Clinical Study Report Appendix 16.1.9

Drug Substance	Breztri PT010
Study Code	D5985C00007

Appendix 16.1.9
Documentation of Statistical Methods and Supporting Statistical Analysis

Statistical Analysis Plan Number	Date	Page Number
Statistical Analysis Plan Edition Number 2.0 External	04 October 2023	33

STATISTICAL ANALYSIS PLAN	
Study Code	D5985C00007
Edition Number	2.0 External
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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)

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LIST OF ABBREVIATIONS

Abbreviation or Specialised Term	Definition
AE	Adverse event
ATC	Anatomical Therapeutic Chemical
AUC	Area under the curve
$AUC_{0\text{-}15\ min}$	Area under the curve from 0 to 15 minutes
BID	Twice daily
BMI	Body Mass Index
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence interval
COVID-19	Coronavirus disease 2019
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CT	Computed tomography
CV	Coefficient of Variation
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
FEV1	Forced expiratory volume in 1 second
FVC	Forced Vital Capacity
HFA	Hydrofluoroalkane
HFO	Hydrofluoroolefin
ICE	Intercurrent events
ICF	Informed Consent Form
IPD	Important Protocol Deviation
ITT	Intent-to-Treat
IV	intravenous
ICH	International Council for Harmonization
IP	Investigational product
IPD	Important Protocol Deviations
IRT	Interactive Response Technology
LRTA	Leukotriene Receptor Antagonists
MedDRA	Medical Dictionary for Regulatory Activities
MDI	Metered Dose Inhaler
NI	Non-inferiority

Abbreviation or Specialised Term	Definition
PI	Principal Investigator
Q3	Third quartile
QRS	ECG interval measured from the onset of the QRS complex to the J point
QT	ECG interval measured from the onset of the QST complex to the end of the T wave
QTcF	QT interval corrected for heart rate using Fridericia's formula
RR	The time between corresponding point on 2 consecutive R waves on ECG
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SoA	Schedule of Activities
SOC	System Organ Class
SOP	Standard Operating Procedure
TEAE	Treatment emergent adverse event
TFL	Table, Figure and Listing

AMENDMENT HISTORY

CATEGORY Change refers to:	Date	Description of change	In line with CSP?	Rationale
N/A	03-Jul-2023	Initial approved SAP	Yes	N/A
Other - Safety endpoints	4-Oct-2023	Update to add details of analyses of safety section, including the analysis of adverse events of special interest and removal of presentation by treatment period. Treatment emergent AEs definition simplified (3.3.1). Study drug compliance definition (section 4.1.9.1) has been changed to use the number of puffs used, instead of dispensed and returned. Clarification on laboratory data to be included for listings (4.6.3).	Yes	Review by safety leads noted updates required.
Other - Visit windows	4-Oct-2023	Additional detail in Visit Window (3.3.2) section for spirometry assessment inclusion.	No	Clarification of timepoint windowing rules and handling situations where multiple measurements are in-window.
Primary or secondary endpoints	4-Oct-2023	Definition of primary analysis set amended - condition regarding missing FEV_1 measurements has been removed and instead included in definitions of the relevant endpoints.	No	Missing data issue separated from estimand definition in line with ICH E9 R1 for primary analysis set.
Data presentations	4-Oct-2023	Concomitant medications (section 4.1.8.2) will be summarised by treatment sequence instead of by analysis period and treatment received, for consistency with prior medications. ATC medication summaries (section 4.1.8.2) will be summarised differently, in adherence with AZ standards. Lab data inclusion (sec 4.6.3.2)	Yes	Review by safety leads noted updates required.

CATEGORY Change refers to:	**Date**	**Description of change**	**In line with CSP?**	**Rationale**
Primary or secondary endpoints	Date	Primary endpoint intercurrent event strategy (section 4.2.1.1) amended - updated to add condition that participants who do not receive complete treatment in both periods will be excluded, consistent with primary analysis set definition. Amended condition of missing FEV_1 measurements. Supplementary analysis of the primary endpoint - Removed specification of participants missing an FEV_1 measurement at 5 minutes, due to change in primary analysis, which would now include these. Removed imputation of FEV_1 at 15 minutes.	No	Missing data issue separated from estimand definition in line with ICH E9 R1 for primary endpoint. Revised handling of missing data for primary endpoint. Supplementary analysis revised due to updates to analysis set definitions.
Derivation of primary or endpoints	Date	Primary endpoint derivation amended (section 4.2.1.2) - participants included if baseline and at least one post-dose measurement included. Multiple observations per participant may be included.	Yes	Derivation updated to align with CSP text that actual observation time to be used.
Statistical analysis method for the primary or secondary endpoints	Date	Primary analysis of primary endpoint (4.2.1.4) model amended to change random intercept per participant to participant within treatment sequence as a random effect, to align with the CSP.	Yes	Model text updated to align with CSP text of a participant within sequence random effect.
CCI [redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other – Statistical analysis method for the exploratory endpoint	Date	Primary analysis of exploratory endpoint amended to use separate models per timepoint.	Yes	Model adjusted as the number of subjects with measurements in both periods will vary by timepoint.

