MDI greater than 4 inhalations once daily, is considered an overdose.

Sponsor does not have treatment for an overdose. Single dosing of HFO or HFA propellant at Treatment Period 1 and Treatment Period 2 will be closely monitored at clinic to avoid any overdose. In the event of an overdose, the investigator/treating physician should:

- Evaluate the participant to determine, in consultation with the Study Clinical Lead, if possible, whether study intervention should be interrupted.
- Closely monitor the participant for any AE/SAE and laboratory abnormalities as medically appropriate and at least until the next scheduled follow-up. Refer to Section 7.4.10 for details of AE/SAE reporting related to overdose.
- Document the quantity of the excess dose as well as the duration of the overdose.

6.9 Prior and Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) or other specific categories of interest that the participant is receiving at the time of enrolment 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, frequency, and route

The Study Clinical Lead should be contacted if there are any questions regarding concomitant or prior therapy.

6.9.1 Prior Medications

Participants eligible for this study are required to be on low-dose ICS daily or low-dose ICS/formoterol as needed (not approved in the US), or SABA as needed, or low-dose ICS whenever SABA as needed is used (low-dose ICS as defined by GINA 2022 in below Table 4) for 4 weeks prior to Visit 1.

Table 4 Low Daily Metered Dose of ICS (Monotherapy or in Combination with LABA)

ICS	Total Daily Dose (µg/day)
Beclomethasone dipropionate (pMDI, DPI, standard particle HFA)	200-500
Beclomethasone dipropionate (pMDI, extrafine particle HFA)	100-200
Budesonide (DPI or pMDI, standard particle HFA)	200-400
Ciclesonide (pMDI, extrafine particle HFA)	80-160
Fluticasone furoate (DPI)	100
Fluticasone propionate (DPI or pMDI, standard particle HFA)	100-250
Mometasone furoate (DPI) [a]	200
Mometasone furoate (pMDI, standard particle HFA)	200-400

Abbreviations: DPI = dry powder inhaler; HFA = hydrofluoroalkane; ICS = inhaled corticosteroid; LABA = long-acting beta$_2$-agonist; pMDI = pressurized metered dose inhaler.

[a] Dose depends on DPI device – see product information for more detail. Mometasone furoate 80 µg delivered via the Breezhaler® has been shown to be non-inferior to mometasone furoate Twisthaler® 200 µg [Buhl 2020] and can therefore be used as a permitted low-dose of ICS in this study.

6.9.2 Concomitant Medications

Any current ongoing medications, including over-the-counter medications, herbal supplements, and vaccinations, will be allowed provided they are not explicitly prohibited by the protocol. Participants should also be instructed to contact the investigator if they develop any illnesses, especially those requiring medicinal interventions.

Medications meeting the stable dosing period prior to Visit 1 are allowed during the study and listed in Table 5.

Table 5 Allowed Medications with Defined Stable Dosing Period Prior to Visit 1

Medication	Minimum Stable Dosing Period
Selective serotonin reuptake inhibitors/serotonin and norepinephrine reuptake inhibitors [a]	4 weeks
Tricyclic antidepressants	2 weeks
Antipsychotics	4 weeks
Anticonvulsants	52 weeks for seizure disorders [b] 12 weeks for other conditions
Intranasal corticosteroids	4 weeks
Intranasal antihistamines or combination products of intranasal antihistamines/corticosteroids	4 weeks
Intranasal ipratropium bromide [c]	4 weeks

[a] Must be on a stable dose for at least 4 weeks prior to Visit 1 and not altered during the screening period.

[b] Must be free of seizures for 1 year prior to Visit 1.
[c] Intranasal ipratropium bromide should be withheld for at least 6 hours prior to each visit.

6.9.2.1 Vaccinations

All participants are recommended to be vaccinated with annual influenza vaccine [GINA 2022] or any other inactive/killed vaccines per local policies, availability, and affordability. If a participant has egg intolerance or refuses to be vaccinated, the vaccination may be omitted. The annual influenza vaccine can be given at CCI or at any other visit throughout the study at the discretion of the investigator; however, administration should occur after obtaining all requisite spirometry assessments for that specific test day. There should be at least 7 days between vaccination and subsequent spirometry assessments.

If a participant is being considered for enrolment into the study and also being considered for COVID-19 vaccination, the participant must not be randomised until at least 7 days after the last dose of vaccine or booster. If COVID-19 vaccination is in the best interest of the participant and the participant is vaccinated during the study, there should be at least 7 days between vaccination and subsequent spirometry assessments.

Live attenuated vaccines are not allowed within 30 days prior to Visit 1 or during the study.

6.9.3 Prohibited Medications

Participants requiring medications presented in Table 6 are prohibited from participating in this study. Participants who recently discontinued use of these medications may be considered for study enrolment provided they have met the minimum cessation period prior to Visit 2. These medications are prohibited throughout the course of the study. If participants require any of the prohibited medications listed in Table 6, the investigator should discuss with the medical monitor the suitability of the participant continuing study intervention.

Table 6 Prohibited Medications Throughout the Study and Prior to Visit 1

Medication	Minimum Cessation Period Prior to Visit 1
LABA including formoterol [a]	48 hours
LAMA	4 weeks
Leukotriene antagonists/modifiers (eg, Zileuton®)	2 weeks (ie, 14 days)
Oral beta$_2$-agonist	3 months
Theophylline	3 months
Oral and intravenous corticosteroids [b]	12 months
Injectable systemic corticosteroids (e.g., depot formulation, intra-articular, intraocular, intradermal, intramuscular)	12 months

Table 6 Prohibited Medications Throughout the Study and Prior to Visit 1

Medication	Minimum Cessation Period Prior to Visit 1
Any marketed (e.g., omalizumab, mepolizumab, benralizumab, reslizumab, tezepelumab) or investigational biological therapy for asthma or any other condition	12 months
Any immunomodulators or immunosuppressants [c]	3 months or 5 half-lives, whichever is longer
Medications not currently licensed for use in the treatment of asthma and not part of current standard of care	30 days
Any drug with potential to significantly prolong the QT interval [d]	14 days or 5 half-lives, whichever is longer
Other investigational drugs	30 days or 5 half-lives, whichever is longer
Live attenuated vaccines	30 days
Non-selective non-ocular β-blocking agents (except carvedilol)	7 days
Monoamine oxidase inhibitors	14 days
Systemic treatment with strong CYP3A4-inhibitors (e.g., ketoconazole, itraconazole, and ritonavir)	30 days
Systemic anticholinergics [e]	7 days
Herbal remedies for the treatment of allergic, inflammatory, or respiratory diseases (e.g., Chinese complementary and alternative bronchodilatory medicines)	10 days

Abbreviations: ICS = inhaled corticosteroid; LABA = long-acting beta$_2$-agonist; LAMA = long-acting muscarinic antagonist.

[a] Participants using ICS/LABA as needed (not approved in the US) must withhold it for 48 hours prior to each study visit for spirometry purposes.

[b] Use of systemic corticosteroids for any other reason except for the acute treatment of a severe asthma exacerbation is prohibited for the duration of the study.

[c] Topical administration of immunosuppressive medication may be allowed at the discretion of the investigator after discussion with the study physician.

