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A Phase II, Randomized, Double-blind, Single-dose, Placebo-controlled, 3-Period, 3-Treatment, Crossover, Multicenter Study to Compare the Bronchodilatory Effect and Safety of PT007 to Placebo MDI and Open-Label Ventolin® Evohaler in Adult Participants with Asthma (MITCHELL)

Sponsor Name: AstraZeneca AB

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Regulatory Agency Identifier Number(s):

Registry	**ID**
IND	136213

This protocol has been participant 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 Evaluating the Effect of Inhaled PT007 (AS MDI) Versus Placebo MDI and Ventolin Evohaler on Lung Function in Adult Participants with Asthma

Study Phase: Phase II

Acronym**:** MITCHELL

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).

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or special term	Explanation
ADE(s)	Adverse device effect(s)
AE(s)	Adverse event(s)
AIM	Aerosol inhalation monitor
AS MDI	Albuterol sulfate metered-dose inhaler
ATS	American Thoracic Society
AUC	Area under the curve
AUC0-4	Area under the curve from time zero to 4 hours
AUC0-6	Area under the curve from time zero to 6 hours
AxMP	Auxiliary medicinal product
BDA	Budesonide/albuterol
β-hCG	β-human chorionic gonadotropin
BID	Twice a day
CE	The CE marking (an acronym for the French “Conformite Europeenne”) certifies that a product has met EU health, safety, and environmental requirements, which ensure consumer safety.
CFR	Code of Federal Regulations
CI	Confidence interval
CRO	Contract research organization
CSR	Clinical study report
CTIS	Clinical Trials Information System
CYP3A4	Cytochrome P450 3A4
DPI	Dry powder inhaler
DUS	Disease under study
eCRF	Electronic case report form
EDC	Electronic data capture
ERS	European Respiratory Society
EU	European Union
EU CTIS	EU Clinical Trials Information System
EudraCT	EU Drug Regulating Authorities Clinical Trials Database
FAS	Full analysis set
FDA	Food and Drug Administration
FEV1	Forced expiratory volume in the first second: the volume delivered in the first second of an FVC maneuver
FVC	Forced vital capacity: the volume delivered during an expiration made as forcefully and completely as possible starting from full inspiration

Abbreviation or special term	Explanation
GCP	Good Clinical Practice
GINA	Global Initiative for Asthma
HFA	Hydrofluoroalkane
IB	Investigator's brochure
ICF(s)	Informed consent form(s)
ICH	International Council for Harmonisation
ICS	Inhaled corticosteroid
IE(s)	Intercurrent event(s)
IEC	Independent Ethics Committee
IMP(s)	Investigational medicinal product(s)
IRB	Institutional Review Board
IRT	Interactive response technology
LABA	Long-acting β2-adrenoreceptor agonist
MAR	Missing at random
MCID	Minimum clinically important difference
MDI	Metered-dose inhalers
MedDRA	Medical Dictionary for Regulatory Activities
NA	Not applicable
NIMP(s)	Non-investigational medicinal product(s)
PFTs	Pulmonary function tests
PI	Prescribing information
pMDI	Pressurized metered-dose inhaler
PN	Predicted normal
Post-BD	Post-bronchodilator
Pre-BD	Pre-bronchodilator
PDV	Premature discontinuation visit
POCBP	Participant(s) of childbearing potential
QID	Four times daily
QTcF	QT interval corrected by Fredericia
SABA(s)	Short-acting β2-adrenoreceptor agonist(s)
SADE(s)	Serious adverse device effect(s)
SAE(s)	Serious adverse event(s)
SAP	Statistical analysis plan
SD	Standard deviation
SmPC	Summary of Product Characteristics
SoA	Schedule of activities

Abbreviation or special term	Explanation
SUSAR(s)	Suspected unexpected serious adverse reaction(s)
UK	United Kingdom
US	United States
USADE(s)	Unanticipated serious adverse device effect(s)
USAN	United States Adopted Names
V	Visit

1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title:

A Phase II, Randomized, Double-blind, Single-dose, Placebo-controlled, 3-Period, 3-Treatment, Crossover, Multicenter Study to Compare the Bronchodilatory Effect and Safety of PT007 to Placebo MDI and Open-Label Ventolin® Evohaler in Adult Participants with Asthma (MITCHELL)

Brief Title:

A Study Evaluating the Effect of Inhaled PT007 (AS MDI) Versus Placebo MDI and Ventolin Evohaler on Lung Function in Adult Participants with Asthma

Regulatory Agency Identifier Number(s):

Registry	ID
IND	136213

Rationale:

Albuterol sulfate is a short-acting β2-adrenoreceptor agonist (SABA) that is used as needed (ie, reliever therapy). The test formulation to be evaluated in this study (PT007) is a metered-dose inhaler (MDI) containing albuterol sulfate (albuterol sulfate [AS] pressurized inhalation suspension; hereafter referred to as AS MDI). This study is designed to assess the bronchodilatory effect of a single dose of 180 µg AS MDI relative to a single dose of 200 µg open-label Ventolin® Evohaler (a pressurized metered-dose inhaler delivering albuterol [as salbutamol sulfate]). A single dose of placebo MDI will also be included as a control.

The objective of the study is to compare the therapeutic efficacy and safety of a single dose of albuterol delivered from AS MDI relative to Ventolin Evohaler on post-dose lung function in adults with asthma.

The primary endpoint is the change from baseline in forced expiratory volume in one second (FEV1) area under the curve from 0 to 6 hours (AUC0-6), and secondary endpoints include the change from baseline in FEV1 area under the curve from 0 to 4 hours (AUC0-4) and the peak change from baseline in FEV1.

Objectives, Endpoints, and Estimands

Objectives	Endpoints/Estimand
Primary	
To demonstrate the non-inferiority of a single dose of albuterol delivered from AS MDI relative to Ventolin Evohaler on post-dose lung function in adults with asthma	Treatment: AS MDI and Ventolin Evohaler Population: Adults with asthma (pre-BD FEV1 of ≥ 40% of the PN value), with demonstrated FEV1 reversibility to Ventolin HFA [a] and who would comply with and complete both the AS MDI and Ventolin Evohaler treatment periods in the study. Participant-level outcome: Change from baseline in FEV1 AUC0-6 Strategy for IEs: Defined as a participant who for any reason does not have post-treatment efficacy data in the AS MDI or Ventolin Evohaler treatment periods. The principal stratum strategy will be implemented such that an IE is captured through the population definition. The IEs identified will include non-compliance with the study protocol [b] and failure to complete both treatment periods (AS MDI and Ventolin Evohaler). Participants that have any IEs will not be included in the analysis. Summary measure: Mean difference in change from baseline in FEV1 AUC0-6
To establish assay sensitivity of a single dose of albuterol delivered from Ventolin Evohaler compared with placebo on post-dose lung function in adults with asthma	Treatment: Ventolin Evohaler and placebo [c] Participant-level outcome: Change from baseline in FEV1 AUC0-6 Summary measure: Mean difference in change from baseline in FEV1 AUC0-6
Secondary	
Key: To demonstrate the therapeutic equivalence of a single dose of albuterol delivered from AS MDI relative to Ventolin Evohaler on post-dose lung function in adults with asthma	Treatment: AS MDI and Ventolin Evohaler [c] Participant-level outcome: Change from baseline in FEV1 AUC0-6 [c] Summary measure: Mean difference in change from baseline in FEV1 AUC0-6
To characterize the non-inferiority/therapeutic equivalence of a single dose of albuterol delivered from AS MDI relative to Ventolin Evohaler on post-dose lung function in adults with asthma	Treatment: AS MDI and Ventolin Evohaler [c] Participant-level outcome: change from baseline in FEV1 AUC0-4 Summary measure: Mean difference in change from baseline in FEV1 AUC0-4
To establish assay sensitivity of a single dose of albuterol delivered from Ventolin Evohaler compared with placebo on post-dose lung function in adults with asthma	Treatment: Ventolin Evohaler and placebo [c] Participant-level outcome: Change from baseline in FEV1 AUC0-4 Summary measure: Mean difference in change from baseline in FEV1 AUC0-4

Objectives	Endpoints/Estimand
To characterize the non-inferiority/therapeutic equivalence of a single dose of albuterol delivered from AS MDI relative to Ventolin Evohaler on post-dose lung function in adults with asthma	Treatment: AS MDI and Ventolin Evohaler [c] Participant-level outcome: Peak change from baseline in FEV1 Summary measure: Mean difference in peak change from baseline in FEV1
To establish assay sensitivity of a single dose of albuterol delivered from Ventolin Evohaler compared with placebo on post-dose lung function in adults with asthma	Treatment: Ventolin Evohaler and placebo [c] Participant-level outcome: Peak change from baseline in FEV1 Summary measure: Mean difference in peak change from baseline in FEV1
Safety	
To evaluate the safety and tolerability of a single dose of albuterol delivered from AS MDI compared to Ventolin Evohaler in adults with asthma	AEs/SAEs
Exploratory	
To compare the therapeutic efficacy of a single dose of albuterol delivered from AS MDI compared to placebo in adults with asthma	Change from baseline in FEV1 AUC0-6 Change from baseline in FEV1 AUC0-4 Peak change from baseline in FEV1
To further characterize the therapeutic efficacy of a single dose of albuterol delivered from AS MDI relative to Ventolin Evohaler in adults with asthma	Change from baseline in FEV1 at each post-dose time point Time to peak FEV1 Percentage of participants achieving 12% improvement in FEV1 from baseline within 30 minutes of dose Percentage of participants achieving 15% improvement in FEV1 from baseline within 30 minutes of dose Time to onset of response Duration of response

[a] A participant is considered to have reversibility to Ventolin HFA if the improvement in FEV1 at 30 minutes post-Ventolin HFA is ≥ 12% and ≥ 200 mL.
[b] Non-compliance includes taking prohibited medication and lung function data judged to be impacted by major protocol deviations.
[c] Population and strategy for IEs attributes are the same as the primary estimand specified for the noninferiority and therapeutic equivalence objectives.

AEs, adverse events; AS MDI, albuterol sulfate metered-dose inhaler; AUC0-4, area under the concentration-time curve from time zero to 4 hours; AUC0-6, area under the concentration-time curve from time zero to 6 hours; FEV1, forced expiratory volume in the first second; HFA, hydrofluoroalkane; IE(s), intercurrent event(s); PN, predicted normal; pre-BD, pre-bronchodilator; SAEs, serious adverse events

Overall Design Synopsis:

This is a randomized, double-blind, single-dose, placebo-controlled, 3-period, 3-treatment, crossover, multicenter study to assess the bronchodilatory effect and safety of AS MDI (180 µg) compared with placebo MDI and open-label Ventolin Evohaler (200 µg) in adult

participants (aged 18 to 65 years, inclusive) with asthma (pre-bronchodilator FEV1 of ≥ 40% of the predicted normal value) and demonstrated FEV1 reversibility to Ventolin hydrofluoroalkane (HFA) (improvement in FEV1 at 30 minutes post-Ventolin HFA dosing of ≥ 12% and ≥ 200 mL). Participants must be receiving either SABA as needed for rescue or low to medium doses of ICS ± LABA as maintenance asthma therapy for at least 30 days prior to screening (Visit 1).

This study consists of a screening/run-in period, a treatment period, and a follow-up phone call.

During the screening/run-in period, all participants in this study will discontinue their current asthma medications at Visit 1 and initiate sponsor-provided asthma medication(s) as follows:

- Participants who were using only SABA as needed for at least 30 days as a consistent regimen before Visit 1 will discontinue their SABA and initiate sponsor-provided Ventolin HFA for use as needed. Sponsor-provided Ventolin HFA is allowed during the screening/run-in period and throughout the study, up until 6 hours before a study visit. The minimum screening/run-in period for these participants will be 3 days.
- Participants who were using a regularly scheduled inhaled corticosteroid (ICS) or ICS/long-acting β2-adrenoreceptor agonist (LABA) for at least 30 days as a consistent regimen before Visit 1 will discontinue their ICS or ICS/LABA and initiate sponsor-provided Pulmicort Flexhaler™ for use as maintenance therapy (either 180 µg or 360 µg twice a day based on the participant's previous ICS therapy, irrespective of LABA use), along with sponsor-provided Ventolin HFA for use as needed. Sponsor-provided background asthma medications, Pulmicort Flexhaler and Ventolin HFA, are allowed during the screening/run-in period and throughout the study, up until 12 and 6 hours, respectively, before a study visit. The minimum run-in period for these participants will be 14 days.

The maximum screening/run-in period for all participants will be 28 days.

Randomization will take place at Visit 2 and will be centralized using interactive response technology. Randomization is planned to be stratified by pre-study background asthma maintenance therapy: participants using an ICS and participants not using an ICS (ie, receiving only SABA as needed).

Eligible participants will be randomized to 1 of 6 predefined treatment sequences in a 1:1:1:1:1:1 ratio. Each sequence will contain AS MDI, placebo MDI, and Ventolin Evohaler in a randomized order.

Eligible participants will receive a single dose of randomized study intervention at each of 3 treatment visits (Visits 2, 3, and 4), with a 3- to 7-day washout period between treatment visits. One of the following treatments is taken during 1 of the 3 treatment visits:

- AS MDI 180 µg (2 actuations of 90 µg/actuation)
- Placebo MDI (2 actuations to match AS MDI)
- Ventolin Evohaler 200 µg (2 actuations of 100 µg/actuation)

At each treatment visit, bronchodilation activity of the study interventions will be assessed through pulmonary function tests. Participants will be required to remain at the clinic until completion of all protocol-defined assessments up to and including the 6-hour post-dose time point. Safety will be assessed by evaluation of adverse events (AEs) and serious adverse events (SAEs).

AS MDI and placebo MDI will be blinded to all participants, study site staff, endpoint assessors, and sponsor personnel, whereas Ventolin Evohaler will be open label. However, to reduce bias, dosing will be performed under the supervision of study staff, and spirometry assessments will be performed by different study personnel who will only enter the room after dosing is completed; thus, the study personnel conducting the spirometry assessments will be blinded to the identity of the study intervention.

Participants who prematurely discontinue the study for any reason before completing all period visits in the study will undergo a premature discontinuation visit (PDV). After the last treatment period or following a PDV, participants will be scheduled for a follow-up telephone call to occur 3 to 7 days after the last dose of study intervention.

This study will be conducted at approximately 25 sites. Approximately 102 participants will be randomized to ensure that at least 90 participants complete the study.

Each participant will be in the study for a minimum of 15 days and up to a maximum of 52 days, including a 3- to 28-day screening/run-in period, a 3-part treatment period, and a follow-up telephone call 3 to 7 days after the final dose of study intervention. The study is anticipated to run for approximately 6 months, including the recruitment period.

Brief Summary:

The purpose of this Phase II, randomized, single-dose, double-blind, placebo-controlled, 3-period, 3-treatment arm, crossover, multicenter, interventional study is to investigate the therapeutic efficacy and safety of inhaled PT007 (referred to as AS MDI) compared with placebo MDI and open-label Ventolin Evohaler in male and female participants aged 18 to 65 years (inclusive) with asthma.

Study details include:

- The study duration will be a minimum of 15 days and up to a maximum of 52 days.
- The study will have a screening/run-in period of 3 to 28 days.
  - A minimum of 14 days for participants who will be switched from ICS or ICS/LABA to sponsor-provided Pulmicort Flexhaler (for maintenance) + sponsor-provided Ventolin HFA (for rescue) at Visit 1.
  - A minimum of 3 days for participants who will be switched from only SABA as needed to sponsor-provided Ventolin HFA (for rescue) at Visit 1.
  - The maximum screening/run-in period for all participants will be 28 days.
- The treatment period (3 clinic visits) will be up to 17 days.
- The visit frequency during the treatment period will be every 3 to 7 days.
- A follow-up telephone call will occur 3 to 7 days after the last dose of study intervention.

Disclosure Statement:

This is a Phase II, randomized, double-blind, single-dose, placebo-controlled, 3-period, 3-treatment arm crossover treatment study of PT007 (AS MDI) where AS MDI and placebo MDI are blinded to all participants and study site staff and the comparator (Ventolin Evohaler) is open label.

Number of Participants:

Approximately 102 participants (17 per treatment sequence) will be randomized to study interventions such that approximately 90 evaluable participants complete the study.

Note: 'Screened' means a participant's agreement to participate in a clinical study following completion of the informed consent process. Potential participants who are screened for the purpose of determining eligibility for the study, but are not randomized/assigned in the study, are considered 'screen failures', unless otherwise specified by the protocol.

Study Arms and Duration:

After a screening/run-in period of 3 to 28 days, eligible participants will be randomized at Visit 2 to 1 of 6 predefined treatment sequences in a 1:1:1:1:1:1 ratio.

One of the following treatments is taken during 1 of the 3 treatment visits within the predefined randomization sequence:

- AS MDI 180 µg (2 actuations of 90 µg/actuation)
- Placebo MDI (2 actuations to match AS MDI)
- Ventolin Evohaler 200 µg (2 actuations of 100 µg/actuation)

Each participant will receive a single dose of randomized study intervention at each of 3 treatment visits (Visits 2, 3, and 4), with a 3- to 7-day washout period between treatment visits.

Each participant will be in the study for a minimum of 15 days and up to a maximum of 52 days, including a screening period of 3 to 28 days, a treatment period of 9 to 17 days, and a telephone call 3 to 7 days after the final dose of study intervention.

Data Monitoring/Other Committee: Not Applicable

No committees have been set up for this study.

Statistical Methods

Analysis Sets

The following analysis set are defined in this study:

- All enrolled set: The enrolled set is defined as all participants for whom informed consent to participate in the study was obtained and have a participant identification number.
- Randomized set: The randomized set is defined as all participants who are randomized to study intervention.
- Full analysis set (FAS): The FAS is defined as all participants who are randomized to study intervention and receive at least one inhalation of the study intervention. Participants will be analyzed in each period according to the study intervention they received.
- Safety analysis set: The safety analysis set is defined as all participants who are randomized to study intervention and receive at least one inhalation of the study intervention. Participants will be analyzed according to the study intervention received rather than per the randomization scheme.

Primary Analysis

The primary endpoint is the mean change from baseline in FEV1 AUC0-6. The AUC0-6 is the area under the curve for the change from baseline in FEV1 calculated using the trapezoidal rule from dosing until 6 hours post-dosing.