1 INTRODUCTION

The purpose of this document is to give details for the statistical analysis of study D5985C00007 supporting the clinical study report. The reader is referred to the Clinical Study Protocol (CSP) and the Case Report Form (CRF) for the details of the study conduct and data collection.

2 CHANGES TO PROTOCOL PLANNED ANALYSES

The Primary Analysis Set was added to support the principal stratum estimand described in the protocol, and to be used as the population for the primary estimand of the primary endpoint, and for the exploratory endpoint.

The acceptable windowing for the start time of spirometry assessments has been added to section 3.3.2 of the Statistical Analysis Plan (SAP) and is not specified in the CSP.

The protocol states that a mixed model repeated measures analysis will be used for the analysis of the primary endpoint. This has been updated to describe the analysis model as a linear mixed model.

The protocol states that the study day of treatment period 1 is day 0. Following the principles of CDISC this has been updated in the SAP to be study day 1 and study day 0 is not defined.

The protocol states that physical examination results will be presented in a data listing. New or aggravated findings, as compared with baseline, on the physical examinations are to be reported as Adverse Events (AE) so will be summarised in the relevant AE summaries.

3 DATA ANALYSIS CONSIDERATIONS

3.1 Timing of Analyses

A final analysis will be conducted when all randomised participants have completed the follow-up/early termination visit, data cleaning has been completed and the database has been locked for analysis.

3.2 Analysis Populations

This study will include the following analysis populations:

Enrolled

Randomised

Primary Analysis Set

Safety.

Enrolled

All participants who signed the Informed Consent Form (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.

Primary Analysis Set

All participants who are randomised to one of the study treatment sequences. Participants who use any Leukotriene receptor antagonists (LTRA) or any inhaled bronchodilator within the restricted window prior to the clinical visit will be excluded from the analysis. Participants who do not receive complete treatment in both periods will be excluded from the analysis (Principal Stratum Strategy). Period level data will be analysed according to the actual treatment received.

Safety

All participants who are randomised to one of the study treatment sequences and have received any amount of the study treatment (i.e. at least 1 puff). Participants will be analysed according to the actual treatment received.

3.3 General Considerations

All analyses outlined in this Statistical Analysis Plan will be conducted by Fortrea, in accordance with the contract with AstraZeneca (UK) and following the SOLIS description of services.

The general principles below will be followed for analyses:

Descriptive statistics will be used for all variables, as appropriate. Continuous variables will be summarised by the number of observations, mean, standard deviation (SD), median, first quartile (Q1), third quartile (Q3), minimum and maximum. For log transformed data it is more appropriate to present geometric mean, coefficient of variation (CV), median, minimum and maximum. Categorical variables will be summarised by frequency counts and percentages for each category.

For qualitative variables, the number (n) and percentage (%) of participants with non-missing data per category will be the default summary presentation, and where appropriate and present, the number of missing values as a "Missing" category. Number of participants in the analysis population will be used as denominator for percentages calculation, unless stated otherwise in Tables, Figures and Listings (TFLs) mock shell(s).

For continuous data, the mean and median will be rounded to 1 additional decimal place compared to the original data. The standard deviation will be rounded to 2 additional decimal places compared to the original data. Minimum and maximum will be displayed with the same accuracy as the original data. For derived continuous data, the decimal places displayed will follow the rules provided, using the precision of the variable included in the calculation with the greatest number of decimal places.

For categorical data, percentages will be rounded to 1 decimal place.

SAS® version 9.4 or higher will be used for all analyses.

It is acceptable to present large numerical values in more appropriate units. For example, an Area Under Curve (AUC) value of 123,000 ng h/mL may be reported as 123 µg h/mL instead. It is however, important to keep the units consistent within the report and the precision consistent with that prior to conversion.

3.3.1 General Study Level Definitions

The date and time of randomisation will be as recorded in the Interactive Response Technology (IRT) system. The date of the last dose of MDI HFA/MDI HFO will be taken from the Discontinuation of Investigational Product (IP) eCRF page. If the date in this eCRF page is missing, alternatively the date of the last visit will be used.

Study treatment will be administered via MDI device as 4 inhalations at visit 2 and visit 3 respectively.

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

CCI [redacted]

CCI [redacted]

Treatment emergent AE (TEAE) will be defined as an AE with the start date on or after the date of treatment during treatment period 1 up to (and including) 7 days after the last dose date.

3.3.1.1 Screening/Baseline

For all participants, the screening period is defined as the period from informed consent to the date of IP dispensation. For some variables, data from more than one assessment within the screening period may be collected prior to the first dose of IP.