[d] Participants who are on medications that have the potential to prolong the QTc interval may be enrolled provided the dose has remained stable for at least 3 months prior to Visit 1, the participant meets all of the electrocardiogram inclusion criteria and none of the electrocardiogram exclusion criteria, and if, in the opinion of the investigator, there are not safety concerns for the participant to participate in the study.

[e] If systemic anticholinergics are used for the treatment of irritable bowel syndrome or overactive bladder and the treatment has been constant for at least 1 month, they are allowed.

Specific prohibited asthma and allergy medications and their required washout periods prior to Visit 2 are displayed in Table 7.

Table 7 Prohibited Asthma and Allergy Medications During the Study Conduct and Required Washout Period Prior to Visit 2

Medication	Minimum Washout Period Prior to Visit 2
SABA[a]	8 hours

Table 7 Prohibited Asthma and Allergy Medications During the Study Conduct and Required Washout Period Prior to Visit 2

Medication	Minimum Washout Period Prior to Visit 2
LABA and LABA containing medications, including formoterol [b]	48 hours
Non-sedating long- and short-acting antihistamines for systemic administration, i.e., pills (topical use of eye drops or nasal spray is allowed).	7 days
Cromoglycate [c]	7 days
Nedocromil [c]	7 days
Ketotifen [c]	7 days
SAMA and SABA fixed combination	7 days

Abbreviations: ICS = inhaled corticosteroid; LABA = long-acting beta$_2$-agonist; SABA = short-acting beta$_2$-agonists; SAMA = short-acting muscarinic antagonists.

[a] SABA (eg, albuterol/salbutamol) must be withheld for 8 hours before spirometry [redacted] and unscheduled visits (if applicable).

[b] Participants using ICS/LABA as needed (not approved in the US) must withhold it for 48 hours prior to each study visit for spirometry purposes.

[c] Cromoglycate, nedocromil, and ketotifen eye drops are allowed for allergic conjunctivitis; no washout period.

6.10 Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix A.

6.11 Discontinuation of Study Intervention

Note that discontinuation from study intervention is *not* the same thing as a discontinuation or withdrawal from the study (see Section 6.12).

If study intervention is permanently discontinued, the participant should, if at all possible, remain in the study. See the SoA (Table 1) 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.

If a participant experiences any of the changes listed below, the study intervention must be discontinued:

- Development of exclusion criteria or other safety reasons as judged by the investigator during the treatment periods
- Pregnancy (Section 7.4.8)

6.12 Participant Discontinuation/Withdrawal from the Study

Discontinuation of the participant from the study by the investigator:

- A participant may be discontinued from the study at any time at the discretion of the investigator for safety, behavioural, compliance, or administrative reasons.
- At the time of discontinuing from the study, if the participant has not been discontinued from the study intervention, see Section 6.11.

Voluntary withdrawal from the study by the participant:

- 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 who wishes to withdraw from the study must be informed by the investigator about modified follow-up options. A participant should be advised to follow his/her usual maintenance therapy prescribed by his/her physician and a withdrawal visit or a follow-up call should be scheduled.
- If the participant withdraws consent for disclosure of future information, AstraZeneca may retain and continue to use any data collected before such a withdrawal of consent.
- If the participant withdraws from the study, AstraZeneca may retain and continue to use any samples collected before such a withdrawal of consent for the purposes the participant originally consented unless the participant withdraws consent for use of samples already collected. If the participant specifically withdraws consent for any use of samples, it must be documented in the site study records by the investigator and the investigator must inform the local and global study teams. Destruction of any samples taken and not yet tested should be carried out in line with documented sample withdrawal wishes in conjunction with what was stated in the informed consent and local regulation.

6.13 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 study site for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible. The participant should be counseled on the importance of maintaining the assigned visit schedule. At this time ascertain whether the participant should or wishes to or 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, telephone calls, texts, emails, 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.

7 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarised in Section 1.3, SoA (Table 1). Protocol waivers or exemptions are not allowed.
- **Spirometry SHOULD be performed in accordance with the specified timing** as indicated in the SoA (Table 1).
- Urgent safety concerns should be discussed with AstraZeneca immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA (Table 1), is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilised for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA (Table 1).
- Instructions for the collection and handling of human biological samples (HBS) will be provided in the study-specific laboratory manual. Samples should be stored in a secure storage space with adequate measures to protect confidentiality. For further details on handling of HBS, see Appendix C.
- In the event of a significant study continuity issue (eg, caused by a pandemic), alternate strategies for participant visits, assessments, medication distribution and monitoring may be implemented by AstraZeneca 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 50 mL or will be in adherence to local laboratory standards. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

7.1 Administrative and General/Baseline Procedures

7.1.1 Demographics and Medical/Surgical History

Demographics and medical/surgical history will be collected CCI and updated during the screening period, if necessary.

7.1.2 Height and Weight

Height and weight will be measured as specified in the SoA (Table 1). Body mass index will be automatically calculated in the eCRF.

7.1.3 Physical Examinations

A complete physical examination will be performed on all participants at screening and withdrawal (if applicable). A brief physical examination will be performed on all participants CCI prior to dose (Section 1.3, SoA).

- A complete physical examination will be performed and include assessments of the following; general appearance, respiratory, cardiovascular, abdomen, skin, head and neck (including ears, eyes, nose, and throat), lymph nodes, thyroid, musculoskeletal (including spine and extremities), and neurological systems.
- A brief physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).

7.1.4 Vital Signs

Vital signs will be performed at timelines as specified in Section 1.3, SoA.

The following variables will be collected after the participant has rested in the supine position for at least 5 minutes:

- Systolic blood pressure (mmHg)
- Diastolic blood pressure (mmHg)
- Pulse rate (beats per minute)
- Body temperature (°C)
- Respiratory rate (breaths per minute)

The measurement of vital signs will be carried out according to the relevant site standard operating procedures.

7.1.5 Electrocardiograms

12-lead ECG will be performed at timepoints as specified in Section 1.3, SoA.

The 12-lead ECG will be taken in supine position after 10 minutes of rest. The investigator or authorized delegate will be responsible for the overall interpretation and determination of clinical significance of any potential ECG findings. In case of discrepancy between the investigator's interpretation and that provided by the ECG machine (if applicable), the investigator's interpretation will take precedence and should be noted on the printout and recorded in the eCRF. A copy of the ECG will be produced and quality checked and kept in

case of further need for re-evaluation.

7.1.6 Clinical Laboratory Tests

Blood and urine samples for determination of clinical chemistry, haematology, and urinalysis will be taken at the visits indicated in the SoA.

Additional samples may be collected if clinically indicated at the discretion of the investigator.

The clinical chemistry, haematology, and urinalysis will be performed at local laboratory.

The following laboratory variables will be measured (see Table 8).

Table 8 Laboratory Variables

Haematology/Haemostasis (whole blood)	**Clinical Chemistry (serum or plasma)**
B-Haemoglobin (Hb)	S/P-Creatinine
B-Leukocyte count	S/P-Bilirubin, total
B-Leukocyte differential count (absolute count)	S/P-Alkaline phosphatase (ALP)
B-Platelet count	S/P-Aspartate transaminase (AST)
	S/P-Alanine transaminase (ALT)
Urinalysis (dipstick)	S/P-Albumin
U-Hb/Erythrocytes/Blood	S/P-Potassium
U-Protein/Albumin	S/P-Calcium, total
U-Glucose	S/P-Sodium
	S/P-Creatine kinase (CK)

7.2 Efficacy Assessments

Not applicable.