Baseline FEV1 will be defined as the period-specific mean of available pre-dose values, eg, the mean of the 60- and 30-minute acceptable pre-dose values. If only one value is available or acceptable, that value will be used as baseline. All observed data will be utilized with the trapezoidal rule to calculate AUC. To aid in interpretation, all AUC values will be normalized by dividing the AUC by the time from the first to the last non-missing value (typically 6 hours).

The change from baseline FEV1 AUC0-6 will be analyzed using a linear mixed model with a random participant effect. The fixed effects in the model will include treatment and period. An additional covariate for average baseline (period-specific baseline FEV1 averaged over the treatment periods) will also be included to remove cross-level bias. For the treatment comparison of AS MDI versus Ventolin Evohaler, the treatment estimates, standard errors, and mean treatment difference and the associated 90% confidence interval (CI) will be provided for the non-inferiority (and equivalence) comparisons.

To demonstrate non-inferiority, the lower bound of the 90% CI for the treatment difference must be > -100 mL.

To establish assay sensitivity, the comparison of Ventolin Evohaler versus placebo for the change from baseline in FEV1 AUC0-6 will be made to establish superiority. The analysis will evaluate the primary estimand based on the FAS using the same linear mixed model as described above.

Treatment estimates, standard errors, and the estimated treatment difference with associated 90% and 95% CIs and p-values will be provided. The comparison of AS MDI versus placebo will also be conducted but will be considered exploratory.

Non-inferiority between AS MDI and Ventolin Evohaler based on the change from baseline in FEV1 AUC0-6 can only be declared if superiority of Ventolin Evohaler compared to placebo is also demonstrated.

Analyses of Secondary Endpoints

If non-inferiority and assay sensitivity are established, a secondary comparison of AS MDI versus Ventolin Evohaler to establish therapeutic equivalence will be made. If the 2-sided 90% CI is entirely enclosed within the equivalence margins of ± 100 mL, it will be concluded that the 2 treatments are equivalent.

The secondary endpoints will be analyzed using an approach similar to that of the primary endpoint.

Safety Analyses

Safety and tolerability data will be assessed by evaluation of AEs/SAEs and summarized descriptively by using tables, listings, and graphs, as appropriate.

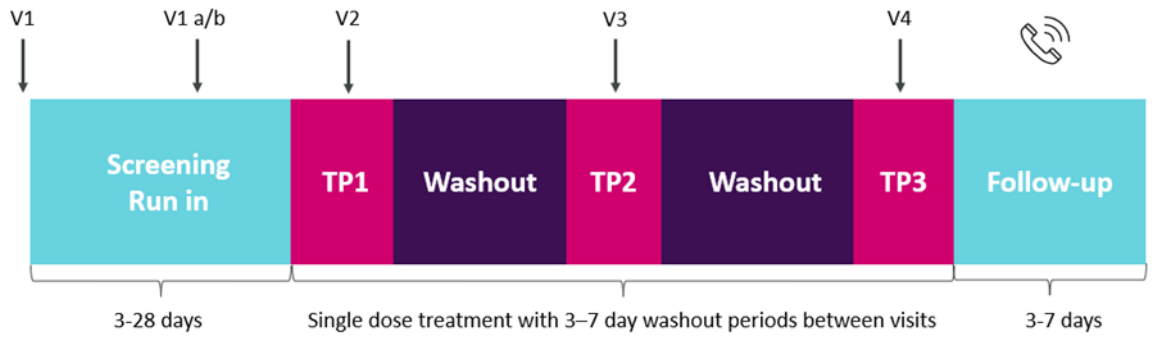
Sample Size

To ensure at least 90 participants complete the study, approximately 102 participants (17 per treatment sequence) will be randomized to account for a 10% dropout rate. Ninety participants will provide > 95% overall probability to demonstrate superiority of each treatment relative to placebo MDI assuming a true treatment difference (active-placebo MDI) of 190 mL, SD of the

period differences of 204 mL, and 2-sided 5% level test. This sample size will also provide around 95% probability of obtaining a 2-sided 90% CI (equivalent to 2 one-sided hypotheses tests each performed at the 5% significance level) for the difference between AS MDI and Ventolin Evohaler within the equivalence bounds of ± 100 mL. This calculation assumes a true between-treatment difference (AS MDI – Ventolin Evohaler) of 28 mL and an SD of the differences of 204 mL. The assumptions of the SD of the differences and the treatment difference were obtained from a 5-treatment, 5-period, placebo-controlled, dose-ranging study that compared AS MDI to placebo MDI and open-label Proventil® HFA in adult and adolescent participants with mild to moderate asthma (Study D6930C00001/PT007001). An assumption of 204 mL for the SD of the differences is supported by the upper limit of the 95% CI of the sampling distribution (184 mL; 95% CI: 164, 204), and a true between-treatment difference assumption of 28 mL is supported by the (magnitude of) average difference between AS MDI and Proventil HFA for the 90 and 180 µg doses.

1.2 Schema

Figure 1 Study Design



For participants who received their regularly inhaled asthma medications and/or SABA on the morning of Visit 1, reversibility will be measured at Visit 1a, which will occur within 10 days of Visit 1. For participants who do not meet the reversibility criteria at Visit 1 or Visit 1a, Visit 1a or Visit 1b, respectively, will be scheduled for a second reversibility test to occur within 7 days. Only 2 reversibility testing attempts are allowed. A follow-up phone call will be scheduled 3 to 7 days after the last dose of study intervention.
TP, treatment period; V, visit

1.3 Schedule of Activities

Table 1 Schedule of Activities

Visit	Screening/Run-in [a]		Treatment periods 1, 2, and 3		Follow-up TC	Details in protocol Section or appendix
	1	1a/b	2, 3, 4 [b]	PDV [c] (if applicable)		
Days	**Day -28 to -1**		**Day 1**		**3 to 7 days after final dose**	
Procedures						
Informed consent	X					5.1, 5.2, 8.1.1, and Appendix A 3
Eligibility criteria	X					5.1 and 5.2
Verify randomization criteria			X [d]			5.2.1
Clinical procedures						
Demographics	X					8.1.3
Medical/surgical history	X					8.1.4
Physical examination	X [e]		X [f]	X		8.3.1
Concomitant medications [g]	X	X	X	X	X	6.9
Inhalation technique practice and verification with Vitalograph AIM™ inhalation training device and device training with placebo MDI [h]	X	X	X			8.1.1, 8.2.1
Ventolin HFA reversibility test [i]	X	X				8.2.4
Adjust asthma medications per protocol [j]	X	X	X	X		6.9.1 and 6.9.2.1
Spirometry	X [k]	X	X [l]			8.2.2 and 8.2.3
Confirm FEV1 baseline stability			X [m]			6.2.2.3, 8.1.2, 8.2.5
Routine safety measurements						
Vital signs (heart rate and blood pressure)	X	X	X [n]	X		8.3.2

Table 1 Schedule of Activities

Visit	Screening/Run-in [a]		Treatment periods 1, 2, and 3		Follow-up TC	Details in protocol Section or appendix
	1	1a/b	2, 3, 4 [b]	PDV [c] (if applicable)		
Days	**Day -28 to -1**		**Day 1**		**3 to 7 days after final dose**	
AEs/SAEs [o]	X	X	X	X	X	8.4, Appendix B, and Appendix C
Pregnancy test [p]	X		X	X		8.3.4 and 8.4.10
Study intervention administration						
Randomization			X [d]			6.3
Study intervention administration			X			6.2.2
Non-investigational medicinal products						
Collect pre-study asthma medications [q]	X					6.9.1 and 8.1.1
Return pre-study asthma medications [r]			X	X		6.9.1, 8.1.2
Collect/return sponsor-provided Pulmicort Flexhaler (if applicable) and Ventolin HFA [s]		X	X	X		6.2.2.2, 8.1.2

[a] Screening period will be 3 to 28 days for participants on only SABA as needed before study entry and 14 to 28 days for participants on ICS or ICS/LABA before study entry.

[b] Participants will return to the clinic 3 to 7 days (washout period) following Visits 2 and 3. Participants should stop sponsor-provided asthma medication: Pulmicort Flexhaler for at least 12 hours before a study visit and Ventolin HFA for at least 6 hours before a study visit.

[c] Participants who prematurely discontinue/withdraw from the study will undergo a PDV.

[d] Visit 2 only.

[e] Includes evaluation of height and weight at Visit 1.

[f] Visit 4 only.

[g] At all visits beyond Visit 1, note the time of the last dose of sponsor-provided asthma medications. The visit must be rescheduled if the last dose of Ventolin HFA was < 6 hours before a study visit or if the last dose of Pulmicort Flexhaler (if assigned) was < 12 hours before a study visit.

[h] At Visit 1 (and Visits 1a and/or 1b, if applicable), Vitalograph AIM inhalation technique training and device training with placebo MDI must be performed prior to spirometry and Ventolin HFA reversibility test, as applicable. At every treatment period (Visits 2, 3, and 4), Vitalograph AIM inhalation technique training and device training with placebo MDI must be performed pre-dose.

[i] For participants who did not administer their morning asthma maintenance medications, as applicable, and/or SABA, reversibility will be measured at Visit 1. For participants who received their regularly inhaled asthma maintenance medications, as applicable, and/or SABA on the morning of Visit 1, reversibility will be measured at Visit 1a, which will occur within 10 days of Visit 1. For participants who do not meet reversibility criteria at Visit 1 or Visit 1a, Visit 1a or Visit 1b, respectively, will be scheduled for a second reversibility test to occur within 7 days. Participants who do not meet reversibility criteria after the second attempt will be screen failed.

[j] At Visit 1, prohibited asthma medications are to be stopped and asthma medications changed as specified in the protocol. At the end of Visit 4 (or upon premature discontinuation or screen failure, if applicable), participants will return to pre-study or other appropriate maintenance asthma medications.

[k] For participants who received their regularly inhaled asthma maintenance medications and/or SABA on the morning of Visit 1, spirometry will be performed at Visit 1a, which will occur within 10 days of Visit 1.

[l] At each treatment visit, spirometry will be obtained 60 and 30 minutes pre-dose and 5, 15, 30, 45, 60, 120, 180, 240, 300, and 360 minutes post-dose. Three tests will be performed at each time point. The highest acceptable value at each time point will be used for the post-dose assessments.

[m] Before the in-clinic dose of study intervention is administered at Visits 3 and 4, the site must confirm that the participant meets FEV1 baseline stability criteria. Participants who do not meet the FEV1 baseline stability criteria at Visits 3 and 4 must be rescheduled as soon as is practical but within the protocol-specified washout window (3 to 7 days).

[n] During treatment visits, vital signs will be measured 60 minutes before study intervention dosing and at the end of the study visit (post-dose, before the participant leaves the clinic).

[o] AEs will be recorded from randomization throughout the treatment period and including the follow-up period (telephone contact). SAEs will be recorded from the time of signing of the ICF.

[p] Urine β-hCG test will be performed at Visit 1, before starting each treatment period, and at the PDV, if applicable (for POCBP).

[q] Pre-study asthma medications include any ICS, SABA, or LABA used by the participant within the 30 days prior to Visit 1.

[r] Pre-study asthma medications will be returned to the participant at the end of Visit 4 (or upon premature discontinuation or screen failure, if applicable).

[s] Participants should bring their sponsor-provided asthma medications (Ventolin HFA and Pulmicort Flexhaler, if assigned) with them to all study visits. The investigator or authorized study staff will collect sponsor-provided asthma medication(s) and ensure that the participant has enough asthma medication to last until the next clinic visit. Sponsor-provided medication(s) will be returned to the participant by the end of the clinic visit. Sponsor-provided background asthma medications should be returned to the site at the end of Visit 4 (or upon premature discontinuation or screen failure, if applicable) for final disposition.

TC, telephone call

2 INTRODUCTION

2.1 Study Rationale

Albuterol sulfate is a SABA that is used as needed (ie, reliever therapy). The test formulation to be evaluated in this study (PT007) is an MDI containing albuterol sulfate (albuterol sulfate pressurized inhalation suspension; hereafter referred to as AS MDI). This study is designed to assess the bronchodilatory effect of a single dose of 180 µg inhaled AS MDI relative to a single dose of 200 µg open-label Ventolin® Evohaler (a pressurized metered-dose inhaler delivering albuterol [as salbutamol sulfate]). A single dose of placebo MDI will also be included as a control.

The objective of the study is to compare the therapeutic efficacy and safety of a single dose of albuterol delivered from AS MDI relative to Ventolin Evohaler on post-dose lung function in adults with asthma.

The primary endpoint is the change from baseline in FEV1 AUC0-6, and secondary endpoints include the change from baseline in FEV1 AUC0-4 and the peak change from baseline in FEV1.

2.2 Background

Asthma is a heterogeneous disease that is characterized by chronic airway inflammation, and it is also usually associated with airway hyperresponsiveness. Asthma is defined by a history of respiratory symptoms such as wheezing, shortness of breath, chest tightness, and cough that vary over time and in intensity, together with variable expiratory airflow limitation (GINA 2024). Asthma can be mild to severe (GINA 2024). A change in asthma symptoms (eg, acute worsening) and lung function (eg, decrease in expiratory workflow or FEV1) from the patient's usual status may result in asthma exacerbation that is potentially life-threatening. Such events pose a significant burden to patients and result in significant direct and indirect economic costs (GINA 2024).

Albuterol sulfate is a SABA that has been used worldwide in the management of asthma (Garcia-Marcos et al 2023, Sriprasart et al 2023). SABAs have been used as rescue medication for the relief of acute symptoms of asthma since the 1950s (Stein and Thiel 2017, Sriprasart et al 2023), with an albuterol MDI being first introduced in 1968 (Sanders 2007, Stein and Thiel 2017). In clinical practice, albuterol is used as needed as a reliever/rescue medication as it provides quick relief of asthma symptoms and bronchoconstriction (GINA 2024).

The study intervention in this clinical protocol, AS MDI, is an MDI containing a SABA. AS MDI is being developed as a mono-component to be investigated in adult patients with asthma. The drug product in clinical development is an MDI formulated as a suspension with

a micronized active pharmaceutical ingredient and Co-suspension™ Delivery Technology, which consists of spray-dried porous particles comprised of the phospholipid 1,2-distearoyl-sn-glycero-3-phosphocholine and calcium chloride suspended in an HFA propellant. When used in MDI products, these particles form strong nonspecific associations with the active pharmaceutical ingredient, providing reproducible drug delivery and long-term stability.

As of 15 May 2023 (IB edition 6 data cut-off date), final results are available from 4 clinical studies that have evaluated AS MDI in participants with asthma:

- Study D6930C00001 (ANTORA) compared the bronchodilatory effect and safety of AS MDI relative to placebo MDI and open-label Proventil in participants with stable asthma receiving as needed rescue SABA or low- to medium-dose maintenance ICS or ICS/LABA. For the primary efficacy endpoint of change from baseline in FEV1 AUC0-6, both doses of AS MDI evaluated (180 µg and 90 µg albuterol base) were statistically superior to placebo MDI and noninferior to Proventil (180 µg and 90 µg albuterol base), respectively. AS MDI was well tolerated and had a favorable safety profile, with no unexpected safety findings.
- Study D6930C00002 (ASPEN) compared cumulative doses of AS MDI (90 µg albuterol base per actuation) to cumulative doses of Proventil (90 µg albuterol base per actuation) in participants with stable mild to moderate asthma receiving as needed rescue SABA or low- to medium-dose maintenance ICS or ICS/LABA. For the primary efficacy endpoint of baseline-adjusted 30-minute FEV1, AS MDI was equivalent to Proventil at all cumulative doses. Cumulative doses up to 1440 µg albuterol from both AS MDI and Proventil were associated with increases in FEV1 from baseline, with similar response trends for both AS MDI and Proventil treatment periods. AS MDI was well tolerated, with no unexpected safety findings.
- Study D6930C00005 (MANDALA) compared BDA MDI (80/180 µg and 160/180 µg budesonide/albuterol combination product) used as needed to AS MDI (180 µg albuterol) used as needed. For the primary endpoint of time to first severe asthma exacerbation, as needed use of BDA MDI in addition to background asthma maintenance therapy in participants aged ≥ 12 years with moderate to severe asthma resulted in statistically significant and clinically meaningful reductions in the risk of a severe exacerbation, compared with AS MDI. AS MDI was well tolerated, and no safety concerns were identified. There were 7 deaths during the treatment period, with one death (due to COVID-19/pneumonia) in the AS MDI treatment group. None of the AEs leading to death were considered by the investigator to be causally related to study interventions or due to asthma.
- Study D6930C00004 (DENALI) compared the efficacy and safety of BDA MDI (80/180 µg or 160/180 µg budesonide/albuterol combination product administered QID) to its mono-components (160 µg budesonide MDI QID and 180 µg AS MDI [albuterol]

QID) and placebo in participants aged ≥ 4 years. For the dual primary endpoints of change from baseline in FEV1 AUC0-6 over 12 weeks and change from baseline in trough FEV1 at Week 12, the study demonstrated that each of the mono-components in BDA MDI (budesonide and albuterol) individually contributed to improvements in lung function in participants with asthma aged ≥ 12 years. AS MDI was well tolerated, with no unexpected safety findings.

A detailed description of the chemistry, pharmacology, efficacy, and safety of AS MDI is provided in the IB edition 6.

Ventolin Evohaler (albuterol sulfate aerosol for oral inhalation use) is the active comparator in this study. Ventolin is a SABA and was initially approved in the US in 1981 and in China in April 2003. Ventolin was initially approved in the EU in 1998. In the US, Ventolin HFA is indicated for treatment or prevention of bronchospasm in patients aged 4 years and older with reversible obstructive airway disease and for the prevention of exercise-induced bronchospasm in patients aged 4 years and older (Ventolin HFA PI 2024). In the EU/UK, Ventolin Evohaler is indicated for the relief of acute asthma symptoms including bronchospasm, chronic therapy, and prevention of allergen- or exercise-induced bronchospasm in patients aged 4 and older (Ventolin Evohaler SmPC 2024). All references to doses of the study intervention refer to the albuterol base: 90 µg (as albuterol sulfate) per actuation for AS MDI and 100 µg (as salbutamol sulfate) per actuation for Ventolin Evohaler.