The baseline value for a variable is therefore defined as the last non-missing value prior to the start date of treatment during each treatment period and, for treatment period 2, after the end date of treatment during treatment period 1. The start date of treatment for each participant will be taken from the exposure as collected eCRF page. For assessments on the day of first dose, where time is not captured, a nominal pre-dose indicator, if available, will serve as sufficient evidence that the assessment occurred prior to first dose. Any observation made after the first dose of study treatment will be considered post-baseline for that treatment period and will be assigned to the nominal visit recorded. For FEV_1 measurements the baseline value will be considered to be the best measurement nominally recorded as pre-dose.

Assessments on the dispensation date of IP during each treatment period, when neither time nor a nominal pre-dose indicator are captured will be considered prior to the first dose if such procedures are required by the protocol to be conducted before first dose.

In all quantitative summaries from baseline, absolute changes from baseline will be calculated at the post-baseline value minus the value at baseline. The percentage change from baseline will be calculated as [(post-baseline value – baseline value) / baseline value] x 100.

3.3.1.2 Analysis periods

Analysis periods do not precisely align with the treatment periods described in the CSP. The analysis period of treatment period i describes the period which adverse events should be attributable to rather than the period where IP is dispensed.

Screening Period

The screening period is defined as the period from informed consent to the first dispensation of IP.

Treatment Period 1

Treatment period 1 is defined as the day of Visit 2 (Day 1) to the earliest of the end of treatment washout period (i.e. day of Visit 3 (Day 1)) or the date of withdrawal visit (if applicable).

Treatment Period 2

Treatment period 2 is defined as the period from the day of Visit 3 (Day 1) to the latest of the day of completion of safety follow-up visit or the date of withdrawal visit (if applicable).

3.3.1.3 Handling of missing dates

Incomplete dates (partial or missing dates where a full date is permissible) will be presented in the data listings as recorded on the eCRF. Every effort will be made to ensure complete information for these dates are available. Missing/incomplete (partial) AE start and end dates will not be imputed for data listings. However, if an AE is missing or has a partial start date then it will be considered to be treatment-emergent during treatment period i as follows:

> If AE start date is completely missing, then the AE is considered as treatment-emergent during treatment period 1.
>
> If AE start date month and day are missing and a participant's treatment periods start in different years then the AE is considered as treatment-emergent during the matching year of the partial start date, otherwise the AE is considered as treatment-emergent during treatment period 1.
>
> If AE start date day is missing and a participant's treatment periods start in different months then the AE is considered as treatment-emergent during the matching month of the partial start date, Otherwise, if the AE occurs during the month after the second treatment start date it is considered as treatment-emergent during treatment period 2, or otherwise the AE is considered as treatment-emergent during treatment period 1.

Missing start and stop dates will be imputed for prior and concomitant medications as follows:

3.3.1.3.1 Partial start dates

If the year is unknown, then the date will not be imputed, and will be assigned a missing value. If the month is unknown, then if the year matches the year of the first dose date in treatment period 1, then impute the month and day of the first dose date. Otherwise, assign the month as July.

If the day is unknown, then if the month and year match the month and year of the first dose date in treatment period 1, then impute the day of the first dose date. Otherwise, assign the day as mid-month (14th for February, 15th for all other months).

3.3.1.3.2 Partial end dates

If the year is unknown, then the date will not be imputed and will be assigned a missing value.

If the month is unknown, then assign July.

If the day is unknown, then assign the day as mid-month (14th for February, 15th for all other months).

If the above rules for end dates result in an illogical date (i.e. end date < start date or end date > participant's date of completion/discontinuation) with regards to the dates the participant was in the study, then the end date will be replaced with the participant's date of completion/discontinuation.

3.3.1.4 Handling of Missing Data

3.3.1.4.1 Handling of Missing Efficacy Data

Missing FEV_1 measurements will not be imputed for the primary efficacy analysis but will be imputed for supplementary analyses. Imputation details are described in section 4.2.1.6.

3.3.1.4.2 Handling of Missing Safety Data

In general, missing clinical laboratory data, vital signs and electrocardiogram (ECG) data will not be imputed. Adverse event imputations for missing intensity or relationship are given in section 4.6.2.1. Unknown or partial medication date imputations are given in section 3.3.1.4 and are to be used only for the assessment of prior / concomitant status for medications.

3.3.2 Visit Window

For all populations, assessments will be assigned to visits based on the nominal visit recorded on the eCRF form. Visit windowing will not be applied for this study.

Spirometry assessments will be considered as in-window providing the start time of the repeated assessments at each scheduled assessment time point (e.g. 4 attempts at 5 minutes post-dose) is performed per the following table. Only results flagged as being a best result will be considered for analysis. These assessments can be considered as in-window for a different assessment time from that targeted (e.g. an assessment recorded as being at the 5-minute post-dose timepoint can be included in the 15 minute post-dose timepoint if it occurred during the 15-minute window). If more than one assessment qualifies as in-window for a given timepoint, the following rules will apply to select one:

30 minutes pre-dose: use the latest assessment

5, 15 and 30 minutes post-dose: use the assessment closest to the planned time. If two or more assessments are equidistant from the planned time, the earliest will be used.