7.3 Safety Assessments

Planned time points for all safety assessments are provided in Section 1.3, SoA.

7.3.1 Asthma Control Questionnaire 5

Asthma Control Questionnaire 5 will only be assessed during screening (Visit 1) for participants' eligibility.

The ACQ [Juniper 1999a] was developed to measure asthma control and has been fully validated for use in adults (18 years and older) and children 6 to 17 years of age. International guidelines for the treatment of asthma have identified that the primary clinical goal of asthma management is to optimize asthma control (minimization of symptoms, activity limitation, bronchoconstriction, and rescue bronchodilator use) and thus reduce the risk of life-threatening exacerbations and long-term morbidity. The ACQ was developed to meet these criteria by measuring both the adequacy of asthma control and change in asthma control, which occurs either spontaneously or as a result of treatment.

The ACQ-5 scores are supported entirely by patient-reported symptoms. Participants are asked 5 symptom questions. Questions are weighted equally and scored from 0 (totally controlled) to 6 (severely uncontrolled). The mean ACQ-5 score is the mean of the responses to items 1 to 5.

A mean score of ≤ 0.75 indicates well-controlled asthma, scores between 0.75 and < 1.5 indicate partly controlled asthma, and a score ≥ 1.5 indicates not well-controlled asthma [Juniper 2006]. Individual changes of at least 0.5 are considered clinically meaningful.

7.3.2 Spirometry

Spirometry will be performed at the following timepoints (see SoA Table 1):

- CCI [redacted]

Spirometry will be performed by a technologist or a qualified designee to ensure participants achieve optimal lung function and using standardized equipment that meets or exceeds the American Thoracic Society/European Respiratory Society joint recommendations [Miller 2005].

If FEV_1 drops > 15% from baseline, measurements should be repeated at Investigator's discretion until FEV_1 values are within 10% of baseline performed that day.

The participant will be in a seated position during spirometry. The following variables will be recorded:

- FEV_1
- FEV_1 percentage of predicted value

Spirometry must meet both acceptability and repeatability criteria according to American Thoracic Society/European Respiratory Society 2019 recommendations [Graham 2019].

Calculated predicted spirometry results will be obtained using the Global Lung Initiative equations [Quanjer 2012].

7.3.2.1 Monitoring for Bronchospasm

CCI [redacted]

Note: FEV_1 measurement at post-dose 30 minutes is for exploratory safety assessment, but not as part of the bronchospasm definition.

7.3.3 Other Safety Assessments

7.3.3.1 Pregnancy testing

A serum pregnancy test (β-human chorionic gonadotropin) will be conducted at CCI [redacted] and urine β-human chorionic gonadotropin tests at the following visits for women of childbearing potential, as specified in the SoA (Table 1).

A serum follicle-stimulating hormone test will be conducted at CCI [redacted] only, for women who have been amenorrhoeic for 12 months without an alternative medical cause, to confirm postmenopausal status.

For all participants who are screen failures, a highly sensitive urine pregnancy test (for women of childbearing potential) must be performed within 7 days of the screen failure date.

7.4 AEs, SAEs, and Other Safety Reporting

The Investigator is responsible for ensuring that all staff involved in the study are familiar with the content of this section.

The definitions of an AE or SAE can be found in Appendix B.

The definitions of medical device-related safety events (medical device AEs and adverse device effects [ADEs], medical device SAEs, serious adverse device effects [SADEs], unanticipated serious adverse device effects [USADEs], and medical device deficiencies), can be found in Appendix D. Medical device deficiencies are covered in Section 7.4.11.

Participants (or, when appropriate, a caregiver, surrogate, or the participant's legally authorised representative) will notify the investigator or designees of symptoms. These must

then be assessed by the investigator and if considered an AE it will be reported by the investigator.

The investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE.

AE variables

The following variables will be collected for each AE:

- AE (verbatim)
- The date and time when the AE started and stopped
- Maximum intensity
- Whether the AE is serious or not
- Investigator causality rating against the study interventions (yes or no)
- Action taken with regard to study interventions
- AE caused participant's withdrawal from the study (yes or no)
- Outcome

In addition, the following variables will be collected for SAEs:

- Date AE met criteria for SAE
- Date investigator became aware of SAE
- AE description
- AE is serious due to
- Date of hospitalisation
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to study procedure(s)
- Causality assessment to other medication

7.4.1 Time Period and Frequency for Collecting AE and SAE Information

Adverse events will be collected from time of signature of the ICF throughout the treatment period and including the follow-up period.

If the investigator becomes aware of an SAE with a suspected causal relationship to the IMP that occurs after the end of the clinical study in a treated participant, the investigator shall,

without undue delay, report the SAE to AstraZeneca.

7.4.2 Follow-up of AEs and SAEs

Any AEs that are unresolved at the participant's last AE assessment in the study are followed up by the investigator for as long as medically indicated, but without further recording in the eCRF. AstraZeneca retains the right to request additional information for any participant with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

7.4.3 Causality Collection

The investigator should assess causal relationship between study intervention and/or investigational medical devices and each AE, and answer 'yes' or 'no' to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by the IMP?'

For SAEs, causal relationship should also be assessed for other medication and study procedures and/or medical devices. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as 'yes'.

A guide to the interpretation of the causality question is found in Appendix B. For medical devices, a guide to the interpretation of the causality question can be found in Appendix D.

7.4.4 AEs Based on Examinations and Tests

Deterioration as compared to baseline in protocol-mandated laboratory values, vital signs should only be reported as AEs if they meet any of the following:

- fulfil any of the SAE criteria
- are the reason for discontinuation of the study interventions
- are clinically relevant as judged by the investigator (which may include but is not limited to consideration as to whether intervention or non-planned visits were required or other action was taken with the IMP, eg, dose adjustment or drug interruption).

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible, the reporting investigator uses the clinical, rather than the laboratory term (eg, anaemia vs low haemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Deterioration of a laboratory value, which is unequivocally due to disease progression, should not be reported as an AE/SAE.

Any new or aggravated clinically relevant abnormal medical finding at a physical examination

as compared with the baseline assessment will be reported as an AE.

The results from the protocol mandated laboratory tests and vital signs will be summarised in the CSR.

7.4.5 AEs Based on Signs and Symptoms

All signs or symptoms spontaneously reported by the participant or reported in response to the open question from the study site staff: "Have you had any health problems since the previous visit/you were last asked?", or revealed by observation will be collected and recorded in the eCRF.

When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

7.4.6 Adverse Events of Special Interest

Adverse events of special interest in this study are respiratory events such as dysphonia, cough, dyspnoea, wheezing, bronchospasm, and asthma exacerbations.

For the purpose of this study, an event of bronchospasm is defined as a reduction in FEV_1 of > 15% from baseline (ie, the FEV_1 value obtained within 30 minutes prior to study intervention administration) at 5 or 15 minutes post-dose with associated symptoms of wheezing, shortness of breath, or cough.