A detailed description of the chemistry, pharmacology, efficacy, and safety of Ventolin is provided in the Ventolin HFA PI 2024 and Ventolin Evohaler SmPC 2024.

2.3 Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected AEs of AS MDI may be found in the IB. More detailed information about the known and expected benefits and risks and reasonably expected AEs of Ventolin may be found in the Ventolin HFA PI 2024 and Ventolin Evohaler SmPC 2024.

2.3.1 Risk Assessment

This study has been designed to evaluate a new formulation of albuterol in adult participants with asthma. The product being tested in this study (AS MDI) is being compared with an approved inhaled albuterol product (Ventolin Evohaler) to assess the bronchodilatory effect of a single dose of AS MDI 180 µg (2 actuations of 90 µg) relative to a single dose of open-label Ventolin Evohaler 200 µg (2 actuations of 100 µg). A single dose (2 actuations) of placebo MDI will also be included as a control.

At Visit 1, all screened participants in this study will be switched from their current asthma medication to sponsor-provided asthma medications: Pulmicort Flexhaler for maintenance and

Ventolin HFA as needed for participants on ICS or ICS/LABA prior to Visit 1 and Ventolin HFA as needed for participants on only SABA as needed prior to Visit 1. Sponsor-provided asthma medications will be used during the screening period and throughout the study, as described in Section 6.9.1 and Section 6.9.2.1. Participants requiring medications other than those specified in Section 6.9.1 to control or treat their asthma symptoms before Visit 1 will be excluded from participation in this study. In addition, to be eligible for randomization, participants must not have used more than 8 actuations/day (ie, 4 doses of 2 actuations/dose) of sponsor-provided Ventolin HFA on more than 3 of the 7 days prior to randomization.

Based on the well-established safety profile of inhaled albuterol, no new or specific risks beyond what is described in the Ventolin HFA PI 2024 and Ventolin Evohaler SmPC 2024 are anticipated with the doses and the dose regimens being used in this study. Investigators will ensure that adequate medical care of the study participants is available at all times throughout the study, including up to a follow-up telephone call 3 to 7 days after the last dose of study intervention.

2.3.2 Benefit Assessment

The participants in this study will not gain any therapeutic benefit from the study as they will only receive single-dose treatments.

2.3.3 Overall Benefit/Risk Conclusion

The participants in this study will not gain any therapeutic benefit from the study as they will only receive single-dose treatments. Based on the well-established safety profile of inhaled albuterol, the eligibility criteria, and the precautions included in the clinical study (eg, use of sponsor-provided asthma medication during the study), the risks to the participants are considered low.

3 OBJECTIVES, ENDPOINTS, AND ESTIMANDS

The objectives, endpoints, and estimands associated with study D6935C00002 (MITCHELL) are presented in Table 2.

Table 2 Objectives and Endpoints, and Estimands

Objectives	Endpoints/Estimands
Primary	
To demonstrate the non-inferiority of a single dose of albuterol delivered from AS MDI relative to Ventolin Evohaler on post-dose lung function in adults with asthma	Treatment: AS MDI and Ventolin Evohaler. Population: Adults with asthma (pre-BD FEV1 of ≥ 40% of the PN value), with demonstrated FEV1 reversibility to Ventolin HFA [a] and who would comply with and complete both the AS MDI and Ventolin Evohaler treatment periods in the study. Participant-level outcome: Change from baseline in FEV1 AUC0-6 Strategy for IEs: Defined as a participant who for any reason does not have post-treatment efficacy data in the AS MDI or Ventolin Evohaler treatment periods. The principal stratum strategy will be implemented such that an IE is captured through the population definition. The IEs identified will include non-compliance with the study protocol [b] and failure to complete both treatment periods (AS MDI and Ventolin Evohaler). Participants that have any IEs will not be included in the analysis. Summary measure: Mean difference in change from baseline in FEV1 AUC0-6
To establish assay sensitivity of a single dose of albuterol delivered from Ventolin Evohaler compared with placebo on post-dose lung function in adults with asthma	Treatment: Ventolin Evohaler and placebo [c] Participant-level outcome: Change from baseline in FEV1 AUC0-6 Summary measure: Mean difference in change from baseline in FEV1 AUC0-6
Secondary	
Key: To demonstrate the therapeutic equivalence of a single dose of albuterol delivered from AS MDI relative to Ventolin Evohaler on post-dose lung function in adults with asthma	Treatment: AS MDI and Ventolin Evohaler [c] Participant-level outcome: Change from baseline in FEV1 AUC0-6 [c] Summary measure: Mean difference in change from baseline in FEV1 AUC0-6
To characterize the non-inferiority/therapeutic equivalence of a single dose of albuterol delivered from AS MDI relative to Ventolin Evohaler on post-dose lung function in adults with asthma	Treatment: AS MDI and Ventolin Evohaler [c] Participant-level outcome: change from baseline in FEV1 AUC0-4 Summary measure: Mean difference in change from baseline in FEV1 AUC0-4

Table 2 Objectives and Endpoints, and Estimands

Objectives	Endpoints/Estimands
To establish assay sensitivity of a single dose of albuterol delivered from Ventolin Evohaler compared with placebo on post-dose lung function in adults with asthma	Treatment: Ventolin Evohaler and placebo [c] Participant-level outcome: Change from baseline in FEV1 AUC0-4 Summary measure: Mean difference in change from baseline in FEV1 AUC0-4
To characterize the non-inferiority/therapeutic equivalence of a single dose of albuterol delivered from AS MDI relative to Ventolin Evohaler on post-dose lung function in adults with asthma	Treatment: AS MDI and Ventolin Evohaler [c] Participant-level outcome: Peak change from baseline in FEV1 Summary measure: Mean difference in peak change from baseline in FEV1
To establish assay sensitivity of a single dose of albuterol delivered from Ventolin Evohaler compared with placebo on post-dose lung function in adults with asthma	Treatment: Ventolin Evohaler and placebo [c] Participant-level outcome: Peak change from baseline in FEV1 Summary measure: Mean difference in peak change from baseline in FEV1
Safety	
To evaluate the safety and tolerability of a single dose of albuterol delivered from AS MDI compared to Ventolin Evohaler in adults with asthma	AEs/SAEs
Exploratory	
To compare the therapeutic efficacy of a single dose of albuterol delivered from AS MDI compared to placebo in adults with asthma	Change form baseline in FEV1 AUC0-6 Change form baseline in FEV1 AUC0-4 Peak change from baseline in FEV1
To further characterize the therapeutic efficacy of a single dose of albuterol delivered from AS MDI relative to Ventolin Evohaler in adults with asthma	Change from baseline in FEV1 at each post-dose time point Time to peak FEV1 Percentage of participants achieving 12% improvement in FEV1 from baseline within 30 minutes of dose Percentage of participants achieving 15% improvement in FEV1 from baseline within 30 minutes of dose Time to onset of response Duration of response

[a] A participant is considered to have reversibility to Ventolin HFA if the improvement in FEV1 at 30 minutes post-Ventolin HFA is ≥ 12% and ≥ 200 mL.
[b] Non-compliance includes taking prohibited medication and lung function data judged to be impacted by major protocol deviations.
[c] Population and strategy for IEs attributes are the same as the primary estimand specified for the non-inferiority and therapeutic equivalence objectives.

4 STUDY DESIGN

4.1 Overall Design

This is a randomized, double-blind, single-dose, placebo-controlled, 3-period, 3-treatment, crossover, multicenter study to assess the bronchodilatory effect and safety of AS MDI (180 µg) compared with placebo MDI and open-label Ventolin Evohaler (200 µg) in adult participants (aged 18 to 65 years, inclusive) with asthma (pre-BD FEV1 of ≥ 40% of the PN value).

A graphical presentation of the study schema is shown in Figure 1, and a list of the study activities is provided in the Section 1.3 SoA.

This study consists of:

- A screening/run-in period
- A treatment phase, which includes 3 randomized treatment periods. Each treatment period will be one day, with a washout period of 3 to 7 days between treatment periods.
- A follow-up telephone call

The screening period begins at Visit 1. At Visit 1, participants will sign the ICF. Inclusion/exclusion criteria will be assessed (Section 5.1 and Section 5.2). To be eligible, participants must be on either a SABA as needed as their only asthma therapy or low to medium doses of ICS (alone or in combination with a LABA) for at least 30 days as a consistent regimen before screening. Participants must have a pre-BD FEV1 of ≥ 40% of the PN value.

All participants must demonstrate FEV1 reversibility to Ventolin HFA (defined as improvement in FEV1 at 30 minutes post-Ventolin HFA dosing of ≥ 12% and ≥ 200 mL) during the screening period; historical reversibility is not acceptable. Characterization of reversibility is described in Section 8.2.4.

- For participants who did not administer their morning asthma maintenance medications, as applicable, and/or SABA, reversibility will be measured at Visit 1.
- For participants who received their morning asthma maintenance medications, as applicable, and/or SABA at Visit 1, reversibility will be measured at Visit 1a, which will occur within 10 days of Visit 1 and after the asthma medications have been held for the appropriate time (Table 8).
- Participants who do not meet reversibility criteria at Visit 1 or Visit 1a may be retested at a subsequent screening visit (Visit 1a or 1b) to occur within 7 days. Only 2 reversibility

testing attempts are allowed. Participants not meeting reversibility criteria after 2 attempts must be screen failed.

Participants meeting eligibility criteria at Visit 1 will continue in the screening/run-in period. During the screening/run-in period, all participants will discontinue their current asthma medications at Visit 1 and initiate sponsor-provided asthma medication(s) as follows:

- Participants who were using only SABA as needed for at least 30 days as a consistent regimen before Visit 1 will discontinue their SABA and initiate sponsor-provided Ventolin HFA for use as needed. Sponsor-provided Ventolin HFA is allowed during the screening/run-in period and throughout the study, up until 6 hours before a study visit. The minimum screening/run-in period for these participants will be 3 days.
- Participants who were using regularly scheduled ICS or ICS/LABA for at least 30 days as a consistent regimen before Visit 1 will discontinue their ICS or ICS/LABA and initiate sponsor-provided Pulmicort Flexhaler for use as maintenance therapy (either 180 µg or 360 µg BID based on the participant's previous ICS therapy, irrespective of LABA use), along with sponsor-provided Ventolin HFA for use as needed. The allowed total daily ICS dosage to qualify ICS usage for the 30 days prior to Visit 1 along with the assigned dose of sponsor-provided Pulmicort Flexhaler is defined in Table 6. Sponsor-provided background asthma medications, Pulmicort Flexhaler and Ventolin HFA, are allowed during the screening/run-in period and throughout the study, up until 12 and 6 hours, respectively, before a study visit. The minimum run-in period for these participants will be 14 days.

The maximum screening/run-in period for all participants will be 28 days.

Randomization will take place at Visit 2. At Visit 2, participants must demonstrate a pre-BD FEV1 of ≥ 40% of the PN value before randomization. An average of 2 acceptable/borderline acceptable pre-BD assessment values are recommended; a minimum of 3 to a maximum of 8 assessments can be performed. (However, if only one acceptable/borderline acceptable value is available after a maximum of 8 attempts, that value will be used, and the participant can be randomized). Participants who do not meet this randomization criterion will be screen failed. The spirometry manual will provide detailed acceptability, usability, and repeatability criteria for FEV1. Randomization criteria is provided in Section 5.2.1.

Randomization will be centralized using IRT. Randomization is planned to be stratified by pre-study background asthma maintenance therapy: participants using an ICS and participants not using an ICS (ie, receiving only SABA as needed).

Eligible participants will be randomized to 1 of 6 predefined treatment sequences in a 1:1:1:1:1:1 ratio. Each sequence will contain AS MDI, placebo MDI, and Ventolin Evohaler in a randomized order, as shown in Table 5.

Eligible participants will receive a single dose of randomized study intervention at each of the 3 treatment visits (Visits 2, 3, and 4), with a 3- to 7-day washout period between treatment visits. One of the following treatments is taken during 1 of the 3 treatment visits:

- AS MDI 180 µg (2 actuations of 90 µg/actuation)
- Placebo MDI (2 actuations to match AS MDI)
- Ventolin Evohaler 200 µg (2 actuations of 100 µg/actuation)

At each treatment visit, bronchodilation activity of the study interventions will be assessed through PFTs. Participants will be required to remain at the clinic until completion of all protocol-defined assessments up to and including the 6-hour post-dose time point (Section 1.3 and Section 8.2.3). Safety will be assessed by evaluation of AEs and SAEs (Section 8.4 and Appendix B).

AS MDI and placebo MDI will be blinded to all participants, study site staff, endpoint assessors, and sponsor personnel, whereas Ventolin Evohaler will be open label. However, to reduce bias, dosing will be performed under the supervision of study staff, and spirometry assessments will be performed by different study personnel who will only enter the room after dosing is completed; thus, the study personnel conducting the spirometry assessments will be blinded to the identity of the study intervention.

Participants who prematurely discontinue/withdraw from the study for any reason before completing all period visits in the study will undergo a PDV. After the last treatment period or following a PDV, participants will be scheduled for a follow-up telephone call to occur 3 to 7 days after the last dose of study intervention.

This study will be conducted at approximately 25 sites. Approximately 102 participants will be randomized to ensure that at least 90 participants complete the study.

Each participant will be in the study for a minimum of 15 days and up to a maximum of 52 days, including the 3- to 28-day screening/run-in period, the 3-part treatment period, and a follow-up telephone call 3 to 7 days after the last dose of study intervention. The study is anticipated to run for approximately 6 months, including the recruitment period.

4.2 Scientific Rationale for Study Design

The primary goal of this study is to confirm the bronchodilatory effect of AS MDI relative to placebo MDI and active control, Ventolin Evohaler, in adult participants with asthma. The

study is based on a 3-period Williams crossover design (Williams 1949) to allow the comparison of AS MDI against placebo MDI and Ventolin Evohaler. The crossover design was selected to ensure acceptable power with a limited participant exposure through within-participant treatment comparisons. This type of design is acceptable for evaluating treatments for chronic conditions, such as asthma, and is frequently used for the evaluation of bronchodilators in equivalence studies (Senn 2002a).

Placebo is included in the study to establish assay sensitivity of a single dose of Ventolin Evohaler and to compare efficacy versus AS MDI on post-dose lung function (Hasselblad and Kong 2001, ICH E10 2001, Senn 2002b).

The dose level of AS MDI and Ventolin Evohaler to be tested is 180 µg (2 actuations of 90 µg) and 200 µg (2 actuations of 100 µg), respectively. For information regarding the justification for the dose selected in this study, see Section 4.3.

In this double-blind, placebo-controlled study, AS MDI and placebo MDI will be blinded to all participants, study site staff, endpoint assessors, and sponsor personnel. Ventolin Evohaler will be open label. However, to reduce bias, dosing will be performed under the supervision of study staff, and spirometry assessments will be performed by different study personnel who will only enter the room after dosing is completed; thus, the study personnel conducting the spirometry assessments will be blinded to the identity of the study intervention.

Participants enrolled in this study are selected to represent the intended patient population for an albuterol product to be used as needed for symptoms, ie, adults currently treated and well controlled with appropriate background standard of care for their asthma severity.

All participants will use only sponsor-provided asthma medication during the study. At Visit 1 (screening), participants who were on only SABA as needed will discontinue their SABA and initiate sponsor-provided Ventolin HFA for use as needed. For these participants, the minimum screening/run-in period will be 3 days. These participants will continue to use Ventolin HFA as needed throughout the study, up until 6 hours before a study visit to allow evaluation of the primary endpoint. Participants who were previously on a low to medium dose of ICS with or without a LABA before study entry will be required to discontinue their previous asthma therapy at Visit 1 and initiate sponsor-provided Pulmicort Flexhaler for maintenance, along with sponsor-provided Ventolin HFA for use as needed. For these participants, the minimum run-in period will be at least 14 days to standardize therapy and to confirm that asthma is adequately treated prior to randomization. These participants will continue to use the assigned regimen of Pulmicort Flexhaler and Ventolin HFA as needed throughout the study, up until 12 and 6 hours, respectively, before a study visit to allow evaluation of the primary endpoint.

AS MDI will be compared to placebo MDI and Ventolin Evohaler on the primary efficacy endpoint, change from baseline in FEV1 AUC0-6, a commonly accepted endpoint for the

assessment of bronchodilation. The duration of 6 hours was selected to capture the expected duration of the effect of albuterol.

4.3 Justification for Dose

The dose level of AS MDI to be tested (180 µg given as 2 actuations of 90 µg) was selected based on over 40 years of clinical experience with inhaled albuterol in asthma patients.

In addition, AS MDI doses of 90 µg or 180 µg have been evaluated in 4 clinical trials in participants with asthma. Both AS MDI doses were efficacious and had an acceptable safety profile. For additional information about these studies, see Section 2.2 and the AS MDI IB edition 6.

It is anticipated that the dose of albuterol delivered from AS MDI will be close to the approved dose of albuterol (as salbutamol) delivered from Ventolin Evohaler. (Additional information is provided in Section 4.3.1.) The planned dose will allow evaluation of the bronchodilatory effect of AS MDI administered at 180 µg relative to placebo MDI and Ventolin Evohaler administered at 200 µg. For patients aged 12 years and older, the recommended dosage of Ventolin Evohaler to relieve acute bronchospasm is one inhalation as a minimum starting dose (2 inhalations if necessary), to prevent allergen- or exercise-induced symptoms is 2 inhalations before challenge, and for chronic therapy is 2 inhalations up to 4 times daily (Ventolin Evohaler SmPC 2024).

Placebo is included in the study to establish assay sensitivity of a single dose of Ventolin Evohaler and to compare efficacy versus AS MDI and on post-dose lung function (Hasselblad and Kong 2001, ICH E10 2001, Senn 2002b).