This is with the exception of area under the curve (AUC) calculations, where multiple post-dose assessments may be included as in-window.

Spirometry assessments performed out of window will be considered to be unscheduled. Out of window assessments will not be included in efficacy analyses and will be listed only.

Table 1: Time windows for spirometry assignments

Scheduled Spirometry Assessment Time	Allowed Start Time Window
30 minutes pre-dose	< first dose time of IP on the same day
5 minutes post-dose	3 to 9 minutes
15 minutes post-dose	10 to 19 minutes
30 minutes post-dose	20 to 59 minutes

3.3.3 Handling of Unscheduled Visits

All unscheduled visits will be included in listings. Unscheduled visits will not be considered for by-visit presentations.

3.3.4 Multiplicity/Multiple Comparisons

No procedures will be applied to handle multiplicity or multiple comparisons.

3.3.5 Handling of Protocol Deviations in Study Analysis

Protocol deviations are defined as any change, divergence, or departure from the study design of procedures defined in the CSP.

Important protocol deviations will be defined by AstraZeneca before database lock following the process described in the protocol deviation management plan and the project specific protocol deviations list. Important protocol deviations are a subset of protocol deviations which may significantly impact the correctness, accuracy, and / or reliability of the study data or that may significantly affect a participant's rights, safety or well-being. The following criteria may be considered as important protocol deviations which may have a major effect on efficacy or that could potentially affect the interpretability of the study results.

1. Informed Consent, such as ICF not signed before project specific assessments or procedures.

2. Study Conduct/Procedures, such as failure to complete or comply with inclusion/exclusion criteria, including discrepancy within source documentation and / or raw data, non-compliance with protocol requirements (Note: this does not include ICF issues), use of prohibited medication or prohibited treatment therapy or a participant's first dose date prior to baseline evaluations.

3. Investigational Product, such as inadequate supply of materials/IP (includes issues with regard to expiration date e.g. participant takes IP which has expired).

4. Safety, such as non-recording of AEs and SAEs by PIs (e.g. recording on time, etc.).

5. Use of LRTA or any inhaled bronchodilator within the restricted window prior to the clinical visit.

4 STATISTICAL ANALYSIS

This section provides information on definitions, derivation and analysis/data presentation per domain.

4.1 Study Population

The domain study population covers subject disposition, analysis sets, protocol deviations, demographics, baseline characteristics, medical history, prior and concomitant medication and study drug compliance.

4.1.1 Subject Disposition and Completion Status

4.1.1.1 Definitions and Derivations

Participants are defined as completing study treatment if the eCRF page "Discontinuation of Investigational Product" has a main reason for IP discontinuation as "Completed". Any other reasons for discontinuation of IP will be presented as "Subjects discontinued treatment". Participants are defined as completing the study if the eCRF page "Disposition" has a participant status of "Completed". Any other reason for discontinuation will be presented as "Withdrawn from Study".

4.1.1.2 Presentation

Participant disposition will be listed and summarised by assigned treatment sequence and in total. The number and percentage of participants in the following categories will be summarised for participants in the enrolled set:

Subjects screened;

Subjects who were screen failures;

Subjects randomised;

Subjects randomised, not treated and associated reasons;

Subjects who started treatment;

Subjects who completed treatment period 1;

Subjects who completed treatment period 2;

Subjects who completed both treatment periods;

Subjects who discontinued treatment and associated reasons;

Subjects who completed the study;

Subjects withdrawn from the study and associated reasons.

The denominator used for percentages will be calculated as follows. No percentages will be presented for the number of participants who were screened, screen failures, randomised and were not randomised. The denominator for participants who started treatment, completed treatment, discontinued treatment, completed the study and withdrew from the study will be calculated using the number of randomised participants per assigned treatment sequence and in total respectively.

Additionally, a summary of recruitment by region, country will be produced for each analysis set. The denominator for the percentages in this summary will be based on the number of participants within each of the analysis sets.

Furthermore, a summary of randomised participants by treatment sequence will present participants who discontinued treatment and withdrew from the study by whether the discontinuation/withdrawal was related to a global/country situation. Another summary of randomised participants by treatment sequence will present the number of participants who had any disruption during the study related to a global/country situation. Participants who discontinued treatment or withdrew from the study will also be listed.

4.1.2 Analysis Sets

4.1.2.1 Definitions and Derivations

The definitions for analysis sets are described in section 3.2.

4.1.2.2 Presentation

The number of participants in each of the analysis sets and the reasons for exclusion from each will be summarised for participants in the enrolled set by assigned treatment sequence and in total. Exclusions from analysis sets will also be listed.