An asthma exacerbation is defined as worsening of asthma that requires a medical intervention.

A moderate asthma exacerbation is defined as worsening of asthma symptoms (shortness of breath, wheezing, chest tightness, cough) that result in additional ICS treatment for at least 3 days.

The worsening of asthma includes deterioration in at least one of the following:

- asthma symptoms (eg, shortness of breath, wheezing, chest tightness, cough)
- night-time awakening due to asthma
- physical exam finding consistent with deterioration of asthma

An asthma exacerbation will be considered severe if it results in at least one of the following:

- A short course of systemic corticosteroids for at least 3 consecutive days to treat symptoms of asthma worsening

- An emergency room or urgent care visit (defined as evaluation and treatment for < 24 hours in an emergency department or urgent care centre) due to asthma that required treatment with systemic corticosteroids

- An in-patient hospitalization (defined as admission to an in-patient facility and/or evaluation and treatment in a health care facility for ≥ 24 hours) due to asthma

- Death related to asthma

7.4.7 Reporting of SAEs

All SAEs must be reported, whether or not considered causally related to the study interventions. All SAEs will be recorded in the eCRF.

If any SAE occurs during the study, investigators or other site personnel will inform the appropriate AstraZeneca representatives within 1 day, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative will work with the investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within 1 calendar day** of initial receipt for fatal and life-threatening events and **within 5 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up will be undertaken immediately. Investigators or other site personnel will inform AstraZeneca representatives of any follow-up information on a previously reported SAE within one calendar day, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

Once the investigators or other site personnel indicate an AE is serious in the electronic data capture (EDC) system, an automated email alert is sent to the designated AstraZeneca representative.

If the EDC system is not available, then the investigator or other study site staff reports the SAE via secure method to the appropriate AstraZeneca representative.

When the EDC is temporarily not accessible, the AstraZeneca study representative should confirm that the investigator/site staff enters the SAE in the AstraZeneca EDC when access resumes.

For further guidance on the definition of an SAE, see Appendix B.

The reference document for definition of expectedness/listedness is the IB for the AstraZeneca study interventions. For HFO MDI and HFA MDI, no serious adverse reactions (SARs) are

considered expected by the sponsor for the purpose of expedited reporting of suspected unexpected serious adverse reactions (SUSARs). Any AE that is deemed to be related to the study drug by the investigator or the company, which is also serious will be treated as a SUSAR and appropriately expedited.

7.4.8 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca except:

- If the pregnancy is discovered before the study participant has received any study intervention
- Pregnancies in the partner of male participants

7.4.8.1 Maternal Exposure

If a participant becomes pregnant during the study, study intervention should be discontinued immediately.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the study intervention may have interfered with the effectiveness of a contraceptive medication. Congenital anomalies/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital anomaly/birth defect) should be followed up and documented even if the participant was discontinued from the study.

If any pregnancy occurs during the study, then the investigator or other site personnel informs the appropriate AstraZeneca representatives immediately but no later than **24 hours** after he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site **within 1 or 5 calendar days** for pregnancies associated with SAEs (see Section 7.4.7) and **within 30 days** for all other pregnancies.

The same timelines apply when outcome information is available.

The PREGREP module in the eCRF is used to report the pregnancy and the paper-based PREGOUT module is used to report the outcome of the pregnancy.

7.4.8.2 Paternal Exposure

There is no restriction on fathering children or donating sperm during the study.

7.4.9 Medication Error, Drug Abuse, and Drug Misuse

7.4.9.1 Timelines

If an event of medication error, drug abuse, **or** drug misuse occurs during the study, then the investigator or other site personnel informs the appropriate AstraZeneca representatives within **1 calendar day**, ie, immediately but **no later than 24 hours** of when they become aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is completed within **1** (initial fatal/life-threatening or follow-up fatal/life-threatening) **or 5** (other serious initial and follow-up) **calendar days** if there is an SAE associated with the event of medication error, drug abuse, or misuse (see Section 7.4.7) and **within 30 days** for all other events.

7.4.9.2 Medication Error

For the purposes of this clinical study, a medication error is an **unintended** failure or mistake in the treatment process for an IMP or AstraZeneca NIMP that either causes harm to the participant or has the potential to cause harm to the participant.

The full definition and examples of medication error can be found in Appendix B 4.

7.4.9.3 Drug Abuse

Drug abuse is the persistent or sporadic **intentional**, non-therapeutic excessive use of IMP or AstraZeneca NIMP for a perceived reward or desired non-therapeutic effect.

The full definition and examples of drug abuse can be found in Appendix B 4.

7.4.9.4 Drug Misuse

Drug misuse is the **intentional** and inappropriate use (by a study participant) of IMP or AstraZeneca NIMP for medicinal purposes outside of the authorised product information, or for unauthorised IMPs or AstraZeneca NIMPs, outside the intended use as specified in the protocol and includes deliberate administration of the product by the wrong route.

The full definition and examples of drug misuse can be found in Appendix B 4.

7.4.10 Reporting of Overdose

Refer to Section 6.8 for definition and treatment of overdose.

- An overdose with associated AEs is recorded as the AE diagnoses/symptoms on the relevant AE modules in the eCRF and on the Overdose eCRF module.
- An overdose without associated symptoms is only reported on the Overdose eCRF module.

If an overdose on an IMP or AstraZeneca NIMP occurs in the course of the study, the investigator or other site personnel inform appropriate AstraZeneca representatives immediately, but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site **within 1 or 5 calendar days** for overdoses associated with an SAE (see Section 7.4.7) and **within 30 days** for all other overdoses.

7.4.11 Medical Device Deficiencies

Combination products with a device constituent (MDIs and DPIs) are being provided for use in this study. In order to fulfil regulatory reporting obligations worldwide, the investigator is responsible for the detection and documentation of events meeting the definition of a medical device deficiency that occur during the study with the combination products.

Medical device deficiencies from this study will be collected and monitored to ensure the safety of participants and improve the safety and performance of the device.

Medical device deficiencies will not be presented in the CSR, but where required by local regulations, deficiencies will be summarised in the relevant periodic report.

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

NOTE: Deficiencies fulfilling the definition of an AE/SAE will also follow the processes outlined in Appendix D.

The AstraZeneca Clinical Study Medical Device/Device Constituent Report Form and/or Product Complaint Intake Form will be used to collect the deficiency.

7.4.11.1 Time Period for Detecting Medical Device Deficiencies

- Medical device incidents or malfunctions of the medical device 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 medical device deficiency at any time after a participant has been discharged from the study, and such incident is considered reasonably related to a medical device provided for the study, the investigator will promptly notify AstraZeneca.

The method of documenting medical device deficiencies is provided in Appendix D.

7.4.11.2 Follow-up of Medical Device Deficiencies

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

7.4.11.3 Prompt Reporting of Medical Device Deficiencies to Sponsor

- Medical device deficiencies will be reported to AstraZeneca within 24 hours after the investigator determines that the event meets the protocol definition of a medical device deficiency.
- The AstraZeneca Clinical Study Medical Device/Device Constituent Report Form and/or Product Complaint Intake Form will be sent to AstraZeneca by email. If email is unavailable, then fax should be utilised.
- Where an SAE has occurred in addition to the malfunction, the SAE will be recorded in the eCRF as detailed in Section 7.4.7.
- AstraZeneca will be the contact for the receipt of medical device deficiency reports.