4.3.1 Justification for Using a Non-US Approved Product from Europe as a Comparator in a Therapeutic Equivalence Trial in the US

This clinical trial aims to compare Ventolin Evohaler (salbutamol sulfate), an inhaler product approved in China, and AS MDI (albuterol sulfate), a new investigational inhaler that was used and approved in the US as a comparator in the development and approval of AIRSUPRA®. The choice of Ventolin Evohaler as reference comparator in this clinical trial is based on ensuring that the trial outcomes meet scientific and regulatory requirements in ex-US countries[1] with different SABA formulations. CCI [redacted] CCI [redacted]

Scientific Rationale/Pharmacologic Equivalence

Both inhalers (Ventolin Evohaler and AS MDI) contain the same SABA referred to as

[1] Ex-US Countries means the rest of the world that does not comprise the US territory.

salbutamol in some ex-US countries. Albuterol is the US adopted name (USAN) for salbutamol. Both are established treatments for relief of airway obstruction globally (GINA 2024, NHLBI 2007). The efficacy and safety of inhaled albuterol has been well documented (FDA 2005, Guerrin et al 1980, Kleerup et al 1996). Ventolin Evohaler is commonly used to treat asthma symptoms in Europe, China, and other regions, thus making it a clinically relevant comparator for assessing the therapeutic equivalence of AS MDI. Ventolin is also available in the US in a different marketed presentation referred to as Ventolin HFA (Ventolin HFA PI 2024), which will be used by the participants for rescue and for reversibility testing in this trial. Each actuation of Ventolin HFA and AS MDI delivers 90 µg of albuterol base into the mouthpiece. Each actuation of Ventolin Evohaler (Ventolin Evohaler SmPC 2024) delivers 100 µg of salbutamol sulfate into the mouthpiece. The prescribing information for Ventolin Evohaler reports the total amount of salbutamol sulfate per actuation, whereas the Ventolin HFA and AS MDI reports the delivered dose of albuterol base per actuation. Overall, the slight difference in doses does not indicate differences in therapeutic outcomes but can be attributed to the delivery system rather than the active base ingredient itself.

4.4 End-of-study Definition

For the purpose of Clinical Trial Transparency (CTT) 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.

The FDA requirements define 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 follow-up telephone call.

The end of study is defined as the last participant's follow-up telephone call.

5 STUDY POPULATION

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

5.1 Inclusion Criteria

Age

1 Participant must be aged 18 to 65 years (inclusive), at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2 Participants should have a documented history of physician-diagnosed asthma ≥ 6 months prior to Visit 1.

3 Must be receiving one of the following required inhaled asthma therapies listed below for at least the last 30 days:

   (a) Only SABA, which is used as needed for rescue.

   (b) Low to medium doses of ICS (alone or in combination with LABA), used regularly as maintenance asthma therapy.

4 Pre-BD FEV1 of ≥ 40% of the PN value at Visit 1, after withholding SABA for ≥ 6 hours (and Visit 1a and/or Visit 1b, if applicable).

5 Confirmed FEV1 reversibility to 4 actuations of Ventolin HFA, defined as a post-Ventolin HFA increase in FEV1 at 30 minutes of ≥ 12% and ≥ 200 mL at either Visit 1, Visit 1a, or Visit 1b; only 2 reversibility testing attempts are allowed.

6 Demonstrate acceptable spirometry performance (ie, meet ATS/ERS acceptability/repeatability criteria).

7 Willing and, in the opinion of the investigator, able to adjust current asthma therapy, as required by the protocol.

8 Demonstrate acceptable MDI administration technique.

   – **Note**: Use of a spacer device during the screening and randomized treatment periods is not permitted.

Weight

9 Body mass index < 40 kg/m^2.

Sex and Contraceptive/Barrier Requirements

10 Contraceptive use by females should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

11 Female participants: A participant of childbearing potential, must have a negative urine pregnancy test at Visit 1 (to be read locally).

- Participants not of childbearing potential are defined as those who are physiologically incapable of becoming pregnant, including any participant who is 2 years postmenopausal, or surgically sterile (defined as having a bilateral oophorectomy, hysterectomy, tubal ligation, or other permanent birth control measures).
- Participants aged ≥ 50 years will be considered postmenopausal if they have been amenorrheic for 12 consecutive months or more following cessation of all exogenous hormonal treatment.
- Participants aged < 50 years will be considered postmenopausal if they have been amenorrheic for 12 consecutive months or more following cessation of exogenous hormonal treatment and in the absence of any alternative medical cause, as judged by the investigator.

12 Participants of childbearing potential must use a highly effective form of contraception from signing of the ICF to 14 days after the last study intervention. 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).
- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation):
  - Oral
  - Intravaginal (eg, NuvaRing®)
  - Transdermal (eg, Evra Patch™, Xulane™)
- Progestogen-only hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Injectable (eg, Depo-Provera™)
  - Implantable (eg, Implanon®)
- Intrauterine device or intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Male partner sterilization/vasectomy 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.
- **Note**: Periodic abstinence (calendar, ovulation, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), declaration of abstinence for the duration of exposure to study intervention, spermicides only, and lactational amenorrhea method are not acceptable methods of contraception.

Informed Consent

13 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.

Other Inclusion Criteria

14 Compliance: must be willing to remain at the study site as required per protocol to complete all visit assessments.

5.2 Exclusion Criteria

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

Medical Conditions and History

1 Any evidence of chronic obstructive pulmonary disease or other significant lung disease (eg, chronic bronchitis, emphysema, bronchiectasis with the need of treatment, cystic fibrosis, or bronchopulmonary dysplasia). 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 efficacy or safety analysis.

2 Life-threatening asthma defined as any history of significant asthma episode(s) requiring intubation associated with hypercapnia, respiratory arrest, hypoxic seizures, or asthma-related syncopal episode(s) within the last 5 years.

3 Upper respiratory infection not resolved within 7 days of Visit 1 and throughout the screening period.

4 Hospitalizations for asthma exacerbation within the last 3 months prior to Visit 1.

5 Historical or current evidence of a clinically significant disease including, but not limited to: cardiovascular (eg, congestive heart failure, known aortic aneurysm, clinically significant cardiac arrhythmia, participants with known QTcF $\geq$ 480 ms, coronary heart disease), hepatic, renal, hematological, neuropsychological, endocrine (eg, uncontrolled diabetes mellitus, uncontrolled thyroid disorder, Addison's disease, Cushing's syndrome), or gastrointestinal (eg, poorly controlled peptic ulcer, gastroesophageal reflux disease). Significant is defined as any disease that, in the opinion of the investigator, would put the safety of the participant at risk through study participation, or that could affect the efficacy or safety analysis if the disease/condition exacerbated during the study.

6 Cancer not in complete remission for at least 5 years prior to Visit 1.

Note: Participants with squamous cell carcinoma of the skin or basal cell carcinoma of the skin or cervical carcinoma in situ are eligible, if in the opinion of the investigator, the condition has been adequately worked up and clinically controlled, and the participant's participation in the study would not represent a safety concern.

7 Hospitalized for psychiatric disorder or attempted suicide within one year prior to Visit 1.

8 History of psychiatric disease, intellectual deficiency, poor motivation, or other conditions limiting informed consent validity.

9 Received a live attenuated vaccination within 7 days of Visit 1.

Prior/Concomitant Therapy

10 Oral/systemic corticosteroid use (any dose) within 6 weeks of Visit 1.

11 Chronic use of oral corticosteroids (≥ 3 weeks of use in the 3 months prior to Visit 1).

12 Received any marketed (eg, omalizumab, mepolizumab, reslizumab) or investigational biologic within 3 months or 5 half-lives, whichever is longer, or any other medication specifically prohibited by the protocol within the indicated exclusionary time periods.

13 Received tiotropium within 2 weeks of Visit 1.

14 Received treatment for lower respiratory infection or asthma exacerbation within 6 weeks of Visit 1.

15 Unable to abstain from protocol-defined prohibited medications during screening and the study.

16 Using any herbal products by inhalation or nebulizer within 2 weeks of Visit 1 and does not agree to stop during the study duration.

Prior/Concurrent Clinical Study Experience

17 Treatment with investigational study intervention (or device) in another clinical study within the last 30 days or 5 half-lives, whichever is longer, prior to Visit 1.

18 Hypersensitivity to β2-agonists or any component of the investigational MDI or any component of Ventolin Evohaler or HFA (or Pulmicort Flexhaler, if applicable).

Other Exclusions

19 Significant abuse of alcohol or drugs in the opinion of the investigator.

20 Current smokers, former smokers with > 10 pack-years history, or former smokers who stopped smoking < 6 months (including all forms of tobacco, e-cigarettes [vaping], and marijuana).

21 Study investigators, sub-investigators, coordinators, and their employees or immediate family members, or employees of the sponsor.

22 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.

23 For female participants only: currently pregnant (confirmed with positive pregnancy test) or breastfeeding.

5.2.1 Randomization Criteria

Each participant must meet the following criteria on the morning of Visit 2 to be randomized:

1 Participants of childbearing potential must have a negative urine pregnancy test.

2 Received no asthma medication other than sponsor-provided Pulmicort Flexhaler 180 µg or 360 µg BID as assigned and/or sponsor-provided Ventolin HFA from Visit 1 to Visit 2, except for allowable allergy medications defined in Table 7.

3 The last dose of sponsor-provided Pulmicort Flexhaler (if applicable) was at least 12 hours before the study visit (morning dose was not administered), and the last dose of sponsor-provided Ventolin HFA was at least 6 hours before the study visit. (If Ventolin HFA or Pulmicort Flexhaler, if assigned, are needed in the morning, the visit must be rescheduled.)

4 Participants must demonstrate an acceptable pre-BD FEV1 of ≥ 40% of the PN value. An average of 2 acceptable/borderline acceptable pre-BD assessment values is recommended; a minimum of 3 to a maximum of 8 assessments can be performed. (However, if only one acceptable/borderline acceptable value is available after a maximum of 8 attempts, that value will be used, and the participant can be randomized).

5 All participants must demonstrate FEV1 reversibility to 4 actuations of Ventolin HFA (defined as improvement in FEV1 at 30 minutes post-Ventolin HFA dosing of ≥ 12% and ≥ 200 mL) during the screening period.

6 Participants must not have used more than 8 actuations per day (ie, 4 doses of 2 actuations/dose) of sponsor-provided Ventolin HFA for rescue on more than 3 of the 7 days prior to randomization.

7 No upper respiratory infection, lower respiratory infection, or asthma exacerbation during the screening period.

8 Demonstrate acceptable MDI administration technique.

9 Able to comply with all study procedures.

Participants who do not meet these randomization criteria will be screen failed.

5.3 Lifestyle Considerations

Illicit drugs or drugs of abuse will not be allowed from Visit 1 to the end of the follow-up telephone call or to whenever the participant is discontinued from the study. If any illicit drugs or drugs of abuse are used by the participant during the study, the dates of use and the amount will be documented, and the participant will be discontinued from the study at the discretion of the investigator. Procedures for discontinuation from the study are provided in Section 7.2. Medical marijuana (edibles and tinctures only; inhaled marijuana is excluded) is not an exclusionary drug if used for medical purposes, and the dose or frequency of consumption does not change during the screening period or throughout the study.

5.3.1 Caffeine, Alcohol, and Tobacco

Participants must not ingest xanthine and/or xanthine analog (caffeine)-containing foods or beverages or caffeine-containing medications for at least 6 hours before a study visit and

throughout the duration of a study visit. Examples of such products include coffee, tea, chocolate, and cola. Decaffeinated beverages are acceptable.

Participants must avoid consuming intoxicants within 8 hours before PFTs (to avoid problems in coordination, comprehension, and physical ability) (Graham et al 2019).

5.3.2 Activity

Participants should abstain from strenuous or vigorous exercise for at least 6 hours before a visit (to avoid potential exercised-induced bronchoconstriction).

5.3.3 Other Restrictions

Wearing clothing that substantially restricts full chest and abdominal expansion should be avoided at clinic visits (to avoid external restrictions on lung function during PFTs) (Graham et al 2019).

5.4 Screen Failures

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

Participants who are screening failures do not fulfill the eligibility criteria for the study, and therefore, must not be randomized.

5.4.1 Rescreening

Individuals who do not meet the inclusion criterion 5 for participation in this study (screening failure) may be rescreened. Only one additional rescreening is allowed in the study. Rescreened participants should be assigned the same participant number as for the initial screening and should sign a new ICF.

- If a participant had Ventolin HFA reversibility measured at Visit 1 and did not meet reversibility criteria, Visit 1a will be scheduled for a second reversibility test to occur within 7 days. Participants who do not meet reversibility criteria after the second attempt will be screen failed.
- If a participant had Ventolin HFA reversibility measured at Visit 1a and did not meet reversibility criteria, Visit 1b will be scheduled for a second reversibility test to occur within 7 days. Participants who do not meet reversibility criteria after the second attempt will be screen failed.

See section 8.1.1 for additional information.

5.5 Criteria for Temporarily Delaying Enrollment/ Randomization/Administration of Study Intervention (Not Applicable)

6 STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

Study interventions are all pre-specified IMPs intended to be administered to the study participants during the study conduct.

6.1 Study Intervention(s) Administered

Study interventions are described in Table 3.

Table 3 Study Interventions

Arm name	AS MDI	Ventolin Evohaler	Placebo MDI
Intervention name	AS MDI	Ventolin Evohaler	Placebo matching AS MDI
Type	Combination product with a device constituent	Combination product with a device constituent	Combination product with a device constituent
Dose formulation	Inhalation aerosol	Inhalation aerosol	Inhalation aerosol
Unit dose strength(s)	90 µg albuterol base per actuation	100 µg albuterol base per actuation	Not applicable
Dosage level(s) [a]	180 µg	200 µg	Not applicable
Route of administration	Oral inhalation	Oral inhalation	Oral inhalation
Regimen [a]	Single dose (2 actuations of 90 µg)	Single dose (2 actuations of 100 µg)	Single dose (2 actuations to match AS MDI)
Use	Experimental	Open-label active comparator	Placebo
IMP or NIMP/AxMP	IMP	IMP	IMP
Sourcing	Provided centrally by AstraZeneca	Provided centrally by AstraZeneca	Provided centrally by AstraZeneca
Packaging and labelling	Study intervention will be packaged in a foil pouch and contained in an individual visit treatment box. Each box and the foil overwrap	Study intervention will be provided in an individual visit treatment box. Each box will be labelled as required per country requirement.	Study intervention will be packaged in a foil pouch and contained in an individual visit treatment box. Each box and the foil overwrap

Table 3 Study Interventions

Arm name	AS MDI	Ventolin Evohaler	Placebo MDI
	will be labelled as required per country requirement.		will be labelled as required per country requirement.
Current/former name(s) or alias(es)	Current names aliases: PT007: albuterol 180 µg inhalation aerosol in a pMDI; also known as AS MDI	Current names aliases: Salbutamol	NA

[a] Each of the 3 treatment visits will include one of the following single-dose treatments, based on the participant's randomized treatment assignment: AS MDI 180 µg (2 actuations of 90 µg/actuation), Ventolin Evohaler 200 µg (2 actuations of 100 µg/actuation), and Placebo MDI (2 actuations).

In addition, participants will perform inhalation training with placebo MDIs supplied by AstraZeneca. Prior to dosing, participants will be given detailed instruction regarding proper use of the MDI device to ensure adequate comprehension and demonstration of MDI techniques.

6.1.1 Sponsor-provided Background Asthma Medications

For the sponsor-provided maintenance (Pulmicort Flexhaler) and rescue (Ventolin HFA) asthma medications and for Ventolin HFA for reversibility testing, commercial DPI/MDIs with dose counters and manufacturer's instructions for use will be provided. These medications are listed in Table 4.

Table 4 Sponsor-provided Background Study Medications

Product Name	Ventolin HFA®	Pulmicort Flexhaler™
Intervention name	NA	NA
Type	Combination product with a device constituent	Combination product with a device constituent
Dose formulation	Inhalation aerosol: pressurized MDI that delivers albuterol. MDI contains 200 actuations	Inhalation powder: DPI with formulation containing 1 mg per actuation of micronized budesonide and micronized lactose monohydrate. DPI contains 120 actuations.
Unit dose strength(s)	90 µg albuterol base per actuation	180 µg delivers 160 µg budesonide per actuation
Dosage level(s)	As needed (rescue) use: 180 µg (2 actuations of 90 µg per dose) Reversibility testing: 360 µg (4 actuations of 90 µg)	180 µg (1 actuation of 180 µg per dose 360 µg (2 actuations of 180 µg per dose)

Table 4 Sponsor-provided Background Study Medications

Product Name	Ventolin HFA®	Pulmicort Flexhaler™
Route of administration	Oral inhalation	Oral inhalation
Regimen	Taken as directed for reversibility testing (Visits 1, 1a, or 1b) and as needed for symptoms during the screening and randomized treatment periods (up to 6 hours before a study visit).	One or 2 actuations BID as directed, starting at Visit 1 and throughout study (up to 12 hours before a study visit). Total daily dose: 360 µg or 720 µg
Use	Rescue medication and reversibility testing	Background
IMP or NIMP/AxMP	AxMP	AxMP
Sourcing	Provided locally by AstraZeneca	Provided locally by AstraZeneca
Packaging and labelling	Study intervention will be provided in commercial package	Study intervention will be provided in commercial package
Current/former name(s) or alias(es)	NA	NA

6.1.2 Medical Devices Including Combination Products with a Device Constituent

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

- AS (albuterol sulfate inhalation aerosol) MDI (Status, Investigational)
- Pulmicort Flexhaler (budesonide inhalation powder) DPI (Status, Approved)

Other combination product with a device constituent (not manufactured by or for AstraZeneca) provided for use in this study is:

- Ventolin (Evohaler and HFA) (albuterol sulfate inhalation aerosol) MDI (Status, Approved)

Other medical devices (not manufactured by or for AstraZeneca) provided for use in this study are

- Spirometer (Status, Approved/CE Marked)

Instructions for medical device use are provided at the following locations:

- AS MDI and Pulmicort Flexhaler: Instructions for use for the AstraZeneca manufactured combination products with a device constituent.

- Ventolin (HFA and Evohaler): Instructions for use for the combination product with a device constituent not manufactured by AstraZeneca.
- Spirometry: The device manual and/or instructions for use provided by the vendor of the third-party device.

The AS MDI, Pulmicort Flexhaler, and Ventolin (HFA and Evohaler) MDI instructions for use are provided in the pharmacy manual.

Spirometer instructions are provided in the spirometry manual.

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 8.4.13) and appropriately managed by AstraZeneca.

6.2 Preparation, Handling, Storage, and Accountability

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 authorization is provided for onsite destruction or removal of all study intervention, 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 intervention 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 authorized site staff may supply, prepare, or administer study intervention. All study intervention must be stored in a secure, environmentally-controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorized site staff.