4.1.3 Protocol Deviations

4.1.3.1 Definitions and Derivations

Important protocol deviations will be defined according to section 3.3.5, and determined prior to database lock as outlined in the protocol deviation management plan.

4.1.3.2 Presentation

All important protocol deviations will be listed and summarised by treatment sequence and in total for the randomised analysis set.

4.1.4 Demographics

4.1.4.1 Definitions and Derivations

The demographic and baseline characteristics include the following:

Age (years);

Age group (18-45);

Sex (male, female);

Race category (White, Black or African American, Asian, Native Hawaiian or Other Pacific Islander, American Indian or Alaskan Native, Other, Not reported);

Ethnic group (Hispanic or Latino, Not Hispanic or Latino);

Participant recruitment country.

4.1.4.2 Presentation

The demographic characteristics will be listed and summarised by treatment sequence and in total for the randomised analysis set. No formal tests of statistical significance will be performed on the demographic and baseline data.

4.1.5 Baseline Characteristics

4.1.5.1 Definitions and Derivations

Baseline body mass index (BMI; kg/m^2) will be calculated as baseline weight/baseline $height^2$ where weight is in kg and height is in m.

4.1.5.2 Presentation

The participant baseline characteristics will be listed and summarised by treatment sequence and in total for the randomised analysis set. They will include:

Baseline height (cm);

Baseline weight (kg);

BMI (kg/m^2).

4.1.6 Disease Characteristics

4.1.6.1 Definitions and Derivations

Not Applicable.

4.1.6.2 Presentation

Not Applicable.

4.1.7 Medical History and Concomitant Disease

4.1.7.1 Definitions and Derivations

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) [Version 26.0 (or a later version if updated during the study)].

4.1.7.2 Presentation

The number and percentage of participants with any medical history will be summarised by treatment sequence and in total for the randomised analysis set. The number and percentage of participants with at least one medical history record within each primary system organ class (SOC) and preferred term (PT) will be presented. The summary will be sorted by international order for SOC and alphabetically by PT. A participant can have one or more PTs reported under a given SOC but will be reported once per PT and SOC.

4.1.8 Prior and Concomitant Medications

4.1.8.1 Definitions and Derivations

Medications received prior to or concomitantly with study treatment will be coded using the WHO Drug Dictionary [Version March 2023 (or a later version if updated during the study)] Anatomical Therapeutic Chemical (ATC) Classification codes.

Prior medications and concomitant medications are defined as follows:

Prior medications are those taken with a stop date prior to, or on the day of, the first dose date of either study treatment.

Concomitant medications during the study are those with a start date after the first dose date of either study treatment, or those with a start date before, and either a stop date on or after the first dose date of either study treatment or those which are ongoing.

If a medication cannot be classified as prior or concomitant after applying imputation rules for missing/incomplete dates, it will be classified as concomitant.

Concomitant medications will be classified as allowed or disallowed by the Fortrea medical data review management team. Allowed and disallowed concomitant medications are described in sections 6.9.2 and 6.9.3 of the CSP respectively. Furthermore, the Fortrea medical data review management team will also classify LTRAs or any inhaled bronchodilator use as intercurrent events (ICEs).

4.1.8.2 Presentation

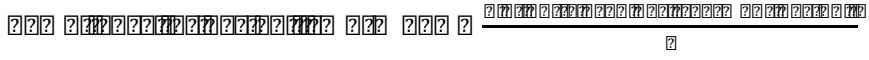
Prior medications and concomitant medications will be listed separately. Prior medications, allowed concomitant medications and disallowed concomitant medications will be summarised separately, by treatment sequence and in total using the randomised analysis set.

The number and percentages of participants using each medication will be displayed together with the number and percentage of participants using at least one medication within each ATC classification and generic drug name. The summaries will be sorted alphabetically by ATC classification and generic drug name.

4.1.9 Study Drug Compliance

4.1.9.1 Definitions and Derivations

The percentage compliance for MDI HFO and MDI HFA will be calculated per participant in each treatment period as:



Where i = 1, 2 for treatment periods 1 and 2 respectively and # of puffs used is taken from the eCRF "Exposure as Collected" page.

The percentage compliance will be calculated separately for treatment periods 1 and 2.

4.1.9.2 Presentation

Compliance will be summarised separately for treatment period 1 and treatment period 2 using the Safety Analysis Set and descriptive statistics (n; Mean; SD; Minimum; 1st quartile; Median, 3rd quartile; Maximum) with the number and proportion of participants in the following compliance categories:

- <100%
- 100%
- >100%

4.2 Endpoint Analyses

This section covers details related to the endpoint analyses such as primary, secondary, other endpoints including sensitivity and supportive analyses.