7.4.11.4 Regulatory Reporting Requirements for Device Deficiencies

- The investigator will promptly report all medical device deficiencies occurring with any medical device provided for use in the study in order for AstraZeneca to fulfil 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 (eg, the head of the medical institution), will comply with the applicable local regulatory requirements relating to the reporting of medical device deficiencies to the institutional review board (IRB).
- For further guidance on the definition of an SAE, see Appendix D.

7.5 Pharmacokinetics

Not applicable.

7.6 Pharmacodynamics

Not applicable.

7.7 Optional Genomics Initiative

Optional Genomics Initiative research is not applicable in this study.

7.8 Biomarkers

Not applicable.

7.9 Immunogenicity Assessments

Not applicable.

7.10 Health Economics OR Medical Resource Utilisation and Health Economics

Health economics/Medical resource utilisation and health economics parameters are not evaluated in this study.

7.11 Study Participant Feedback Questionnaire

Not applicable.

8 STATISTICAL CONSIDERATIONS

The Statistical Analysis Plan (SAP) will be finalised prior to unblinding and it will include a more technical and detailed description of the planned statistical analyses. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

8.1 Statistical Hypotheses

The null hypothesis tested in this study for the primary objective is that HFO MDI (test arm) is inferior to HFA MDI (reference arm) in terms of the change from baseline in FEV_1 $AUC_{0\text{-}15\ min}$, versus the alternative hypothesis that the test arm is non-inferior to the reference arm.

H_0: $\mu_{Test} - \mu_{Reference} \leq -200$ mL

H_A: $\mu_{Test} - \mu_{Reference} > -200$ mL

The non-inferiority (NI) margin is set at –200 mL. If the lower limit of the 2-sided 95% confidence interval (CI) for the difference in the mean change from baseline of HFO MDI minus HFA MDI is > −200 mL, then NI will be demonstrated.

8.2 Sample Size Determination

CCI

[redacted]

CCI [redacted]

[redacted].

8.3 Populations for Analyses

The following populations are defined:

Table 9 Populations for Analysis

Population/analysis set	Description
Enrolled	All participants who sign the ICF. The Enrolled Analysis Set will be used to summarise disposition.
Randomised	All enrolled participants who are randomised to one of the study treatment sequences. The Randomised Analysis Set will be used to summarise baseline characteristics.
Safety	All participants who are randomised to one of the study treatment sequences and have received any amount of the study treatment (ie, at least 1 puff). Participants will be analysed according to the actual treatment received.

Abbreviations: ICF = informed consent form.

8.4 Statistical Analyses

8.4.1 General Considerations

An NI comparison will be performed between HFO MDI and HFA MDI at a one-sided significance level of 0.025 for primary safety endpoint change from baseline in FEV_1 $AUC_{0\text{-}15\text{-}min}$ post-dose.

For secondary safety endpoints and other safety assessments, no formal statistical analyses will be performed. Descriptive summaries will be produced and any clinically relevant differences will be noted and discussed.

In general, the baseline value for statistical analysis is the last non-missing value prior to administration of the first dose of study intervention during each treatment period.

Analyses will be performed by the sponsor or its representatives. Demographic and baseline characteristics data will be summarised by treatment sequence. Categorical variables will be summarised using frequency and percentages, where the denominator for calculation is the underlying analysis set population unless otherwise specified. Continuous variables will be summarised with descriptive statistics using number of available observations, mean, standard deviation, median, minimum, and maximum, and quartiles where appropriate.

Specific details regarding the statistical analyses will be provided in the SAP.

8.4.1.1 Intercurrent Events

Relevant intercurrent events (ICEs) include use of any leukotriene receptor antagonists (LTRA's) or any inhaled bronchodilator within the restricted time window prior to a clinic visit that would directly affect airway calibre and the primary and exploratory endpoints.

8.4.1.2 Strategy for Intercurrent Events

If use of an LTRA or any inhaled bronchodilator occurs prior to a scheduled clinic visit, optimally, the FEV_1 assessment should be delayed (time permitting) or rescheduled. However, if a spirometry assessment is performed and it's later discovered and confirmed that an LTRA or any inhaled bronchodilator was used within the restricted window prior to the clinical visit, the resulting data from that visit will not be included in the primary and exploratory analysis, and will be considered an important protocol deviation.

8.4.2 Safety

Safety data will be presented using descriptive statistics unless otherwise specified.

8.4.2.1 Primary Endpoint

The primary endpoint is defined as change from baseline in FEV_1 $AUC_{0\text{-}15\ min}$ post-dose. The analysis will be performed based on the Safety Analysis Set using a Principal Stratum estimand.

Change in FEV_1 $AUC_{0\text{-}15\ min}$ post-dose will be calculated from FEV_1 change from baseline at 5 and 15 minutes post-dose using the trapezoidal rule, divided by the actual observation time from the first to the last non-missing value, for each treatment period. Baseline is the FEV_1 value obtained within 30 minutes prior to study intervention administration in each treatment period.

A Mixed Model Repeated Measures analysis with treatment sequence, period, average baseline FEV_1, and treatment as fixed effects, and participant within sequence as the random effect will be used. Average baseline (period-specific baseline FEV_1 averaged over the treatment periods) is included to account for cross-level bias. Adjusted mean change from baseline estimates per treatment group and corresponding 2-sided 95% CIs along with an overall estimate of the treatment difference (HFO MDI minus HFA MDI) will be presented. If

the lower limit of the 2-sided 95% CI for the difference in mean change from baseline of HFO MDI minus HFA MDI is > −200 mL, the null hypothesis of inferiority will be rejected and NI will be demonstrated.

Descriptive summaries for FEV_1 at 30 minutes pre-dose, 5 and 15 minutes post-dose, and change in FEV_1 $AUC_{0\text{-}15\ min}$ post-dose, will be reported by treatment and period.

8.4.2.2 Secondary Endpoints

8.4.2.2.1 Cumulative Incidence of Bronchospasm

An event of bronchospasm is defined as a reduction in FEV_1 of > 15% from baseline (ie, the FEV_1 value obtained within 30 minutes prior to study intervention administration) at 5 or 15 minutes post-dose with associated symptoms of wheezing, shortness of breath, or cough.

The secondary endpoint is defined as cumulative incidence of bronchospasm events. The analysis will be performed based on the Safety Analysis Set. McNemar's test for the bronchospasm event rate analysis will be applied given the crossover design. For each treatment, the proportion of participants who experience an event along with the 2-sided 95% CI (if applicable) will be reported. The difference in proportions along with the 2-sided 95% CI (if applicable) will also be reported.

8.4.2.2.2 Adverse Events

Adverse events will be coded using the most recent version of the Medical Dictionary for Regulatory Activities that will have been released for execution at AstraZeneca/designee. All AE summaries will be performed based on Safety Analysis Set.