Note: The clinical supplies storage area at the site must be monitored by the site staff for temperature consistency with the acceptable storage temperature range specified in the product label. Documentation of temperature monitoring should be maintained. The study intervention label specifies the appropriate storage. Commercially-sourced medications (study intervention [Ventolin Evohaler] and sponsor-provided background asthma medications [Ventolin HFA and Pulmicort Flexhaler]) should be stored as indicated on the respective product label.

The investigator or authorized site staff 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 and sponsor-provided background asthma medications are provided in the pharmacy manual.

6.2.1 Dose Preparation

6.2.1.1 Randomized Study Interventions

The dose of AS MDI, Ventolin Evohaler, and placebo MDI for study intervention administration must be prepared by the pharmacy staff members (or an appropriate designee trained in study intervention preparation), in compliance with local regulations and site requirements.

Refer to the pharmacy manual for detailed information on dose preparation, administration, and handling procedures for AS MDI, placebo MDI, and open-label Ventolin Evohaler.

AS MDI and Placebo MDI

Individual AS MDIs and placebo MDIs will be packaged in a foil pouch and contained in an individual visit treatment box. Both the visit treatment box and the foil overwrap will have a label with a kit ID number. Confirm that the identifier given by IRT and the kit ID number on the label are the same.

All MDIs must be primed by study personnel before use. Priming involves shaking followed by releasing 4 sprays into the air before the first use of the inhaler. Shaking and priming the inhaler fills a chamber inside the canister with the correct dose and mix of medication so that it is ready to use.

To prime the inhaler, gently shake the inhaler for 5 to 10 seconds and then spray once into the air away from yourself and others. Wait approximately 30 seconds and repeat the process 3 more times.

AS MDI must be primed in a separate room from the participant treatment area. Since the MDI is primed in a separate room before dosing, there is a possibility that there may be a delay between priming and dosing; therefore, the MDIs are to be gently shaken (5 to 10 seconds) immediately before each actuation (inhalation) to ensure consistency in the administration for all participants.

Each dose will consist of 2 actuations from the MDI.

Open-label Ventolin Evohaler

Individual Ventolin Evohaler MDIs will be contained in an individual visit treatment box. The visit treatment box will have a label with a kit ID number. Confirm that the identifier given by the IRT and the kit ID number written on the label are the same.

Ventolin Evohaler should be primed by study personnel (in a separate room from the participant treatment area) per manufacturer's instructions before use.

To prime Ventolin Evohaler, shake well and release 4 sprays into the air away from the face, **shaking well before each spray.**

Ventolin Evohaler must be primed in a separate room from the participant treatment area. Since Ventolin Evohaler is primed in a separate room before dosing, there is a possibility that there may be a delay between priming and dosing; therefore, the MDIs are to be gently shaken (5 to 10 seconds) immediately before each actuation (inhalation) to ensure consistency in the administration for all participants.

Each dose will consist of 2 actuations from the MDI.

6.2.1.2 Sponsor-provided Background Asthma Therapies

Refer to the pharmacy manual for detailed information on dose preparation, administration, and handling procedures for sponsor-provided Ventolin HFA and Pulmicort Flexhaler.

Ventolin HFA

Ventolin HFA (for rescue therapy) will be provided by the sponsor and stored in a secured location within the clinic or pharmacy facilities. Ventolin HFA should be stored at room temperature by the participant.

Ventolin HFA should be primed per manufacturer's instructions before dispensing to participant. Priming instructions are provided in Section 6.2.1.1.

Study personnel will record the number on the dose counter at the time of dispensing (following priming) and upon return.

Each dose for rescue will consist of 2 actuations from the MDI.

Pulmicort Flexhaler

Pulmicort Flexhaler (for maintenance therapy) will be provided by the sponsor and stored in a secured location within the clinic or pharmacy facilities. Pulmicort Flexhaler should be stored at room temperature by the participant.

Pulmicort Flexhaler should be primed per manufacturer's instructions before dispensing to participant.

To prime the DPI, hold the inhaler by the brown grip so that the white cover points upward (upright position). With the other hand, turn the white cover and lift off. Continue to hold the Pulmicort Flexhaler upright and use the other hand to hold the inhaler in the middle. Do not hold the inhaler at the top of the mouthpiece. Twist the brown grip as far as it will go in one direction and then fully back again in the other direction until it stops. (It does not matter what way it is turned first.) You will hear a clicking sound during one of the twisting movements. Repeat the twisting movements one more time to finish priming the inhaler.

Study personnel will record the number on the dose counter when dispensing (following priming) and upon return.

The assigned dose (see the guidance in Table 6) will consist of either 1 or 2 actuations BID from the DPI.

6.2.2 Dose Administration

6.2.2.1 Randomized Study Interventions

AS MDI, Placebo for AS MDI, and Ventolin Evohaler

The inhalers should be stored at room temperature as directed by the label.

Randomized study interventions will be administered at the study site. Study intervention should be dispensed as follows:

- At 15 to 30 minutes before dosing, the seal around the study day treatment box should be opened and the instructions for administration of study intervention on the inner flap of the study day treatment box should be followed.
- Refer to Section 6.2.1.1 for detailed instructions for preparation of treatments for administration. These instructions are to be adhered to and are relevant to all study treatment visits.
- Participant will administer the dose of assigned study intervention at the clinic:
  - One dose consists of 2 inhalations; the in-clinic dosing time will be recorded as the time of administration of the second actuation of study intervention.
  - Site personnel will instruct participants not to take any non-study asthma medications without site personnel permission during the visit, until all study procedures have been completed, and the participant is discharged. Site personnel should take every precaution to prevent use of non-study any asthma medications during the test day.
  - If a participant is experiencing severe symptoms and requires Ventolin HFA for relief of asthma symptoms at any time during a study visit, site personnel must note the

time and justification for use in the participant's chart and all spirometry assessments should be stopped during the current treatment visit. Safety assessments should be continued at the discretion of the investigator.

Detailed instructions for use of AS MDI, placebo MDI, and Ventolin Evohaler are provided in the pharmacy manual.

6.2.2.2 Sponsor-provided Background Asthma Therapies

Manufacturer's instructions for use of Ventolin HFA and Pulmicort Flexhaler are provided in the pharmacy manual.

Ventolin HFA

The inhaler should be stored at room temperature as directed by the label.

Ventolin HFA will be provided by the sponsor to be used as needed (rescue) from Visit 1 and throughout the study including the washout periods, up until 6 hours before a study visit.

Participants should bring their sponsor-provided Ventolin HFA with them to the clinic visits. The investigator or authorized study staff will collect sponsor-provided Ventolin HFA as indicated in the Section 1.3 SoA and will ensure that the participant has enough medication to last until the next clinic visit. Sponsor-provided Ventolin HFA will be returned to the participant by the end of the clinic visit.

Sponsor-provided Ventolin HFA should be returned to the site at the end of Visit 4 (or upon premature discontinuation or screen failure, if applicable) for final disposition.

Pulmicort Flexhaler

Pulmicort Flexhaler should be stored in a dry place at controlled room temperature 20-25 °C (68-77 °F) with the cover tightly in place.

If required per protocol, Pulmicort Flexhaler will be provided by the sponsor to be used BID from Visit 1 and throughout the study including the washout periods and should be withheld for at least 12 hours before a study visit.

The dose of sponsor-provided Pulmicort Flexhaler assigned to the participant will be based on the participant's pre-study ICS, irrespective of LABA use (Table 6).

Participants should bring their sponsor-provided Pulmicort Flexhaler, if assigned, with them to the clinic visits. The investigator or authorized study staff will collect sponsor-provided Pulmicort Flexhaler as indicated in the Section 1.3 SoA and will ensure that the participant has enough medication to last until the next clinic visit. Sponsor-provided Pulmicort Flexhaler will be returned to the participant by the end of the clinic visit.

Sponsor-provided Pulmicort Flexhaler should be returned to the site at the end of Visit 4 (or upon premature discontinuation or screen failure, if applicable) for final disposition.

6.2.2.3 Visit Rescheduling

At the start of each treatment visit (Visits 2, 3, and 4), before any study procedures are performed, site personnel must confirm the participant has withheld all asthma medications. The last Pulmicort Flexhaler dose (if assigned) should be at least 12 hours before a study visit). The last dose of Ventolin HFA should be at least 6 hours before a study visit. Confirm the last time of dosing.

Participants who did not withhold their Ventolin HFA or Pulmicort Flexhaler dose, if applicable, before the start of study procedures (as described above) must have their visit rescheduled as soon as is practical, but within the protocol-specified washout window (3 to 7 days between treatment visits). In addition, before the in-clinic dose of study intervention is administered at Visits 3 and 4, the site must confirm the participant meets FEV1 baseline stability criteria (Section 8.2.5).

Participants who do not meet the FEV1 baseline stability criteria at Visits 3 or 4 must be rescheduled as soon as is practical but within the protocol-specified washout window (3 to 7 days between treatment visits). Participants who fail to meet stability criteria after 2 attempts for a treatment visit will be discontinued/withdrawn from the study. Study procedures for study discontinuation/withdrawal are found in Section 7.2.

6.3 Assignment to Study Intervention

All participants will be centrally assigned to randomized study intervention using an IRT.

All participants who undergo screening will be assigned a unique screening identification number at Visit 1. Only participants continuing to meet all inclusion criteria and none of the exclusion criteria at Visit 2 and who meet randomization criteria at Visit 2 will be assigned a unique participant randomization number. Once a randomization number has been allocated to one participant, it may not be assigned to another participant.

The randomization scheme will be generated by the sponsor or designee using computer software incorporating a random number generator. All participants will be centrally assigned to 1 of 6 treatment sequences in a 1:1:1:1:1:1 ratio based on a Williams design (Williams 1949). Before the study is initiated, the telephone number and call-in directions for the IRT will be provided to each site.

Each sequence will comprise all 3 study interventions in a randomized order. All sequences will contain AS MDI 180 µg, placebo MDI, and Ventolin Evohaler 200 µg (Table 5).

Table 5 Williams Design for the 3-Treatment, 3-Period Crossover Trial

Sequence Number	Period 1	Period 2	Period 3
1	Comparator	Placebo	Study intervention
2	Study intervention	Comparator	Placebo
3	Placebo	Study intervention	Comparator
4	Study intervention	Placebo	Comparator
5	Placebo	Comparator	Study intervention
6	Comparator	Study intervention	Placebo

Three-period, 3-treatment crossover trial is based on a Williams design (Williams 1949). Study design table has been modified from Wang et al 2009.
Study intervention, AS MDI 180 µg; Comparator, Ventolin Evohaler 200 µg; Placebo, placebo matching AS MDI.

Randomization will be centralized and stratified by pre-study background therapy: participants using an ICS and participants not using an ICS (ie, receiving only SABA as needed).

Study intervention will be administered at the study visits indicated in the SoA (Section 1.3).

6.4 Blinding

6.4.1 Methods for Ensuring Blinding

AS MDI and placebo MDI will be blinded to all participants, study site staff, endpoint assessors, and sponsor personnel. Placebo MDI is designed to mimic the appearance, smell, and taste of AS MDI. No double-dummy will be used. Packaging and labelling of AS MDI and placebo MDI will be designed to ensure blinding.

The IRT will provide to the investigator(s) or pharmacist(s) the kit identification number to be allocated to the participant at the dispensing visits as summarized in the SoA (Section 1.3). Routines for this will be described in the IRT user manual that will be provided to each study site.

Randomized Ventolin Evohaler is open label. However, to reduce bias, dosing will be performed under the supervision of study staff, and spirometry assessments will be performed by different study personnel who will only enter the room after dosing is completed; thus, the study personnel conducting the spirometry assessments will be blinded to the identity of the study intervention.

6.4.2 Methods for Unblinding

Individual treatment codes, indicating the treatment randomization sequence for each randomized participant, will be available to the investigator(s) or pharmacists from the IRT. Routines for this will be described in the IRT user manual that will be provided to each study

site.

The randomization code should not be broken except in medical emergencies when the appropriate management of the participant requires knowledge of the treatment randomization. The investigator documents and reports the action to AstraZeneca, without revealing the treatment given to participant to the AstraZeneca staff.

AstraZeneca retains the right to break the code for SAEs that are unexpected and are suspected to be causally related to a study intervention and that potentially require expedited reporting to regulatory authorities. Randomization 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 participant's 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, AstraZeneca 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 the participant to the AstraZeneca staff.

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

6.5 Study Intervention Compliance

Participants are dosed at the site, and they will receive study intervention(s) directly from the investigator or designee, under medical supervision. The date and time, if applicable, of dose administered in the clinic will be recorded in the source documents and recorded in the 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 administering the study intervention.

6.6 Dose Modification (Not Applicable)

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

There will be no continued access to study intervention either after the participant completes his/her participation in the study or after the end of the study.

6.8 Treatment of Overdose

An overdose is defined as any dose greater than the dose investigated in this study that results in clinical signs and symptoms. AstraZeneca does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator/treating physician should:

- Use their best clinical judgment in treating the overdose, and the sponsor's medical monitor should also be contacted.
- Refer to the relevant document(s) for detailed information regarding warnings, precautions, contraindications, AEs, and other significant data pertaining to the study intervention(s) being administered. Such document(s) may include but are not limited to the IB for AS MDI and approved product labelling for open-label products.
- Closely monitor the participant for any AE/SAE and laboratory abnormalities as medically appropriate and at least until the next scheduled visit or follow-up. Refer to Section 8.4.12 for details of AE/SAE reporting related to overdose.

6.9 Prior and Concomitant Therapy

6.9.1 Prior Medications

All prescription and over-the-counter medications, as well as any herbal or vitamin supplements, taken by the participant within 30 days of Visit 1 should be recorded on the prior/concomitant medications eCRF page. Indication, total daily dose, and route and dates of drug administration should be captured to the best of the participant's and site's ability.

Some participants eligible for this study will be on regular inhaled asthma maintenance therapy, defined as a stable low to medium dose of an inhaled ICS with or without a LABA for at least 30 days prior to Visit 1. These participants will be switched to Pulmicort Flexhaler 180 µg BID or 360 µg BID. The allowed total daily ICS dosage to qualify ICS usage for the 30 days prior to Visit 1, along with the assigned dose of sponsor-provided Pulmicort Flexhaler is defined in Table 6. LABA (if applicable) will be discontinued.

Table 6 Dose of Sponsor-provided Pulmicort Flexhaler to be Assigned Based on Pre-study ICS or ICS/LABA Dose

Pre-study asthma inhaled corticosteroid	Total daily dose of pre-study inhaled corticosteroid (µg/day)	Dose of sponsor-provided Pulmicort Flexhaler (µg/day)
Beclomethasone dipropionate (pMDI, standard particle, HFA)	200 to ≤ 500	360
Beclomethasone dipropionate (pMDI, standard particle, HFA)	> 500 to ≤ 1000	720
Beclomethasone dipropionate (DPI or pMDI, extra fine particle, HFA)	100 to ≤ 200	360
Beclomethasone dipropionate (DPI or pMDI, extra fine particle, HFA)	> 200 to ≤ 400	720
Budesonide (DPI or pMDI, standard particle, HFA)	200 to ≤ 400	360
Budesonide (DPI or pMDI, standard particle, HFA)	> 400 to ≤ 800	720
Ciclesonide (pMDI, extra fine particle, HFA)	80 to ≤ 160	360
Ciclesonide (pMDI, extra fine particle, HFA)	> 160 to ≤ 320	720
Fluticasone furoate (DPI)	100	360
Fluticasone propionate (DPI or pMDI, standard particle, HFA)	100 to ≤ 250	360
Fluticasone propionate (DPI or pMDI, standard particle, HFA)	> 250 to ≤ 500	720
Mometasone furoate (pMDI, standard particle, HFA) [a]	200	360
Mometasone furoate (pMDI, standard particle, HFA) [a]	> 200 to ≤ 400	720

[a] Consult the study physician if using mometasone furoate (DPI) due to complexity around devices/formulation.

Some participants will be using only SABA as needed (for rescue) for at least 30 days prior to Visit 1. These participants will discontinue their SABA and initiate sponsor-provided Ventolin HFA for use as needed (Section 4.1).

Participants will be asked to turn in their own inhaled asthma maintenance (if applicable) and reliever products being used prior to Visit 1 to the investigational sites for storage during study participation. Pre-study asthma medications will be returned to the participant at the end of Visit 4 (or upon premature discontinuation or screen failure, if applicable).

6.9.2 Concomitant Medications

Any current ongoing medications, including over-the-counter medications and herbal supplements, will be allowed provided they are not explicitly prohibited by the protocol (Table 8 and Table 9).

Any medication (including over-the-counter or prescription medicines, recreational drugs, vitamins, and/or herbal supplements) or vaccine that the participant (except for screen failures) is receiving from Visit 1 or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including total daily dose, frequency, and route

Any additions, deletions, or changes in the dose of these medications while in the study should be entered in the eCRF. Participants should also be instructed to contact the investigator if they develop any illnesses, especially those requiring medicinal intervention.

The study clinical lead should be contacted if there are any questions regarding concomitant or prior therapy.

6.9.2.1 Required Concomitant Medications

Participants who were receiving a regularly scheduled ICS or ICS/LABA before study entry will be switched to Pulmicort Flexhaler 180 µg BID or 360 µg BID as described in Section 6.9.1. LABA (if applicable) will be discontinued. These participants will continue to use sponsor-provided Pulmicort Flexhaler 180 µg BID or 360 µg BID, as assigned at Visit 1, throughout the screening period and during the study, including the randomized treatment periods and washout periods, up until 12 hours before a study visit.

No other asthma medications are allowed for the remainder of the study, except for sponsor-provided Ventolin HFA for rescue. Participants will continue to use sponsor-provided Ventolin HFA for rescue throughout the screening period and throughout the study, including the randomized treatment periods and washout periods, up to 6 hours before a study visit.

6.9.2.2 Allowed Allergy Medications

Table 7 lists allergy medications that are allowed as long as the participant has been on a stable dose for at least 30 days before Visit 1 and remains on a stable dose throughout the study.