Table 2: Endpoint overview

Statistical category	Endpoint	Population	Intercurrent event (ICE) strategy	Population level summary (analysis)	Details in section
Objective 1: To assess the potential change in FEV1 induced by HFO MDI as compared with HFA MDI in participants with asthma					
Primary	Change from baseline in FEV_1 $AUC_{0\text{-}15\ min}$ post-dose	Primary Analysis Set	Participants who use Leukotriene receptor antagonists (LTRAs) or any inhaled bronchodilator within the restricted time window prior to a clinic visit that would directly affect airway calibre will be considered an ICE and will be treated using a principal stratum estimand. Participants who do not receive complete	The difference in the adjusted mean FEV_1 $AUC_{0\text{-}15\ min}$ estimates between treatment groups and corresponding 95% confidence interval (CI) as determined using a linear mixed model analysis	4.2.1

Statistical category	Endpoint	Population	Intercurrent event (ICE) strategy	Population level summary (analysis)	Details in section
			treatment in both periods will be excluded from the analysis using a principal stratum estimand. Participants missing FEV_1 measurements at baseline or post-dose up to 15 minutes in either treatment period will be removed from the analysis using a principal stratum estimand.		
Primary - Supplementary	Change from baseline in FEV_1 $AUC_{0\text{-}15\ min}$ post-dose	Safety Analysis Set	Participants who use LTRAs or any inhaled bronchodilator within the restricted time window prior to a clinic visit that would directly affect airway calibre will be considered an ICE and will be treated using a while on treatment strategy (i.e. observations after the ICE will be removed from the analysis). Participants missing FEV_1 measurements at baseline or post-dose up to 15 minutes in either treatment period will be removed from the analysis using a principal stratum estimand.	The difference in the adjusted mean FEV_1 $AUC_{0\text{-}15\ min}$ estimates between treatment groups and corresponding 95% CI as determined using a linear mixed model analysis	4.2.1.6
Objective 2: To assess the potential of bronchospasm induced by HFO MDI as compared with HFA MDI in participants with asthma					

Statistical category	Endpoint	Population	Intercurrent event (ICE) strategy	Population level summary (analysis)	Details in section
Secondary	Cumulative incidence of bronchospasm events	Safety Analysis Set	No ICE will be considered for analysis	The difference in the proportion of patients who experience an event by treatment and corresponding 2-sided 95% CI	4.2.2
Objective 3: To assess the safety and tolerability of HFO MDI as compared with HFA MDI in participants with asthma					
Secondary	Safety and tolerability will be evaluated in terms of AEs	Safety Analysis Set	No ICE will be considered for analysis	The number of adverse events for each treatment and for each treatment period will be summarised	4.6
Objective 4: To compare the FEV1 measurements between HFO MDI versus HFA MDI in participants with asthma					
CCI [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Statistical category	Endpoint	Population	Intercurrent event (ICE) strategy	Population level summary (analysis)	Details in section
			CCI [redacted]		

4.2.1 Primary Endpoint

Change from baseline in FEV_1 $AUC_{0\text{-}15\ min}$ post-dose

4.2.1.1 Definition

Primary estimand definition:

- Population: Participants with asthma, well controlled or partially controlled on SABA with or without low-dose ICS who are randomised to one of the study treatment sequences.
- Endpoint: Change from baseline in FEV_1 $AUC_{0\text{-}15\ min}$ post-dose
- Intercurrent event strategy: Participants who use Leukotriene receptor antagonists (LTRAs) or any inhaled bronchodilator within the restricted time window prior to a clinic visit that would directly affect airway calibre will be considered an ICE and will be treated using a principal stratum estimand (i.e. removed from the analysis). Participants who do not receive complete treatment in both periods will be excluded from the analysis using a principal stratum estimand. Participants missing FEV_1 measurements at baseline or up to 15 minutes in either treatment period will be removed from the analysis using a principal stratum estimand.
- Population level summary (analysis): The difference in the adjusted mean FEV_1 $AUC_{0\text{-}15\ min}$ estimates between treatment groups and corresponding 95% CI as determined using a linear mixed model analysis.

4.2.1.2 Derivations

Pre-dose spirometry will be performed at the scheduled time points of 30 minutes prior to dosing ($FEV_{1(0)}$), and post-dose spirometry at 5, 15 and 30 minutes after dosing. All measurements immediately after dosing up to the 15-minute window upper bound (i.e. 19 minutes per 3.3.2) will be used in the derivation of the primary endpoint, this may include multiple post-dose measurements per participant if these are available..

During each treatment period the change from baseline in FEV_1 $AUC_{0\text{-}15min}$ post-dose will be calculated using the trapezoidal rule:

$$Change\ from\ baseline\ in\ FEV_1\ AUC_{0-15min}\ post-dose = \frac{\sum_i \frac{\left(FEV_{1(i)} + FEV_{1(i+1)}\right) \times (T_{i+1} - T_i)}{2}}{T_{Total}} - FEV_{1(0)}$$

Where $FEV_{1(i)}$ and $FEV_{1(i+1)}$ are FEV_1 at time i and i+1, $FEV_{1(0)}$ is the pre-dose measurement, T_i and T_{i+1} are the observed times after the end time of dosing in minutes of the FEV_1 measurement and T_{Total} is the total observed time for the measurement from T_0 = 0. Measurements at pre-dose (in this calculation, included as T_0=0) and post-dose at 5 and 15 minutes will be included in the calculation.