Adverse events will be presented for each treatment and for each treatment period by system organ class, and/or preferred term covering number and percentage of participants reporting at least one event and number of events where appropriate. The number and rate of AEs will be summarized for each treatment.

An overview of treatment-emergent AEs will be presented for each treatment group summarizing the number and percentage of participants with any AE, AEs with outcome of death, serious AEs, and AEs leading to discontinuation of IP as well as the number of individual occurrences in those categories.

Separate AE tables will be provided taken into consideration relationship as assessed by the investigator, maximum intensity, seriousness, death, and events leading to discontinuation of IP as well as other action taken related to IP.

An additional table will be presented summarizing the number and percentage of participants with most common AEs.

Full details of AE analyses will be provided in the SAP.

CCI [redacted]

8.4.3 Other Analyses

8.4.3.1 Physical Examinations

Physical examination data will be presented in a data listing.

8.4.3.2 Vital Signs

Vital signs data will be presented in a data listing.

8.4.3.3 Electrocardiogram

Electrocardiogram data will be presented in a data listing.

8.5 Interim Analyses

No interim analysis is planned.

8.6 Data Monitoring/Other Committee

Not applicable.

9 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

Appendix A Regulatory, Ethical, and Study Oversight Considerations

A 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 as amended at 64th WMA General Assembly, Fortaleza, Brazil, October 2013 and Council for International Organizations of Medical Sciences International Ethical Guidelines
  - Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines
  - Applicable laws and regulations
- The protocol, revised protocol, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB by the investigator and reviewed and approved by the IRB before the study is initiated.
- Any revised protocol will require IRB and applicable Regulatory Authority approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- AstraZeneca will be responsible for obtaining the required authorisations to conduct the study from the concerned Regulatory Authority. This responsibility may be delegated to a CRO, but the accountability remains with AstraZeneca.
- The investigator will be responsible for providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR) 312.120, ICH guidelines, the IRB, European Regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations.

Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to AstraZeneca of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- AstraZeneca has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. AstraZeneca will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB, and investigators.
- For all studies except those utilising medical devices, investigator safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

- Adherence to European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from AstraZeneca will review and then file it along with the IB and will notify the IRB, if appropriate according to local requirements.

Regulatory Reporting Requirements for Serious Breaches

- Prompt notification by the investigator to AstraZeneca of any (potential) serious breach of the protocol or regulations is essential so that legal and ethical obligations are met.
  - A 'serious breach' means a breach likely to affect to a significant degree the safety and rights of a participant or the reliability and robustness of the data generated in the clinical study.
- If any (potential) serious breach occurs in the course of the study, investigators or other site personnel will inform the appropriate AstraZeneca representatives immediately after he or she becomes aware of it.
- In certain regions/countries, AstraZeneca has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about such breaches.
  - AstraZeneca will comply with country-specific regulatory requirements relating to serious breach reporting to the regulatory authority, IRB, and investigators. If EU Clinical Trials Regulation 536/2014 applies, AstraZeneca is required to enter details of serious breaches into the European Medicines Agency Clinical Trial Information System. It is important to note that redacted versions of serious breach reports will be available to the public via Clinical Trial Information System.
- The investigator should have a process in place to ensure that:
    - The site staff or service providers delegated by the investigator/institution are able to identify the occurrence of a (potential) serious breach
  - A (potential) serious breach is promptly reported to AstraZeneca or delegated party, through the contacts (email address or telephone number) provided by AstraZeneca.

A 2 Financial Disclosure

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

A 3 Informed Consent Process

- The investigator or their representative will explain the nature of the study to the participant or their legally authorised representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary, and they are free to refuse to participate and may withdraw their consent at any time and for any reason during the study. Participants or their legally authorised representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB or study centre.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorised person obtaining the informed consent must also sign the ICF.
- If new information requires changes to the ICF, consider if participants must be re-consented and if so, this must be to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorised representative.

Participants who are rescreened are required to sign a new ICF.

A 4 Data Protection

- Participants will be assigned a unique identifier by AstraZeneca. Any participant records or datasets that are transferred to AstraZeneca will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that their personal study-related data will be used by AstraZeneca in accordance with local data protection law. The level of disclosure and use of their data must also be explained to the participant in the informed consent.
- The participant must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorised personnel appointed by AstraZeneca, by appropriate IRB members, and by inspectors from regulatory authorities.
- The participant must be informed that data will be collected only for the business needs. We will only collect and use the minimum amount of personal data to support our business activities and will not make personal data available to anyone (including internal staff) who is not authorised or does not have a business need to know the information.
- The participant must be informed that in some cases their data may be pseudonymised. The General data Protection Regulation defines pseudonymisation as the processing of

personal data in such a way that the personal data can no longer be attributed to a specific individual without the use of additional information, provided that such additional information is kept separately and protected by technical and organisational measures to ensure that the personal data are not attributed to an identified or identifiable natural person.

A 5 Committees Structure

Not applicable.

A 6 Dissemination of Clinical Study Data

Any results both technical and lay summaries for this trial, will be submitted to EU CTIS within a year from global End of Trial Date in all participating countries, due to scientific reasons, as otherwise statistical analysis is not relevant.

A description of this clinical study will be available on http://astrazenecagrouptrials.pharmacm.com and http://www.clinicaltrials.gov as will the summary of the main study results when they are available. The clinical study and/or summary of main study results may also be available on other websites according to the regulations of the countries in which the main study is conducted.

A 7 Data Quality Assurance

- All participant data relating to the study will be recorded on eCRF unless transmitted to AstraZeneca or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The investigator must permit study-related monitoring, audits, IRB review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy, including definition of study-critical data items and processes (eg, 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 included in the Monitoring Plan.
- AstraZeneca or designee is responsible for medical oversight throughout the conduct of the study which includes clinical reviews of study data in accordance with the currently approved protocol. Monitoring details describing clinical reviews of study data from a medical perspective are included in more detail in the Monitoring Plan.

- AstraZeneca or designee is responsible for the data management of this study, including quality checking of the data.
- AstraZeneca assumes accountability for actions delegated to other individuals (eg, CROs).
- Study monitors will perform ongoing source data verification as per the Monitoring Plan(s) to confirm that data entered into the eCRF by authorised 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.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for a minimum of 25 years after study archiving or as required by local regulations, according to the AstraZeneca Global Retention and Disposal (GRAD) schedule. No records may be destroyed during the retention period without the written approval of AstraZeneca. No records may be transferred to another location or party without written notification to AstraZeneca.

A 8 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 entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data and its origin can be found in Source Data Identification Form provided by Labcorp.

A 9 Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the first site open and will be the study start date.

AstraZeneca designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of AstraZeneca. 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 AstraZeneca or the investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB or local health authorities, AstraZeneca's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development

If the study is prematurely terminated or suspended, AstraZeneca shall promptly inform the investigators, the IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or 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.

A 10 Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to AstraZeneca before submission. This allows AstraZeneca to protect proprietary information and to provide comments.
- AstraZeneca will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, AstraZeneca will generally support publication of multicentre studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Appendix B AEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

B 1 Definition of AEs

An AE is the development of any untoward medical occurrence in a patient or clinical study participant administered a medicinal product, and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (eg, an abnormal laboratory finding), symptom (for example nausea, chest pain), or disease temporally associated with the use of a medicinal product, whether it's considered related to the medicinal product.