Table 7 Allowed Allergy Medications

Non-sedating long-acting antihistamines [a]
Allergen immunotherapy
Intranasal corticosteroids
Intranasal antihistamines or combination products of intranasal antihistamines/corticosteroids

[a] Short-acting antihistamines (eg, diphenhydramine) are also permitted for use as needed, but not regularly.

6.9.2.3 Prohibited Medications

Prohibited Asthma and Allergy Medications and Washout Periods

Specific prohibited asthma and allergy medications are listed in Table 8. Participants taking any of these prohibited medications are required to stop taking them at Visit 1 and are required to attend Visit 1a for Ventolin HFA reversibility testing. The required washout period for each medication before reversibility testing is shown in Table 8.

Table 8 Prohibited Asthma and Allergy Medications That Must be Discontinued at Visit 1 and Required Washout Period Prior to Visit 1

Medication [a]	Minimum Washout Period Prior to Visit 1a
Short-acting muscarinic antagonist [a]	8 hours
Oral β2-agonists	2 days
Theophylline	2 days
Cromoglycate	7 days
Nedocromil	7 days
Ketotifen [b]	7 days
Zileuton	7 days
LABAs	In combination with an ICS
Indacaterol, olodaterol, vilanterol	7 days
Salmeterol, formoterol	48 hours
Leukotriene receptor antagonist s (eg, Singulair™)	7 days

[a] Administered as fixed or loose combinations.
[b] Ketotifen eye drops are allowed; no washout required.

Prohibited Non-asthma and Non-respiratory Medications

Participants requiring medications listed in Table 9 are prohibited from participating in this study. Participants who recently discontinued use of these medications may be considered for study enrollment provided they have met the minimum cessation period prior to Visit 1. These medications are prohibited throughout the study. If participants require any of the prohibited medications listed in Table 9, the investigator should discuss with the study physician the suitability of the participant continuing study intervention.

Note: Use of systemic corticosteroids (eg, oral, parenteral, intraocular, intraarticular) is prohibited for the duration of the study, including both the screening and randomized treatment periods. If a participant requires a systemic corticosteroid to treat an asthma worsening or asthma exacerbation, the participant will be discontinued from the study. Procedures for study discontinuation are provided in Section 7.2.

Table 9 Prohibited Non-Asthma and Non-Respiratory Medications

Class of medication	Minimum cessation period prior to Visit 1 and prohibited throughout the study
Any drug with potential to significantly prolong the QT interval [a, b]	14 days or 5 half-lives, whichever is longer
Other investigational drugs	30 days or 5 half-lives, whichever is longer
Non-selective non-ocular β-blocking agents	7 days
Non-selective ocular β-blocking agents (eg, ophthalmic timolol)	24 hours or 5-half-lifes, whichever is longer
Cardiac anti-arrhythmics (Class Ia, III)	7 days, unless amiodarone, then 3 months
Anticonvulsants for seizure disorder [c, d]	Allowed if stable dose for 12 months and free of seizures for 1 year
Antipsychotic drugs [e]	30 days
Tricyclic antidepressants [e]	14 days
Monoamine oxidase inhibitors	14 days
Antitumor necrosis factor α antibodies (eg, infliximab and any other members of this class of drugs) [d]	30 days or 5 half-lives, whichever is longer
Monoclonal antibodies [d, f]	30 days or 5 half-lives, whichever is longer
Systemic treatment with strong CYP3A4 inhibitors (eg, ketoconazole, itraconazole, ritonavir) [d]	30 days

Benzodiazepines are not exclusionary. Serotonin norepinephrine reuptake inhibitors and selective serotonin reuptake inhibitors are not excluded as long as the participant has been on a stable dose for at least 30 days before Visit 1 and throughout the screening and treatment periods, and the dose does not exceed the maximum recommended.

[a] 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 before Visit 1, the participant does not meet the QTcF exclusion criterion 5, and if, in the opinion of the investigator, there are no safety concerns for the participant to participate in the study. Initiation of medications with the potential to significantly prolong the QT interval is prohibited throughout the screening and treatment periods.

[b] Short courses of macrolide and quinolone antibiotics to treat infections are permitted.

[c] Anticonvulsants for conditions other than seizures may be started and stopped at any time before the study and throughout the screening and treatment periods.

[d] Only applicable for participants using an ICS at the time of screening and background Pulmicort Flexhaler during the study.

[e] Antipsychotic agents and tricyclic antidepressants used for previously diagnosed underlying medical conditions are allowed if, in the opinion of the investigator, there are no concerns regarding patient safety, and if the participant has been on a stable dose for at least 6 weeks.

[f] Investigators should contact the medical monitor to determine the appropriateness and safety of continuing study intervention on a case-by- basis (eg, Prolia® [denosumab] for osteoporosis, may be allowed after consultation).

6.9.2.4 Other Concomitant Treatment

Medication other than that described above, which is considered necessary for the participant's safety and wellbeing, may be given at the discretion of the investigator and should be recorded in the appropriate sections of the eCRF.

6.9.3 Rescue Medicine

All participants will use only sponsor-provided asthma medication as needed (for rescue) during the study. At Visit 1 (screening), participants will discontinue their SABA and initiate sponsor-provided Ventolin HFA, for use as needed, up until 6 hours before a study visit.

7 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.

7.1 Discontinuation of Study Intervention

Discontinuation of study intervention is not applicable for a single-dose study.

Participants who discontinue from the study will complete the PDV (Section 1.3). Participant discontinuation/withdrawal from the study is explained below.

7.2 Participant Discontinuation/Withdrawal From the Study

Discontinuation of the participant from the study by the investigator:

Participants experiencing any of the changes of concern listed below should be discontinued/withdrawn from the study.

- Asthma worsening requiring change in asthma treatment other than sponsor-provided Pulmicort Flexhaler, if assigned, and as needed sponsor-provided Ventolin HFA.

  Note: Participants experiencing an asthma exacerbation during the study will be evaluated by the investigator and treated with medications for asthma deemed medically necessary and will be discontinued/withdrawn from the study.
- FEV1 stability criteria: Fails to meet FEV1 stability criteria after 2 consecutive attempts (Section 8.2.5)
- Requires any of the prohibited medications listed in Section 6.9.2.3
- Any safety reason as judged by the investigator and/or sponsor
- Pregnancy (Section 8.4.10)
- The participant's treatment code is prematurely broken by the investigator

A participant may be discontinued from the study at any time at the discretion of the investigator, for compliance or safety reasons, or for any of the reasons described above.

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 (eg, telephone contact, a contact with a relative or treating physician, or information from medical records).
- 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.

Participants who are prematurely discontinue from the study for any reason before completing all period visits in the study will undergo a PDV. After the PDV, participants will be scheduled for a follow-up telephone call to occur 3 to 7 days after the last dose of study intervention. See the SoA (Section 1.3) for data to be collected at the time of study discontinuation/withdrawal and follow-up and for any evaluations that need to be completed.

7.3 Lost to Follow-up

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

The following actions must be taken if a participant fails to return to the 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 continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls, 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 been lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the Section 1.3 SoA. Protocol waivers or exemptions are not allowed.

Urgent safety concerns should be discussed with AstraZeneca immediately upon occurrence or awareness to determine if the participant should continue or be discontinued from the study.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. 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.

The investigator will ensure that data are recorded on the eCRFs as specified in the clinical study protocol and in accordance with the instructions provided.

The investigator ensures the accuracy, completeness, and timeliness of the data recorded and of the provision of answers to data queries according to the clinical study agreement. The investigator will sign the completed eCRFs. A copy of the completed eCRFs will be archived at the study site.

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.

8.1 Administrative and General/Baseline Procedures

8.1.1 Screening/Run-in Period

Written informed consent must be obtained from each participant prior to initiating any screening procedure. All procedures will be performed according to the Section 1.3 SoA.

At screening, participants are assessed to ensure they meet the study eligibility criteria (Section 5.1 and Section 5.2).

Visit 1

- Participants who were using only SABA as needed for at least 30 days as a consistent regimen before Visit 1 will be switched to sponsor-provided Ventolin HFA as needed for symptoms at Visit 1. Participants will be asked to turn in their own inhaled asthma reliever product to the investigational sites for storage until the individual participant's

last clinic visit. Sponsor-provided Ventolin HFA is allowed from Visit 1 and throughout the study, including washout periods, up until 6 hours before a study visit. The minimum screening/run-in period for these participants will be 3 days.

- Participants who were using ICS and ICS/LABA for at least 30 days as a consistent regimen before Visit 1 will be switched to sponsor-provided Pulmicort Flexhaler (180 µg BID or 360 µg BID) based on the participant's previous ICS therapy, irrespective of LABA use. The allowed total daily ICS dosage to qualify ICS usage for the 30 days prior to Visit 1 along with the assigned dose of sponsor-provided Pulmicort Flexhaler is defined in Table 6. These participants will also receive sponsor-provided Ventolin HFA as needed for symptoms at Visit 1. Participants will be asked to turn in their own inhaled asthma maintenance and reliever products to the investigational sites for storage until the individual participant's last clinic visit. Sponsor-provided background asthma medications, Pulmicort Flexhaler and Ventolin HFA, are allowed during the screening/run-in period and throughout the study, up until 12 and 6 hours, respectively, before a study visit. The minimum run-in period for these participants will be 14 days.

The maximum screening/run-in period for all participants will be 28 days. The screening period should be as short as possible; however, the duration will be determined by the investigator.

For participants who **have not taken** their regular morning doses of asthma maintenance medications (at least 12 hours before the study visit) and/or SABA (at least 6 hours before the study visit), the following activities will also be performed at Visit 1:

- Perform Vitalograph AIM™ inhalation technique training (Section 8.2.1)
- Perform inhalation training with placebo MDIs to ensure adequate demonstration of MDI technique (Section 8.2.1)
- Conduct spirometry assessments (FEV1) (Section 8.2.3)
- Perform Ventolin HFA reversibility test (Section 8.2.4).

Visit 1a

For participants who received their regularly inhaled asthma medications and/or SABA on the morning of Visit 1(at least 12 and 6 hours, respectively, before the study visit), spirometry and Ventolin HFA reversibility will be measured at Visit 1a. Vitalograph AIM and placebo MDI inhalation technique training will be performed before these assessments. This visit will occur within 10 days of Visit 1 and after the asthma medications have been withheld for the appropriate time (Table 8).

Participants who fail to meet reversibility criteria at Visit 1 will have second reversibility test at Visit 1a (Section 5.4.1). This visit will occur within 7 days of Visit 1. Only 2 reversibility

testing attempts are allowed. Participants not meeting reversibility criteria after 2 attempts must be screen failed.

Visit 1b

Visit 1b may only be scheduled for participants who did not perform Ventolin HFA reversibility testing at Visit 1 and did not meet Ventolin HFA reversibility criteria at Visit 1a (Section 5.4.1). For these participants, Visit 1b will be scheduled to occur within 7 days of Visit 1a for a second reversibility test. Vitalograph AIM and placebo MDI inhalation technique training will be performed before the assessment. Only 2 reversibility testing attempts are allowed. Participants not meeting reversibility criteria after 2 attempts must be screen failed.

All participants must demonstrate pre-BD FEV1 of ≥ 40% of the PN value after withholding SABA for ≥ 6 hours and FEV1 reversibility to Ventolin HFA (defined as improvement in FEV1 at 30 minutes post-Ventolin HFA dosing of ≥ 12% and ≥ 200 mL) during the screening period (Section 8.2.4).

8.1.2 Treatment Periods and Follow-up

At the start of each treatment visit, before any study procedures are performed, site personnel must confirm that the participant has withheld all sponsor-provided asthma medications. Note the time of the last dose of sponsor-provided asthma medications; the last dose of Pulmicort Flexhaler (if assigned) and Ventolin HFA should be at least 12 and 6 hours, respectively, before the study visit. Confirm the last time of dosing meets the study requirements indicated above.

Participants should bring their sponsor-provided Ventolin HFA and sponsor-provided Pulmicort Flexhaler, if assigned, with them to the clinic to be collected by the investigator or authorized study staff.

Note: Participants who did not withhold their Pulmicort Flexhaler (if assigned) or Ventolin HFA dose, as described above, before the start of study procedures must have their visit rescheduled as soon as is practical, but within the protocol-specified washout window.

Before randomization at Visit 2, the investigator must confirm that the participant has met the randomization criteria (Section 5.2.1). Participants who do not meet these randomization criteria will be screen failed. In addition, before the in-clinic dose is administered at Visits 3 and 4, the site must confirm the participant meets FEV1 baseline stability criteria (Section 8.2.5).

For dose preparation and administration of AS MDI, placebo MDI, and open-label Ventolin Evohaler, see Section 6.2.1.1 and Section 6.2.2.1, respectively. AS MDI, placebo MDI, or open-label Ventolin Evohaler instructions for use are provided in the pharmacy manual. Before dosing, the investigator or authorized study staff should confirm that the participant

has an acceptable MDI device technique (Section 8.2.1).

Pre-dose and post-dose spirometry will be performed at the visits indicated in the SoA (Section 1.3) and following the guidelines in Section 8.2.3.

Participants will administer the dose of assigned study intervention at the clinic:

- The in-clinic dosing time will be recorded as the time of administration of the second actuation of study intervention.
- If a participant is experiencing severe symptoms and requires Ventolin HFA for relief of asthma symptoms at any time during a study visit, site personnel must note the time and justification for use in the participant's chart, and all spirometry assessments should be stopped during the current treatment visit. Safety assessments should be continued at the discretion of the investigator.
- After the final spirometry test (6-hour post-dose), the investigator or authorized study staff will ensure that the participant has enough sponsor-provided asthma medication to last until the next treatment visit and return the medication (rescue Ventolin HFA for all participants and Pulmicort Flexhaler for participants who were on ICS or ICS/LABA before study entry) to the participant by the end of the clinic visit.

Participants who are prematurely discontinued/withdrawn from the study for any reason before completing all period visits in the study will undergo a PDV (see Section 7.2 for details about study discontinuation/withdrawal).

Sponsor-provided Ventolin HFA and Pulmicort Flexhaler, if assigned, should be returned to the site at the end of Visit 4 (or upon premature discontinuation or screen failure, if applicable) for final disposition.

Pre-study asthma medications will be returned to the participant at the end of Visit 4 (or upon premature discontinuation or screen failure, if applicable).

After the last treatment period or following a PDV, participants will be scheduled for a follow-up telephone call to occur 3 to 7 days from the date of the last study intervention dose.

See the SoA (Section 1.3) for data to be collected at the PDV and follow-up and for any further evaluations that need to be completed.

8.1.3 Demographics

Demographic data will be collected and include age, sex, race, and ethnicity.

8.1.4 Medical/Surgical History and Prior/Current Medications

Medical/surgical history and prior/current medications assessment will include the following:

- Previous and current medical conditions (including age of onset of asthma) and hospitalizations
- Surgical history
- Prior and current medications including use of ICS, SABA, and LABA (Section 5.1 and Section 6.9)
- Alcohol and drug consumption (Section 5.2)
- Nicotine intake history (Section 5.2)

8.2 Efficacy Assessments

Planned time points for all efficacy assessments are provided in the Section 1.3 SoA.

Efficacy will be assessed through PFTs. Forced expiratory spirometry for derivation of FEV1 as defined in ATS/ERS guidelines will be performed in accordance with ATS/ERS acceptability and repeatability criteria (Graham et al 2019) using a centralized spirometer that meets or exceeds minimum performance recommendations. Calculated predicted spirometry results will be obtained using the Global Lung Initiative equations (Quanjer et al 2012).

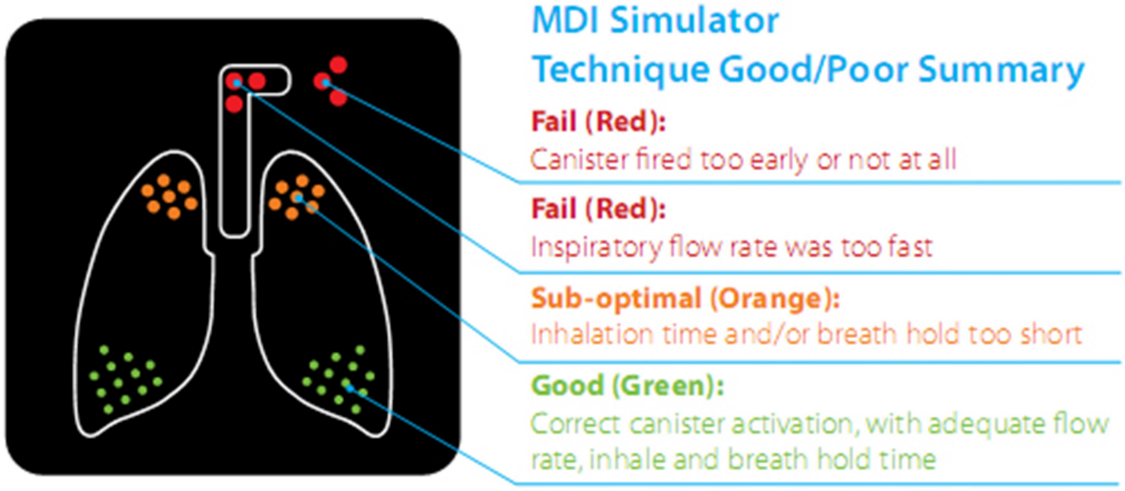
8.2.1 Inhalation and Device Training

To ensure that participants are able to perform inhalation according to instructions and to achieve reproducibility in inhalation techniques, inhalation techniques will be practiced with the Vitalograph AIM inhalation training device. For the timing of device and inhalation training refer to the Section 1.3 SoA.

In addition, participants will perform inhalation training with placebo MDIs and will be provided with detailed instructions on the use of the MDI devices. All participants must demonstrate adequate MDI administration techniques in order to be treated.

The Vitalograph AIM training device uses disposable DPI and pMDI simulators to train participants on good inhalation technique. The AIM training device measures and evaluates the actuation, the duration of inhalation and breath hold, the timing of firing the MDI inhaler simulator, time of inhalation within target flow range, and the inspiratory flow rate. A lung display illustrates whether the inhalation technique achieved deposition of the medication into the lungs (Haidl et al 2016; Vitalograph AIM Instruction for Use 2021). An example of results displayed by the device is shown in Figure 2. Vitalograph AIM instructions for use will be provided in the pharmacy manual.