CCI [redacted]

4.2.1.5 Sensitivity Analyses of the Primary Endpoint

No sensitivity analysis will be conducted to evaluate missing data assumptions.

4.2.1.6 Supplementary Analyses of the Primary Endpoint

As a supplementary analysis the following estimand will be applied:

Population: Participants with asthma, well controlled or partially controlled on SABA with or without low-dose ICS who randomised to one of the study treatment sequences and have received any amount of the study treatment.

Endpoint: Change from baseline in FEV_1 $AUC_{0\text{-}15\ min}$ post-dose.

Intercurrent event strategy: Participants who use LTRAs or any inhaled bronchodilator within the restricted time window prior to a clinic visit that would directly affect airway calibre will be considered an ICE and will be treated using a while on treatment strategy (i.e. observations after the ICE will be removed from the analysis). Participants missing FEV_1 measurements at pre-dose or post-dose up to 15 minutes in either treatment period will be removed from the analysis using a principal stratum estimand.

Population level summary (analysis): The difference in the adjusted mean FEV_1 $AUC_{0\text{-}15\ min}$ estimates between treatment groups and corresponding 95% CI as determined using a linear mixed model analysis.

The analysis method will be as specified in section 4.2.1.4.

4.2.1.7 Subgroup Analyses

No subgroup analyses are planned for the primary endpoint.

4.2.2 Secondary Endpoint

Cumulative incidence of bronchospasm events.

4.2.2.1 Definition

Cumulative incidence of bronchospasm events in the safety analysis set. 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 administration) at 5 or 15 minutes post-dose with associated symptoms of wheezing, shortness of breath, or cough. The difference in the proportion of patients who experience a bronchospasm event between treatment groups will be summarised along with the 2-sided 95% CI.

4.2.2.2 Derivations

An event of bronchospasm per treatment period will be detected using either (i) information from the Adverse Event form and a MedDRA narrow SMQ of “Asthma/bronchospasm”, (ii) 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 an

associated AE during the day of study intervention administration with a preferred term of either “Wheezing”, “Dyspnoea” or “Cough”.

4.2.2.3 Handling of Dropouts and Missing Data

No adjustment for dropout or missing data will be applied.

4.2.2.4 Primary Analysis of Secondary Endpoint

The proportion of participants with a bronchospasm event by treatment received will be analysed using McNemar’s test of marginal homogeneity. 95% CIs for the proportions will be calculated using a generalised linear mixed model with a binomial distribution and an identity link and with dependent variable of Bronchospasm event and independent variables of actual treatment received, treatment period and actual treatment sequence. A per participant random intercept effect will be included in the model. The least square mean estimates (proportion) and 95% CI per actual treatment received, and the difference in least square mean (proportions) with 95% CI will be presented.

4.2.2.5 Sensitivity Analyses of the Secondary Endpoint

No sensitivity analyses are planned for the secondary endpoint.

4.2.2.6 Supplementary Analyses of the Secondary Endpoint

No supplementary analyses are planned for the secondary endpoint.

4.2.2.7 Subgroup Analyses

No subgroup analyses are planned for the secondary endpoint.

CCI [redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]

CCI [redacted]

4.3 Pharmacodynamic Endpoint(s)

Not Applicable.

4.4 Pharmacokinetics

Not Applicable.

4.5 Immunogenicity

Not Applicable.

4.6 Safety Analyses

The domain safety covers exposure, adverse events, clinical laboratory, vital signs, and ECG.

Tables are provided for the safety analysis set; listings are provided for all participants or the safety set depending on the availability of data.

4.6.1 Exposure

4.6.1.1 Definitions and Derivations

Exposure (i.e. duration of treatment) will be defined per treatment period as follows:

> Total duration of exposure during treatment period i = last dose date during treatment period i where puff>0 – first dose date during treatment period i + 1

Per protocol this should be 1 day per participant per treatment period. Interruption of treatment is not considered in the calculation of exposure.

4.6.1.2 Presentation

Total duration of exposure (days) per treatment period i will be summarised and listed by actual treatment sequence for the safety analysis set by the following: mean, standard deviation, minimum, maximum, median and number of observations. The listing will include date of first exposure to treatment, total duration of exposure and, for each visit, the prescribed dose per administration and planned dose.

4.6.2 Adverse Events

4.6.2.1 Definitions and Derivations

All Adverse events, non-serious and serious adverse events (SAEs), will be collected from time of signature of the informed consent form, throughout the treatment period including during the follow-up period. Treatment emergent adverse events are defined in section 3.3.1.