The term AE is used to include both serious and non-serious AEs and can include a deterioration of a pre-existing medical occurrence. An AE may occur at any time, including run-in or washout periods, even if no study intervention has been administered.

B 2 Definition of SAEs

An SAE is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up), that fulfils one or more of the following criteria:

- Results in death.
- Is immediately life-threatening.
- Requires in-patient hospitalisation or prolongation of existing hospitalisation.
- Results in persistent or significant disability or incapacity.
- Is a congenital anomaly or birth defect.
- Is an important medical event that may jeopardise the participant or may require medical treatment to prevent one of the outcomes listed above.

Adverse Events for **malignant tumours** reported during a study should generally be assessed as **SAEs**. If no other seriousness criteria apply, the 'Important Medical Event' criterion should be used. In certain situations, however, medical judgement on an individual event basis should be applied to clarify that the malignant tumour event should be assessed and reported as a **non-SAE**. For example, if the tumour is included as medical history and progression occurs during the study, but the progression does not change treatment and/or prognosis of the malignant tumour, the AE may not fulfil the attributes for being assessed as serious, although reporting of the progression of the malignant tumour as an AE is valid and should occur. Also, some types of malignant tumours, which do not spread remotely after a routine treatment that does not require hospitalisation, may be assessed as non-serious; examples in adults include Stage 1 basal cell carcinoma and Stage 1A1 cervical cancer removed via cone biopsy.

Life-threatening

'Life-threatening' means that the participant was at immediate risk of death from the AE as it occurred, or it is suspected that use or continued use of the medicinal product would result in the participant's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

Hospitalisation

Outpatient treatment in an emergency room is not in itself a SAE, although the reasons for it may be (eg, bronchospasm, laryngeal oedema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the participant was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important Medical Event or Medical Treatment

Medical and scientific judgement should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life threatening or result in death, hospitalisation, disability or incapacity but may jeopardise the participant or may require medical treatment to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgement must be used.

Examples include:

- Angioedema not severe enough to require intubation but requiring intravenous hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (eg, neutropenia or anaemia requiring blood transfusion, etc.) or convulsions that do not result in hospitalisation
- Development of drug dependency or drug abuse

Intensity Rating Scale

- Mild (awareness of sign or symptom, but easily tolerated)
- Moderate (discomfort sufficient to cause interference with normal activities)
- Severe (incapacitating, with inability to perform normal activities)

It is important to distinguish between serious and severe AEs. Severity is a measure of

intensity whereas seriousness is defined by the criteria in Appendix B 2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not an SAE unless it meets the criteria shown in Appendix B 2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be an SAE when it satisfies the criteria shown in Appendix B 2.

B 3 A Guide to Interpreting the Causality Question

When assessing causality consider the following factors when deciding if there is a 'reasonable possibility' that an AE may have been caused by the medicinal product.

- Time course. Exposure to suspect drug. Has the participant received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?
- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?
- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?
- No alternative cause. The AE cannot be reasonably explained by another aetiology such as the underlying disease, other drugs, other host, or environmental factors.
- Re-challenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a re-challenge.
- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

In difficult cases, other factors could be considered such as:

- Is this a recognised feature of overdose of the drug?
- Is there a known mechanism?

Causality of 'related' is made if following a review of the relevant data, there is evidence for a 'reasonable possibility' of a causal relationship for the individual case. The expression 'reasonable possibility' of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

The causality assessment is performed based on the available data including enough

information to make an informed judgment. With no available facts or arguments to suggest a causal relationship, the event(s) will be assessed as 'not related'.

Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as 'no reasonable possibility'.

B 4 Medication Error, Drug Abuse, and Drug Misuse

Medication Error

For the purposes of this clinical study a medication error is an unintended failure or mistake in the treatment process for an IMP or AstraZeneca NIMP that either causes harm to the participant or has the potential to cause harm to the participant.

A medication error is not lack of efficacy of the drug, but rather a human or process related failure while the drug is in control of the study site staff or participant.

Medication error includes situations where an error:

- Occurred
- **Was identified and** intercepted before the participant received the drug
- Did not occur, but circumstances were recognised that could have led to an error

Examples of events to be reported in clinical studies as medication errors:

- Drug name confusion
- Dispensing error, eg, medication prepared incorrectly, even if it was not actually given to the participant
- Drug not administered as indicated, eg, wrong route or wrong site of administration
- Drug not taken as indicated, eg, tablet dissolved in water when it should be taken as a solid tablet
- Drug not stored as instructed, eg, kept in the refrigerators when it should be at room temperature
- Wrong participant received the medication (excluding IRT/RTSM errors)
- Wrong drug administered to participant (excluding IRT/RTSM errors)

Examples of events that **do not** require reporting as medication errors in clinical studies:

- Errors related to or resulting from IRT/RTSM - including those which led to one of the above listed events that would otherwise have been a medication error
- Participant accidentally missed drug dose(s), eg, forgot to take medication

- Accidental overdose (will be captured as an overdose)
- Participant failed to return unused medication or empty packaging

Medication errors are not regarded as AEs but AEs may occur as a consequence of the medication error.

Drug Abuse

For the purpose of this study, drug abuse is defined as the persistent or sporadic intentional, non-therapeutic excessive use of IMP or AstraZeneca NIMP for a perceived reward or desired non-therapeutic effect.

Any events of drug abuse, with or without associated AEs, are to be captured and forwarded to the data entry site using the Drug Abuse Report Form. This form should be used both if the drug abuse happened in a study participant or if the drug abuse involves a person not enrolled in the study (such as a relative of the study participant).

Examples of drug abuse include but are not limited to:

- The drug is used with the intent of getting a perceived reward (by the study participant or a person not enrolled in the study)
- The drug in the form of a tablet is crushed and injected or snorted with the intent of getting high

Drug Misuse

Drug misuse is the intentional and inappropriate use (by a study participant) of IMP or AstraZeneca NIMP for medicinal purposes outside of the authorised product information, or for unauthorised IMPs or AstraZeneca NIMPs, outside the intended use as specified in the protocol and includes deliberate administration of the product by the wrong route.

Events of drug misuse, with or without associated AEs, are to be captured and forwarded to the data entry site using the Drug Misuse Report Form. This form should be used both if the drug misuse happened in a study participant or if the drug misuse regards a person not enrolled in the study (such as a relative of the study participant).

Examples of drug misuse include but are not limited to:

- The drug is used with the intention to cause an effect in another person
- The drug is sold to other people for recreational purposes
- The drug is used to facilitate assault in another person
- The drug is deliberately administered by the wrong route

- The drug is split in half because it is easier to swallow, when it is stated in the protocol that it must be swallowed whole
- Only half the dose is taken because the study participant feels that he/she is feeling better when not taking the whole dose
- Someone who is not enrolled in the study intentionally takes the drug

Appendix C Handling of Human Biological Samples

C 1 Chain of Custody

A full chain of custody is maintained for all samples throughout their lifecycle.

The investigator at each centre keeps full traceability of collected biological samples from the participants while in storage at the centre until shipment or disposal (where appropriate) and records relevant processing information related to the samples whilst at the site.