Figure 2 AIM Trainer Summary of MDI Technique



Source: Vitalograph AIM Instruction for Use 2021

8.2.2 Standardization of Spirometry Collections

The central spirometry vendor is responsible for assuring that the spirometer at the study site meets ATS/ERS recommendations (Graham et al 2019) and that the study site personnel who will be performing the testing are properly certified. Additional details will be provided in the spirometry manual.

8.2.3 Spirometry Schedule and Assessment of FEV1

8.2.3.1 Spirometry Schedule

Spirometry will be conducted at all visits except the PDV (when applicable).

Spirometry will be performed by the investigator or trained designee according to ATS/ERS guidelines (Graham et al 2019).

For Visits 2, 3, and 4, participants will be required to return to the clinic at approximately the same time of the day (± 1 hour) as Visit 1. All pre-dose (trough) spirometry must be conducted in the morning (0800 ± 2 hours).

During the screening and treatment periods, sites should call participants 24 to 48 hours prior to each visit to remind them the following:

- Their morning dose of Pulmicort Flexhaler must be withheld until after all pre-dose assessments are completed in the clinic (ie, last dose should be **at least** 12 hours before a study visit).
- Their last dose of Ventolin HFA should be **at least** 6 hours before a study visit.

- They should bring their sponsor-provided Ventolin HFA and sponsor-provided Pulmicort Flexhaler (if assigned) with them to the clinic visit.
- They should not engage in strenuous exertion for at least 6 hours prior to the study visit (Section 5.3.2).
- They should refrain from ingesting xanthine-containing foods and beverages and caffeine-containing medications for at least 6 hours before the study visit and for the duration of a study visit (Section 5.3.1).
- They must avoid consuming intoxicants within 8 hours before PFTs (to avoid problems in coordination, comprehension, and physical ability (Section 5.3.1).
- They should avoid wearing clothing that substantially restricts full chest and abdominal expansion should be avoided at clinic visits (to avoid external restrictions on lung function during PFTs) (Section 5.3.3)

All in-clinic dosing should occur prior to 1000 (± 1-hour allowance) in the morning.

Participants will be required to remain at the clinic until completion of all protocol-defined assessments and procedures.

8.2.3.2 FEV1 Assessments

During PFTs, the study staff performing spirometry should be reminded of the following:

- For repeated measurements, eg, to assess the best of 3 efforts, a short pause (one minute) between measurements is recommended.
- The measurements are to be made with the participant seated in an upright position with shoulders slightly back and chin slightly elevated and feet flat on the floor (preferably). If not comfortable, a standing position is also acceptable (Graham et al 2019).
- The same position should be used for all spirometry measurements performed on the participant during the entire study.
- The head must not be tilted during spirometry measurements.

Screening FEV1: Spirometry at Visits 1, 1a, and/or 1b, and 2 will be used to satisfy enrollment and randomization criteria. Multiple forced expiratory efforts (at least 3 but no more than 8 attempts) will be performed, and the 2 best efforts that meet the ATS/ERS acceptability and reproducibility criteria (Graham et al 2019) will be recorded. The best efforts will be based on the highest FEV1. The average of these 2 assessments will be used to calculate the screening FEV1.

Pre-dose FEV1: At each treatment visit after Visit 2 (Visits 3 and 4), participants must meet the FEV1 baseline stability criteria (Section 8.2.5) before dosing. At all treatment visits

(Visits 2, 3, and 4), spirometry will be conducted 60 and 30 minutes before administration of study intervention. The average of these 2 assessments will be used to calculate morning pre-dose FEV1.

Post-dose FEV1: Following study intervention administration at each visit, spirometry will be obtained 5, 15, 30, 45, 60, 120, 180, 240, 300, and 360 minutes after dose administration. Three test maneuvers will be performed at each time point. The highest value at each time point meeting acceptability/borderline acceptability criteria per ATS guideline will be used for these post-dose assessments.

Bronchodilator Responsiveness Testing

Bronchodilator responsiveness testing will be performed following the recommendations in the 2019 ATS/ERS spirometry standard (Graham et al 2019) and will be calculated using the following equation (Stanojevic et al 2022):

$$\text{Bronchodilator response} = \frac{\text{post-bronchodilator value (L)} - \text{pre-bronchodilator values (L)}}{\text{Predicted value (L)}^{*}} \times 100$$

* The predicted value should be determined using the appropriate Global Lung Function Initiative spirometry equation.

Detailed information regarding spirometry equipment and procedures as well as data collection, validation, analysis, and reporting will be provided in the spirometry manual.

8.2.4 Characterization of Reversibility

Reversibility to Ventolin HFA will be evaluated at Visit 1, 1a, and/or 1b. Participants must demonstrate reversibility to Ventolin HFA to be randomized into the study; no more than 2 reversibility test attempts are allowed. Reversibility testing is performed as follows:

1 Determine if morning doses of all maintenance asthma ICS/LABA, if applicable, were withheld for at least 12 hours and that SABAs were not administered within 6 hours of testing.
2 Perform pre-BD PFTs (minimum of 3 to a maximum of 8 tests allowed if assessment values did not meet acceptable/repeatability criteria) at 30 minutes before administration of Ventolin HFA.
3 Administer 4 actuations of Ventolin HFA (90 µg per actuation; total 360 µg) per instructions for use (to be provided in the pharmacy manual).
4 Perform post-BD PFTs (minimum of 3 to a maximum of 8 tests allowed if assessment values did not meet acceptable/repeatability criteria) 30 minutes after the administration of Ventolin HFA.

Reversibility will be a comparison of the best FEV1 effort obtained at 30 minutes pre-BD to the best FEV1 effort obtained at 30 minutes post-BD following administration of Ventolin HFA. A participant is considered reversible to Ventolin HFA if the improvement in FEV1 at 30 minutes post-Ventolin HFA dosing is ≥ 12% and ≥ 200 mL relative to pre-BD PFTs.

8.2.5 FEV1 Baseline Stability Criteria

It is important to ensure that lung function at each study visit is stable and reflective of asthma severity at randomization. As such, the average of the 60- and 30-minute FEV1 pre-dose values at each treatment visit after Visit 2 (Visits 3 and 4) must be within ± 20% (absolute value) of the average of the 60- and 30-minute FEV1 pre-dose values at Visit 2. At Visit 3, if the pre-dose FEV1 average is outside of the ± 20% range but the 30-minute pre-dose assessment is within ± 20%, then another assessment may be conducted 30 minutes later. If the last 2 assessments meet the baseline stability requirements (ie, within ± 20%), the initial 60-minute pre-dose assessment will not be used, and the last 2 assessments will be used to establish the eligibility criteria.

Participants who do not meet the FEV1 baseline stability criteria at Visits 3 and 4 must be rescheduled as soon as is practical but within the protocol-specified washout window (3 to 7 days). Participants who fail to meet stability criteria after 2 attempts for a treatment visit will be discontinued/withdrawn from the study. Participant discontinuation/withdrawal from the study is described in Section 7.2. Assessments to be completed at the PDV and follow-up are listed in the Section 1.3 SoA.

8.3 Safety Assessments

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

8.3.1 Physical Examinations

Physical examination will be performed at time points as specified in the Section 1.3 SoA.

A complete physical examination will be performed and include assessments of the following: general appearance, skin, head, ears, eyes, nose, throat, neck (including thyroid), lymph nodes, chest, heart, abdomen, and musculoskeletal (including spine and extremities) and nervous systems.

Additionally, weight (assessed in ordinary indoor clothing with shoes off) and height will be recorded at Visit 1 only.

If examinations suggest a worsening of asthma, refer to Section 8.4.8. For appropriate AE reporting based on examinations and tests, see Section 8.4.4.

8.3.2 Vital Signs

Vital signs will be measured at the time points specified in the Section 1.3 SoA.

Pulse rate and blood pressure will be measured at all study visits (Visits 1 to 4) and the PDV, if applicable. Systolic and diastolic blood pressure will be assessed after the participant is supine or seated for 5 minutes. If, in the opinion of the investigator, a clinically significant change occurs, then the measurement should be repeated at medically appropriate intervals until the value returns to within an acceptable range. If the value does not return to baseline, the investigator should determine if this is an AE (Section 8.4.4).

If examinations suggest a worsening of asthma, refer to Section 8.4.8. For appropriate AE reporting based on examinations and tests, see Section 8.4.4.

8.3.3 Electrocardiograms (Not Applicable)

Electrocardiograms will not be conducted in this study.

8.3.4 Clinical Safety Laboratory Tests

Urine β-hCG test will be performed at Visit 1, before starting each treatment period (Visits 2 to 4), and at the PDV, if applicable (for POCBP only).

Participants of childbearing potential must have a negative urine pregnancy test at Visit 2 before randomization. A POCBP who is found to be pregnant at Visit 2 will be excluded from the study and be considered a screen failure.

Procedures to be implemented if a POCBP becomes pregnant during the study and pregnancy reporting requirements are found in Section 8.4.10.

8.4 AEs, SAEs, and Other Safety Reporting

The principal 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 ADEs, medical device SAEs, SADEs, USADEs, and medical device deficiencies) can be found in Appendix C. Medical device deficiencies are covered in Section 8.4.13.

Participants (or, when appropriate, a caregiver, surrogate, or the participant's legally authorized 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 intervention(s) (yes or no)
- Action taken with regard to study intervention(s)
- 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 hospitalization
- 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

8.4.1 Time Period and Frequency for Collecting AE and SAE Information

Adverse events will be collected from randomization throughout the treatment period and including the follow-up period (telephone contact).

Serious adverse events will be recorded from the time of signing of the ICF.

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

investigator shall, without undue delay, report the SAE to AstraZeneca.

8.4.2 Follow-up of AEs and SAEs

Any AEs that are unresolved at the participant's last visit (follow-up by telephone contact) 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.

8.4.3 Causality Collection

The investigator should assess causal relationship between the study intervention and each AE and/or incident, 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 study intervention?'

For SAEs and serious incidents, 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 C.

8.4.4 AEs Based on Examinations and Tests

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

- Fulfill any of the SAE criteria
- Are the reason for discontinuation from the study
- 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 study intervention, eg, dose adjustment or drug interruption).

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

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 unless unequivocally related to the DUS (Section 8.4.8).

The results from the protocol-mandated vital signs will be summarized in the CSR.

8.4.5 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.

8.4.6 Hy's Law (Not Applicable)

8.4.7 Disease Progression (Not Applicable)

8.4.8 Disease Under Study

Any event attributable to DUS (ie, asthma) and/or its progression (increase in the symptoms of the disease, eg, dyspnea, chest tightness, cough, etc), and/or increase in the severity of the disease should be considered as DUS. Events which are unequivocally due to DUS should not be reported as AEs during the study unless they meet SAE criteria, are not consistent with a participant's previous history of asthma, or lead to discontinuation from the study.

8.4.9 Reporting of SAEs

All SAEs must be reported whether or not considered causally related to the study intervention. 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 one 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 one 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 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 is the IB for the AstraZeneca IMP and the label of the current effective version of the SmPC (Ventolin Evohaler SmPC 2024) for the active comparator product.

8.4.10 Pregnancy

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

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

8.4.10.1 Maternal Exposure

If a participant becomes pregnant during the study, the participant will be discontinued from the study. Procedures for discontinuation from the study are provided in Section 7.2.

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**

one or 5 calendar days for pregnancies associated with SAEs (Section 8.4.9) 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.

8.4.11 Medication Error, Drug Abuse, and Drug Misuse

8.4.11.1 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 **one 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 **one** (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 (Section 8.4.9) and **within 30 days** for all other events.

8.4.11.2 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.

8.4.11.3 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.

8.4.11.4 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 authorized product information, or for unauthorized 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.

8.4.12 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 during 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 one or 5 calendar days** for overdoses associated with an SAE (Section 8.4.9) and **within 30 days** for all other overdoses.

8.4.13 Medical Device Deficiencies

Medical devices and combination products with a device constituent are being provided for use in this study. In order to fulfill 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 device constituent of AS MDI (albuterol sulfate inhalation aerosol), Ventolin (albuterol sulfate inhalation aerosol), and Pulmicort Flexhaler (budesonide inhalation powder) combination products and/or with third-party medical devices.

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 summarized 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 C.

The AstraZeneca clinical study medical device/device constituent report form and/or product

complaint intake form and/or third-party manufacturer's own medical device complaint report form will be used to collect the deficiency. For third-party medical devices, the deficiency will be reported to the manufacturer, who will be responsible for fulfilling their regulatory obligations.

8.4.13.1 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 C .

8.4.13.2 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.

8.4.13.3 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 and/or third-party manufacturer's own medical device complaint report form will be sent to AstraZeneca by email.
- Where an SAE has occurred in addition to the malfunction, the SAE will be recorded in the eCRF as detailed in Section 8.4.9.
- AstraZeneca will be the contact for the receipt of medical device deficiency reports.

8.4.13.4 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 fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.

The investigator, or responsible person according to local requirements (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 IRB/IEC.

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

8.5 Pharmacokinetics (Not Applicable)

Pharmacokinetics will not be evaluated in this study.

8.6 Pharmacodynamics (Not Applicable)

Pharmacodynamics will not be evaluated in this study.

8.7 Optional Genomics Initiative (Not Applicable)

Optional Genomics Initiative research is not applicable in this study.

8.8 Biomarkers (Not Applicable)

Biomarkers will not be evaluated in this study.

8.9 Immunogenicity Assessments (Not Applicable)

Immunogenicity will not be evaluated in this study.

8.10 Medical Resource Utilization and Health Economics (Not Applicable)

Medical resource utilization and health economics parameters will not be evaluated in this study.

8.11 Study Participant Feedback Questionnaire (Not Applicable)

This study will not provide a study participant feedback questionnaire to study participants.

9 STATISTICAL CONSIDERATIONS

The SAP will be finalized prior to database lock and 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.

Data processing, statistical screening, descriptive reporting, and analysis of the efficacy and safety data will be performed using the SAS (SAS Institute, Cary, NC, US) implemented at the time of database lock.

9.1 Statistical Hypotheses

The primary objective of this study is to demonstrate the non-inferiority of a single dose of

albuterol delivered from AS MDI to Ventolin Evohaler. The mean treatment difference in change from baseline in FEV1 AUC0-6 (μ_D) will be estimated, and the following one-sided hypothesis will be tested at a 5% significance level:

Non-inferiority

- H_0: $\mu_D \leq$ -100 mL
- H_A: $\mu_D >$ -100 mL

where H_0 is the null hypothesis, and H_A is the alternative hypothesis. The null hypothesis will be rejected when the lower limit of the 90% CI bound for the estimated mean treatment difference is > -100 mL.

The objective to establish assay sensitivity (superiority) of a single dose of albuterol delivered from Ventolin Evohaler compared with placebo on post-dose lung function in adults with asthma will be evaluated using the following 2-sided hypotheses:

Assay Sensitivity

- H_0: $\mu_D = 0$
- H_A: $\mu_D \neq 0$

where the H_0 and H_A are the null hypothesis and alternative hypothesis, respectively.

The null hypothesis is rejected at the 5% significance level if the probability of observing a test statistic as extreme as or more extreme than that observed is less than 0.05 (p-value < 0.05).

Non-inferiority between AS MDI and Ventolin Evohaler can only be declared if superiority of Ventolin Evohaler compared to placebo is also demonstrated.

The key secondary objective is to demonstrate the therapeutic equivalence of a single dose of albuterol delivered from AS MDI relative to Ventolin Evohaler on post-dose lung function in adults with asthma. To test for equivalence, the non-inferiority null hypothesis must be tested first (see above), followed by a hypothesis test that the mean treatment difference is less than the upper equivalence limit. The following one-sided hypothesis will be tested at a 5% significance level:

Upper Equivalence Limit

- H_0: $\mu_D \geq$ 100 mL
- H_A: $\mu_D <$ 100 mL

The null hypothesis is rejected when the 90% CI upper bound for the estimated mean

treatment difference is < 100 mL. To establish equivalence, the non-inferiority null hypothesis must be rejected first, such that the 90% CI bounds for the treatment difference lies entirely within the equivalence limits of ± 100 mL.

Statistical hypotheses testing will be type I error controlled at 5% for the primary and key secondary treatment comparisons via a hierarchical testing procedure. The above specified hypotheses will be tested in the following sequential order:

1 Non-inferiority: AS MDI versus Ventolin Evohaler
2 Assay sensitivity: Ventolin Evohaler versus placebo
3 Upper equivalence limit: AS MDI versus Ventolin Evohaler

Inference for a test in the defined order is dependent on statistical significance being achieved in the preceding tests. Therefore, where this is not achieved, then nominal p-values will be provided thereafter. The superiority of AS MDI compared with placebo will also be tested, but it will be considered an exploratory endpoint and will not be controlled for type I error. The statistical success criteria will follow the same 2-sided hypothesis testing as for the Ventolin Evohaler versus placebo comparison above.

Similarly, the secondary objectives/endpoints (change from baseline in FEV1 AUC0-4 and peak change from baseline FEV1) will be tested to establish non-inferiority, assay sensitivity, and equivalence and will follow the same testing as the primary and key secondary objectives. However, these tests are not controlled for type I error.

9.2 Sample Size Determination

To ensure at least 90 participants complete the study, approximately 102 participants (17 per treatment sequence) will be randomized to account for a 10% dropout rate. Ninety participants will provide > 95% overall probability to demonstrate superiority of each treatment relative to placebo MDI assuming a true treatment difference (active-placebo MDI) of 190 mL, SD of the period differences of 204 mL, and 2-sided 5% level test. This sample size will also provide around 95% probability of obtaining a 2-sided 90% CI (equivalent to 2 one-sided hypotheses tests each performed at the 5% significance level) for the difference between AS MDI and Ventolin Evohaler within the equivalence bounds of ± 100 mL. This calculation assumes a true between-treatment difference (AS MDI – Ventolin Evohaler) of 28 mL and an SD of the differences of 204 mL. The assumptions of the SD of the differences and the treatment difference were obtained from a 5-treatment, 5-period, placebo-controlled, dose-ranging study that compared AS MDI to placebo MDI and open-label Proventil® HFA in adult and adolescent participants with mild to moderate asthma (Study D6930C00001/PT007001). An assumption of 204 mL for the SD of the differences is supported by the upper limit of the 95% CI of the sampling distribution (184 mL; 95% CI: 164, 204), and a true between-treatment difference assumption of 28 mL is supported by the (magnitude of) average

difference between AS MDI and Proventil HFA for the 90 and 180 µg doses.