Adverse events of special interest (AESIs) in this study are respiratory events such as dysphonia, cough, dyspnoea, wheezing, bronchospasm, and asthma exacerbations. See section 7.4.6 of the CSP for details.

Adverse events will be assigned to the respective treatment period based on the AE start date and time according to the treatment period definitions in section 3.3.1.2. Adverse

events which occur during treatment period i, will be assigned to the treatment received by that participant during that treatment period.

MedDRA [Version 26.0 (or a later version if updated during the study)] will be used to classify AEs SOC and PT.

Every effort should be made to collect the maximum intensity and relationship to treatment for all AEs. However, if the maximum intensity is missing for a TEAE then it will be considered as severe only in the overall category in the summary tables. If the relationship to treatment is missing, then the AE will be considered as possibly related to treatment.

Deaths

All adverse events leading to death, including those not related to an AE, will be collected until the end of the study.

4.6.2.2 Presentation

4.6.2.2.1 Overall AE Summary

An overall summary table of the number of participants experiencing each category of AEs will be produced using the safety analysis set. Analyses will include all TEAEs and will be presented for each treatment group.

Treatment emergent adverse events occurring prior to first dose of IP (i.e. before study day 1) which subsequently worsen in severity following dosing will be presented in the summary tables. All other AEs occurring prior to first dose of IP (i.e. before study day 1) or more than 7 days after the discontinuation of IP will be noted in the listings of adverse events.

An overview table will summarise the number and percentage of participants with at least one of the following AEs, where participants with more than one AE in a particular category are counted only once in that category, and the number of events. The summary table will be presented for each treatment group:

Any AE

Any SAE

Any SAE with outcome of death

Any AE leading to discontinuation of IP

Any possibly related AE

Any possibly related SAE

Any AESI.

4.6.2.2.2 Number of subjects with AEs

The number of participants reporting each AE will be summarised by SOC and PT. Tables will be sorted by international order for SOC and PTs will be sorted alphabetically. Summaries will be presented for each treatment group. The following summaries will be produced using the safety analysis set:

AEs

Possibly related AEs

AEs by maximum intensity

AEs leading to discontinuation of IP

Non-serious AEs occurring in more than 5% of subjects

SAEs

SAEs with outcome of death

Possibly related SAEs

AESIs

Possibly related AESIs

AESIs by maximum intensity.

A summary table of AEs sorted by decreasing frequency of PT in the HFO treatment group will be presented.

All AE data will be listed for all participants including information on AE duration, intensity, seriousness, action taken, outcome, relationship as assessed by the investigator, timing of onset of AE in relation to the date of study treatment, study treatment and treatment period at the time of event. Tables will present key subject information for all AEs leading to discontinuation of IP, SAEs with outcome of death and SAEs.

4.6.3 Clinical Laboratory

4.6.3.1 Definitions and Derivations

Clinical laboratory (serum and urine) assessments are scheduled to be conducted at screening only.

4.6.3.2 Presentations

Clinical laboratory data will be listed where available for the Safety Analysis Set.

4.6.4 Other Laboratory Evaluations

4.6.4.1 Definitions and Derivations

Not Applicable.

4.6.4.2 Presentations

Not Applicable.

4.6.5 Vital Signs

4.6.5.1 Definitions and Derivations

Vital signs will be evaluated and assessed at screening (visit 1), pre-dose in treatment period 1/day 1 (visit 2), pre-dose in treatment period 2/day 1 (visit 3) and at the withdrawal visit according to the SoA. Vital signs include systolic blood pressure (mmHg), diastolic blood pressure (mmHg), pulse rate (beats per minute), body temperature (ºC) and respiratory rate (breaths per minute).

4.6.5.2 Presentations

Vital sign values will be listed only for the Safety Analysis Set.

4.6.6 Electrocardiogram

4.6.6.1 Definitions and Derivations

Electrocardiogram (ECG) assessments will be performed at screening only according to the SoA. ECG parameters will include heart rate (beats/min), PR interval (msec), RR interval (msec), QRS duration (msec), QT interval (msec) and QTcF (msec).

4.6.6.2 Presentations

ECG data will be listed for the Safety Analysis Set.

4.6.7 Other Safety Assessments

4.6.7.1 Definitions and Derivations

The Asthma Control Questionnaire (ACQ) 5 will be assessed during screening (Visit 1) to confirm participant’s eligibility. Physical examination assessments will be performed

during screening (Visit 1), Treatment Period 1/Day 1 (Visit 2), Treatment Period 2/Day 1 (Visit 3) and withdrawal visit as required according to the SoA.

4.6.7.2 Presentations

ACQ-5 responses and total score will be listed. Physical examination results will not be listed as new or aggravated findings, as compared with baseline, are to be reported as AEs.

5 INTERIM ANALYSIS

Not Applicable.

6 REFERENCES

Not Applicable.

7 APPENDIX

Not Applicable.