The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed of or until further shipment, and keeps record of receipt of arrival and onward shipment or disposal.

AstraZeneca or delegated representatives will keep oversight of the entire life cycle through internal procedures, monitoring of study sites, auditing or process checks, and contractual requirements of external laboratory providers

Samples retained for further use will be stored in the AstraZeneca-assigned biobanks or other sample archive facilities and will be tracked by the appropriate AstraZeneca team for the remainder of the sample life cycle.

All appropriately consented samples will be retained for maximum 15 years from last subject last visit.

If required, AstraZeneca will ensure that remaining biological samples are returned to the site according to local regulations or at the end of the retention period, whichever is the sooner.

C 2 Withdrawal of Informed Consent for Donated Biological Samples

If a participant withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed/repatriated, and the action documented. If samples are already analysed, AstraZeneca is not obliged to destroy the results of this research.

Following withdrawal of consent for biological samples, further study participation should be considered in relation to the withdrawal processes outlined in the informed consent.

The investigator:

- Ensures the participant's withdrawal of informed consent to the use of donated samples is highlighted immediately to AstraZeneca or delegate.
- Ensures that relevant HBS from that participant, if stored at the study site, are immediately identified, disposed of as appropriate, and the action documented.
- Ensures that the participant and AstraZeneca are informed about the sample disposal.

AstraZeneca ensures the organisation(s) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of or repatriated as appropriate, and the action is documented, and study site is notified.

C 3 International Air Transport Association Guidance Document 62nd edition

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

The International Air Transport Association (IATA) (**https://www.iata.org/whatwedo/cargo/dgr/Pages/download.aspx**) classifies infectious substances into 3 categories: Category A, Category B, or Exempt

Category A Infectious Substances are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals.
Category A Pathogens are, eg, Ebola, Lassa fever virus. Infectious substances meeting these criteria which cause disease in humans or both in humans and animals must be assigned to UN 2814. Infectious substances which cause disease only in animals must be assigned to UN 2900.

Category B Infectious Substances are infectious substances that do not meet the criteria for inclusion in Category A. Category B pathogens are, eg, Hepatitis A, C, D, and E viruses. They are assigned the following UN number and proper shipping name:

- UN 3373 – Biological Substance, Category B
- Are to be packed in accordance with UN 3373 and IATA 650

Exempt Substances are substances which do not contain infectious substances, or substances which are unlikely to cause disease in humans or animals, are not subject to these regulations unless they meet the criteria for inclusion in another class.

- Clinical study samples will fall into Category B or exempt under IATA regulations.
- Clinical study samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging (https://www.iata.org/contentassets/b08040a138dc4442a4f066e6fb99fe2a/dgr-62-en-pi650.pdf).
- Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content.

Appendix D Medical Device AEs, ADEs, SAEs, SADEs, USADEs, and Medical Device Deficiencies: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

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

D 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 unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medical device. This definition includes events related to the medical device or comparator and events related to the procedures involved except for events in users or other persons, which only include events related to medical devices.
- ADE is defined as an AE related to the use of a medical device. This definition includes any AE resulting from insufficient or inadequate instructions for use, 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.

D 2 Definition of Medical Device SAE, SADE, and USADE

A Medical Device SAE is an any AE 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 hospitalisation. Planned hospitalisation 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 (European Medical Device Regulation 2017/745).

c. Led to foetal distress, foetal death, or a congenital anomaly or birth defect.

A Medical Device SADE is:

- Any ADE that has resulted in any of the consequences characteristic of an SAE.
- Any medical 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.

USADE Definition:

- A USADE (also identified as UADE in the US Regulation 21 CFR 812.3) is defined as a SADE 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).

D 3 Definition of Medical Device Deficiency

Medical 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.

D 4 Recording and Follow-up of Medical Device AE and/or SAE and Medical Device Deficiencies

AE, SAE, and Medical Device Deficiency Recording

- When an AE/SAE/medical device deficiency occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE/medical 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 sponsor or designated CRO in lieu of completion of the AE/SAE/medical device deficiency form.
- There may be instances when copies of medical records for certain cases are requested by the sponsor. In this case, all participant identifiers, except for the participant number, will be redacted on the copies of the medical records before submission to the sponsor.

- 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 medical 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 medical device deficiency. This includes any protocol revision to the medical device design to prevent recurrence.

Assessment of Intensity

The investigator will assess intensity for each AE/SAE/medical device deficiency reported during the study and assign it to one of the following categories:

- Mild (awareness of sign or symptom, but easily tolerated)
- Moderate (discomfort sufficient to cause interference with normal activities)
- Severe (incapacitating, with inability to perform normal activities)

Other measures to evaluate AEs and SAEs may be used (eg, National Cancer Institute Common Terminology Criteria for Adverse Events).

Assessment of Causality

- The investigator is obligated to assess the causal relationship between study intervention and each occurrence of AE/SAE/medical device deficiency.
- A 'reasonable possibility' of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship.
- The investigator will use clinical judgment to determine the relationship.
- 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.
- The investigator will also consult the IB and/or Investigational Directions for Use (IDFU) or Product Information, for marketed products in their assessment.
- For each AE/SAE/medical device deficiency, the investigator **must** document in the medical notes that they have reviewed the AE/SAE/medical device deficiency and have provided an assessment of causality.
- There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report to the sponsor. 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 the sponsor.

- 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.

Causality of 'related' is made if following a review of the relevant data, there is evidence for a 'reasonable possibility' of a causal relationship for the individual case. The expression 'reasonable possibility' of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

The causality assessment is performed based on the available data including enough information to make an informed judgment. With no available facts or arguments to suggest a causal relationship, the event(s) will be assessed as 'not related'.

Follow-up of AE/SAE/Medical 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 the sponsor to elucidate the nature and/or causality of the AE/SAE/medical 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 recognised follow-up period, the investigator will provide the sponsor with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the original form used to report the deficiency.
- The investigator will submit any updated SAE data to the sponsor **within 24 hours** of receipt of the information.

D 5 Reporting of Medical Device SAEs and SADEs

- All medical device SAEs will be reported in accordance with Section 7.4.7.

NOTE: There are additional reporting obligations for SADEs that must fulfil 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 medical device deficiency that is associated with an SAE must be reported to AstraZeneca **within 24 hours** after the investigator determines that the event meets the definition of a medical device deficiency.
- In addition to the reporting process described in Section 7.4.7, the AstraZeneca Clinical Study Medical Device/Device Constituent Report Form will be used to capture details of the device and related deficiency.

- Facsimile transmission of the AstraZeneca Clinical Study Medical Device/Device Constituent Report Form is the preferred method to transmit this information to the Study Clinical Lead/SAE coordinator.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the AstraZeneca Clinical Study Medical Device/Device Constituent Report Form sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the AstraZeneca Clinical Study Medical Device/Device Constituent Report Form within the designated reporting time frames.
- AstraZeneca will review all medical device deficiencies and determine and document in writing whether they could have led to an SAE. These medical device deficiencies will be reported to the regulatory authorities and IRBs as required by national regulations.
- Contacts for SAE reporting can be found in the Safety Handling Plan.

10 REFERENCES

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