Note: 'Screened' means a participant's-agreement to participate in a clinical study following completion of the informed consent process. Potential participants who are screened for the purpose of determining eligibility for the study, but are not randomized/assigned in the study, are considered 'screen failures', unless otherwise specified by the protocol.

9.3 Populations for Analyses

The following populations are defined in Table 10:

Table 10 Populations for Analysis

Population/analysis set	Description
All enrolled set	The enrolled set is defined as all participants for whom informed consent to participate in the study was obtained and have a participant identification number.
Randomized set	The randomized set is defined as all participants who are randomized to study intervention.
Full analysis set (FAS)	The FAS is defined as all participants who are randomized to study intervention and receive at least one inhalation of the study intervention. Participants will be analyzed in each period according to the study intervention they received.
Safety analysis set	The safety analysis set is defined as all participants who are randomized to study intervention and receive at least one inhalation of the study intervention. Participants will be analyzed according to the study intervention received rather than per the randomization scheme.

9.4 Statistical Analyses

The SAP will be finalized prior to database lock and unblinding, and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and secondary endpoints.

9.4.1 General Considerations

Participant demographics and baseline characteristics will be summarized on the full analysis set (overall and by randomized sequence) by means of summary descriptive statistics.

In general, continuous variables will be summarized by treatment with descriptive statistics: the number of non-missing values, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized by treatment with frequency counts and percentages.

Missing data following an IE will be imputed assuming MAR (Section 3). Handling of missing data will be described in detail in the SAP.

Analyses will be performed by the sponsor or its representatives.

9.4.2 Efficacy

9.4.2.1 Primary Endpoint(s)

The primary endpoint is the mean change from baseline in FEV1 AUC0-6. The AUC0-6 is the area under the curve for the change from baseline in FEV1 calculated using the trapezoidal rule from dosing until 6 hours post-dosing.

Baseline FEV1 will be defined as the period-specific mean of available pre-dose values, eg, the mean of the 60- and 30-minute acceptable pre-dose values. If only one value is available or acceptable, that value will be used as baseline. Details of the definition of baseline will be described in the SAP. All observed data will be utilized with the trapezoidal rule to calculate AUC. To aid in interpretation, all AUC values will be normalized by dividing the AUC by the time from the first to the last non-missing value (typically 6 hours). Baseline and only one non-missing, post-dose value 0 to 3 hours and one non-missing, post-dose value 3 to 6 hours, is required for the calculation of AUC.

The change from baseline FEV1 AUC0-6 will be analyzed using a linear mixed model with a random participant effect using the primary analysis set and a principal stratum estimand. The fixed effects in the model will include treatment and period. An additional covariate for average baseline (period-specific baseline FEV1 averaged over the treatment periods) will also be included to remove cross-level bias (Kenward and Roger 2010).

The primary estimand will be evaluated first to establish non-inferiority. However, non-inferiority between AS MDI and Ventolin Evohaler based on the change from baseline FEV1 AUC0-6 can only be declared if superiority of Ventolin Evohaler compared to placebo is also demonstrated. If non-inferiority is established, then equivalence will be tested as a key secondary objective (see Section 9.1 for hypotheses to be tested).

Non-inferiority Comparison

The non-inferiority comparison will evaluate the principal stratum estimand in the FAS. The principal stratum is defined by the absence of the occurrence of IEs in the 2 treatment arms (AS MDI and Ventolin Evohaler). The 5 attributes describing the estimand that will be used to define the treatment effect of interest are provided in Section 3.

Based on the linear mixed model described above, the 90% CI for the difference between AS MDI and Ventolin Evohaler for the primary endpoint will be presented. The null hypothesis is rejected if the lower limit for the 90% CI for the mean difference is > -100 mL, and noninferiority will be declared. The justification for the non-inferiority margin is provided in

Section 9.4.2.2.

Assay Sensitivity

To establish the superiority comparison of Ventolin Evohaler versus placebo for the change from baseline FEV1 AUC0-6, the analysis will evaluate the primary estimand based on the FAS for the treatment group comparison, using the same linear mixed model as described above.

The 5 attributes describing the estimand that will be used to define the treatment effect of interest for the treatment comparison of Ventolin Evohaler versus placebo are provided in Section 3.

The population will be adults with asthma (pre-BD FEV1 of ≥ 40% of the PN value), with demonstrated FEV1 reversibility to Ventolin HFA, and who have post-treatment efficacy data in AS MDI and placebo treatment periods in the study.

A 2-sided alpha level of 0.05 will be used. The null hypothesis to be tested for each of the superiority comparisons is that the treatment is equivalent to placebo. The alternative hypothesis is that the mean treatment difference is not equal. Treatment estimates, standard errors, and the estimated treatment differences with associated 90% and 95% CIs and p-values will be provided. The comparison of AS MDI versus placebo will also be conducted but will be considered exploratory.

9.4.2.2 Secondary Endpoint(s)

The equivalence comparison between AS MDI and Ventolin Evohaler (based on the change from baseline in FEV1 AUC0-6 as a key secondary endpoint) will evaluate the principal stratum estimand in the FAS. The principal stratum is defined by the absence of the occurrence of IEs in the 2 treatment arms (AS MDI and Ventolin Evohaler). The 5 attributes describing the estimand that will be used to define the treatment effect of interest for the equivalence analysis are provided in Section 3.

Equivalence will be based on 2 one-sided hypothesis tests (Schuirmann 1987). To establish equivalence, non-inferiority must first be established, followed by a test that the mean treatment difference is less than the upper equivalence limit. Therefore, the statistical null hypothesis for the AS MDI versus Ventolin Evohaler equivalence comparison will be the composite of the 2 one-sided tests that the mean treatment difference is ≤ -100 mL or ≥ 100 mL (see Section 9.1 for hypotheses to be tested). The null hypothesis is rejected if the 90% CI for the mean difference is contained within the limits of -100 mL and +100 mL. The equivalence limits for FEV1 AUC0-6 are based on the MCID of 100 mL. Currently, there is no widely accepted MCID for FEV1 in asthma. The sponsor considers the proposed equivalence margin of ± 100 mL to be acceptable based on the minimal participant perceivable improvement of 230 mL for FEV1 in participants with asthma, as reported by

Santanello et al 1999, such that the equivalence margin is < 50% of this threshold. This margin is also consistent with other studies in the BDA MDI program, in particular, the Phase II study comparing AS MDI with Proventil HFA (Study D6930C00001 [ANTORA]) in adult and adolescent participants with asthma, which included a non-inferiority margin of 100 mL.

For the treatment comparison of AS MDI versus Ventolin Evohaler, the treatment estimates, standard errors, and mean treatment difference and the associated 90% CI will be provided for the equivalence comparison. If the 2-sided 90% CI is entirely enclosed within the margins of ± 100 mL, it will be concluded that the 2 treatments are equivalent.

The secondary endpoints will be analyzed using a similar approach to that proposed for the primary endpoint. The above defined non-inferiority, equivalence, and superiority comparisons will be made for the secondary endpoints (mean change from baseline in FEV1 AUC0-4 and mean peak change from baseline in FEV1) and will evaluate the principal stratum estimand in the FAS using the same linear model as the primary analysis and using the same margins and approach to hypothesis testing. Secondary endpoint comparisons are not in the statistical testing hierarchy and will not be controlled for type I error.

The peak change from baseline in FEV1 will be calculated using the largest FEV1 value measured during the 6-hour post-dosing period (ie, up through the 6-hour nominal time point).

The FEV1 AUC0-4 will be calculated in a similar manner as FEV1 AUC0-6; however, the trapezoidal rule will only be implemented through the 4-hour nominal time point. The AUC values will be normalized accordingly.

9.4.2.3 Tertiary/Exploratory Endpoint(s)

Detailed descriptions for the analyses of exploratory endpoints will be provided in the SAP.

9.4.2.4 Type I Error Control

The type I error rate will be controlled at the 5% level for the primary and key secondary comparisons based on change from baseline in FEV1 AUC0-6 (see Section 9.1).

9.4.3 Safety

No formal statistical analysis of safety data is planned. Safety analyses will be performed using the safety analysis set. Safety and tolerability data will be assessed by evaluation of AEs/SAEs. Safety data will be presented using descriptive statistics unless otherwise specified. Participants will be analyzed according to the actual treatment received.

9.4.3.1 Adverse Events

Adverse events occurring during each treatment period will be summarized by the number and percentage of participants reporting at least one event and number of events where appropriate

and tabulated at the level of the MedDRA system organ class and preferred term. Adverse events will be coded using the most recent version of MedDRA that will have been released for execution at AstraZeneca. An overview of AEs will present for each treatment group: the number and percentage of participants with any AE, SAEs, AEs with outcome of death, and AEs leading to discontinuation/withdrawal.

Separate AE tables will be provided taking into consideration seriousness, maximum intensity, and relationship to study intervention. Separate tables will show the overall incidence of AEs, SAEs, and AEs leading to discontinuation and the incidence for each treatment.

An additional table will present number and percentage of participants with most common AEs. Most common will be defined in the SAP.

No hypothesis tests will be performed. Full details of AE analyses will be provided in the SAP.

9.4.3.2 Vital Signs

Descriptive statistics (mean, median, standard deviation, and range) for change from baseline will be tabulated by vital sign parameter and treatment for each scheduled assessment time.

For vital signs, baseline will be defined as the average of the values prior to dosing on the day of randomization. In addition, potentially clinically significant values will be identified and summarized.

Details of vital sign analyses including definition of abnormality criteria (eg, potentially clinically significant) will be provided in the SAP.

9.4.4 Other Analyses (Not Applicable)

9.5 Interim Analyses (Not Applicable)

9.6 Data Monitoring Committee (Not Applicable)

10 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 World Medical Association (WMA) General Assembly, Fortaleza, Brazil, October 2013 and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH GCP Guidelines
  - Applicable laws and regulations
- The protocol, revised protocol, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any revised protocol will require IRB/IEC 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 authorizations 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 CFR 312.120, ICH guidelines, the IRB/IEC, European Regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations.

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/IEC, and investigators.
- For all studies except those utilizing medical devices, investigator safety reports must be prepared for SUSARs 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/IEC, if appropriate according to local requirements.

Regulatory Reporting Requirements for Serious Breaches of Protocol or GCP

Prompt notification by the investigator to AstraZeneca of any (potential) serious breach of the protocol or regulations is essential so that legal obligations 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 trial.

AstraZeneca will comply with country-specific regulatory requirements relating to serious breach reporting to the regulatory authority, IRB/IEC, and investigators.

- Where the EU Clinical Trials Regulation 536/2014 applies, AstraZeneca has in place processes to enter details of serious breaches into the European Medicines Agency CTIS. It is important to note that redacted versions of serious breach reports will be available to the public via CTIS.

If any (potential) serious breach occurs in the course of the study, investigators or other site personnel will inform the appropriate AstraZeneca representatives immediately.

In certain regions/countries, AstraZeneca has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about such breaches.

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 one 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 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 will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB/IEC or study center.
- 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 authorized 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 authorized 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 authorized personnel appointed by AstraZeneca, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- The participant must be informed that data will be collected only for 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 authorized or does not have a business need to know the information.
- The participant must be informed that in some cases their data may be pseudonymized. The General Data Protection Regulation (GDPR) defines pseudonymization 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 organizational measures to ensure that the personal data are not attributed to an identified or identifiable natural person.

Personal Data Breaches

A 'personal data breach' means a breach of security leading to the accidental or unlawful destruction, loss, alteration, unauthorized disclosure of, or access to, personal data transmitted, stored, or otherwise processed.

- In compliance with applicable laws, the data controller[2] for the processing activity where the personal data breach occurred (AstraZeneca or respectively the site), will notify the data protection authorities without undue delay within the legal terms provided for such notification and within the prescribed form and content.
- While AstraZeneca has processes in place to deal with personal data breaches it is important that investigators that work with AstraZeneca have controls in place to protect patient data privacy.

The investigator should have a process in place to ensure that:

- Allow site staff or service providers delegated by the investigator/institution to identify the occurrence of a (potential) personal data breaches.
- Any (potential) personal data breach is promptly reported to AstraZeneca or delegated party, through the contacts (email address or telephone number) provided by AstraZeneca.

AstraZeneca and the site must demonstrate that they:

- Have taken all necessary steps to avoid personal data breaches and
- Have undertaken measures to prevent such breaches from occurring in the first place and to mitigate the impact of occurred data breaches (eg, applying encryption, maintaining, and keeping systems and IT security measures up-to-date, regular reviews and testing, regular training of employees, and developed security policies and standards).
- Where possible, have developed an internal data breach reporting and investigation process and internal protocols with guidance on how to respond swiftly and diligently to the occurrence of a personal data breach.
- Where it has not been possible to develop an internal data breach reporting and investigation process, the site follows AstraZeneca's instructions.

Notification of personal data breach to participants:

[2] The **data controller** determines the **purposes** for which and the **means** by which personal data are processed, as defined by the European Commission.

- Notification to participants is done by the site for the data breaches that occurred within the processing activities for which the site is the data controller and for data breaches occurred within the processing activities of AstraZeneca as the data controller, the notification is done in collaboration with the site and is performed by the site and/or principal investigator, acting on behalf of AstraZeneca, so that AstraZeneca has no access to the identifying personal information of the participants. The site and/or principal investigator shall conduct the notification by contacting the participants using the information that they gave for communication purposes in clinical research.
- If a personal data breach occurs in a processor's systems, engaged by AstraZeneca, the processor under contractual obligations with AstraZeneca promptly and in due course after discovering the breach notifies AstraZeneca and provides full cooperation with the investigation. In these cases, to the extent AstraZeneca is the data controller for the processing activity where the breach occurred, it will be responsible for the notification to data protection authorities and, if applicable, to participants. If the personal data breach needs to be notified to the participants, the notification to participants is done in collaboration with the site and is performed by the site and/or principal investigator, acting on behalf of the Sponsor, so that AstraZeneca has no access to the identifying personal information of the participants.
- If a personal data breach involving an AstraZeneca's representative device (ie, study monitor laptop), AstraZeneca representative will provide AstraZeneca with all of the information needed for notification of the breach, without disclosing data that allows AstraZeneca directly or indirectly to identify the participants. The notification will be done by AstraZeneca solely with the information provided by the study monitor and in no event with access to information that could entail a risk of re-identification of the participants. If the data breach must be notified to the data participants, the notification will be done directly by the study monitor in collaboration with the site and/or principal investigator, acting on behalf of the sponsor, so that AstraZeneca has no access to the identifying personal information of the participants. The contract between AstraZeneca and the study monitor shall expressly specify these conditions.
- The contract between the site and AstraZeneca for performing the clinical research includes the provisions and rules regarding who is responsible for coordinating and directing the actions in relation to the breaches and performing the mandatory notifications to authorities and participants, where applicable.

A 5 Committees Structure

No committees have been set up for this study.

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 www.astrazenecaclinicaltrials.com http://www.clinicaltrials.gov and https://euclinicaltrials.eu/ as will the summary of the study results when they are available. The clinical study and/or summary of study results may also be available on other websites according to the regulations of the countries in which the 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/IEC 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 non-compliance 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 authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with

the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

- 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 monitoring plan.

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/IEC 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/IECs, 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 multicenter 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 unfavorable 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 or not 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 fulfills one or more of the following criteria:

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

Adverse Events for **malignant tumors** 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 judgment on an individual event basis should be applied to clarify that the malignant tumor event should be assessed and reported as a **non-SAE**. For example, if the tumor is included as medical history and progression occurs during the study, but the progression does not change treatment and/or prognosis of the malignant tumor, the AE may not fulfill the attributes for being assessed as serious, although reporting of the progression of the malignant tumor as an AE is valid and should occur. Also, some types of malignant tumors, which do not spread remotely after a routine treatment that does not require hospitalization, 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).

Hospitalization

Outpatient treatment in an emergency room is not in itself an SAE, although the reasons for it may be (eg, bronchospasm, laryngeal edema). 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 judgment 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, hospitalization, disability, or incapacity but may jeopardize 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 judgment must be used.

Examples of important medical events that require judgment to determine if they are to be considered an SAE:

- 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 anemia requiring blood transfusion, etc) or convulsions that do not result in hospitalization
- 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 etiology 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 recognized 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 DUS 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 recognized 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 refrigerator when it should be at room temperature
- Wrong participant received the medication (excluding IRT errors)
- Wrong drug administered to participant (excluding IRT errors)

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

- Errors related to or resulting from IRT - 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 authorized product information, or for unauthorized 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 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 Sections 6.1 and/or 6.1.2 for the list of sponsors combination products.

C 1 Definition of Medical Device AE and ADE

Medical Device AE and ADE Definition

- A medical device AE is any untoward medical occurrence in a clinical study participant, users, or other persons, temporally associated with the use of study intervention, whether or not considered related to the medical device. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medical device. This definition includes events related to the medical device or comparator and events related to the procedures involved except for events in users or other persons, which only include events related to medical devices.
- Adverse device effect 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.

C 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 hospitalization. Planned hospitalization for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered an SAE.
- Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function.
- Chronic disease (European Medical Device Regulation 2017/745).

c. Led to fetal distress, fetal 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

- An USADE; (also identified as UADE in 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 (Section 2.3).

C 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.

C 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 AstraZeneca in lieu of completion of the AstraZeneca AE/SAE/medical device deficiency form.
- There may be instances when copies of medical records for certain cases are requested by AstraZeneca. In this case, all participant identifiers, except for the participant number, will be redacted on the copies of the medical records before submission to AstraZeneca.

- 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 [CTCAE]).

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 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 AstraZeneca. 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 AstraZeneca.

- 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 AstraZeneca 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 recognized follow-up period, the investigator will provide AstraZeneca with a copy of any postmortem 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 AstraZeneca **within 24 hours** of receipt of the information.

C 5 Reporting of Medical Device SAEs and SADEs

- All medical device SAEs will be reported in accordance with Section 8.4.9.

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

- Any 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 8.4.9, the AstraZeneca clinical study medical device/device constituent report form will be used to capture details of the device and related deficiency.
- 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/IECs as required by national regulations.

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