STATISTICAL ANALYSIS PLAN	
Study Code	D6935C00002
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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)

Redacted for Public Disclosure

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LIST OF ABBREVIATIONS

Abbreviation or Specialized Term	Definition
AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
AUC	Area Under Curve
BD	Bronchodilator
BMI	Body Mass Index
BP	Blood pressure
CI	Confidence Interval
CRF	Case Report Form
CSP	Clinical Study Protocol
CSR	Clinical Study Report
EAIR	Exposure Adjusted Incidence Rate
eCRF	electronic Case Report Form
ePRO	Electronic Patient-reported Outcomes
FEV_1	Forced Expiratory Volume in One Second
FVC	Forced Vital Capacity
HFA	Hydrofluoroalkane
ICE	Intercurrent Event
ICF	Informed Consent Form
ICS	Inhaled Corticosteroid
ICU	Intensive Care Unit
IPD	Important Protocol Deviation
IRT	Interactive Response Technology
LABA	Long-acting $Beta_2$-agonist
LSMD	Least Square Mean Difference
MAR	Missing at Random
MDI	Metered-dose Inhaler
MedDRA	Medical Dictionary for Regulatory Activities
PD	Protocol Deviation
PDV	Premature Discontinuation Visit
PFT	Pulmonary Function Test
PN	Predicted Normal
PP	Percent Predicted
Pre-BD	Pre-bronchodilator

PT	Preferred Term
Q1	1st Quartile
Q3	3rd Quartile
SABA	Short-acting $Beta_2$-adrenoreceptor Agonist
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOC	System Organ Class
TP	Treatment Period
WHO	World Health Organisation

AMENDMENT HISTORY

CATEGORY **Change refers to:**	**Date (MM/DD/YYYY)**	**Description of change**	**In line with CSP?**	**Rationale**
N/A		Initial approved SAP	N/A	N/A
Primary endpoint(s)	08/27/2025	Randomisation stratum (prior ICS use, yes/no) is added to statistical models	No	Per ICH guideline, randomisation stratum should be part of the covariates in the statistical models
Secondary endpoint(s)	08/27/2025	Randomisation stratum (prior ICS use, yes/no) is added to statistical models	No	Per ICH guideline, randomisation stratum should be part of the covariates in the statistical models
Data presentation	08/27/2025	- Remove region from the recruitment summary - Add stratification stratum summary - Add prior maintenance therapy use summary (ICS containing medications, and SABA only) - Separate lung function summaries at screening visit(s) and at randomisation visit	N/A	To better align with data collections

Data presentation	08/27/2025	Clarify definitions of baseline for different endpoints	Yes	Clarifications made in order to be clearer for the baseline used for different endpoints
Data presentation	08/27/2025	Remove exposure adjusted incidence rate summaries	N/A	Single dose for each treatment, thus, exposure adjustment is not applicable.
Data presentation	08/27/2025	Clarify rescue medication provided by sponsor is not included in the concomitant medication summary Only important protocol deviation could be regarded as potential intercurrent event	N/A	Clarifications made to be clearer in data presentation
Data presentation	08/27/2025	Add SAS code section	N/A	More details on how to implement the methodologies in the plan
Data presentation	08/30/2025	Add additional analysis sets for peak change from baseline endpoints	N/A	Add more accurate analysis sets for the endpoints

1 INTRODUCTION

The purpose of this document is to give details for the statistical analysis of study D6935C00002 supporting the clinical study report (CSR).

Current analysis plan is based on the clinical study protocol (CSP), version 1.0, dated September 10, 2024.

The reader should refer to the CSP and Case Report Form (CRF) for details on study conduct and data collection.

1.1 Study Objectives

The study objectives and endpoints are listed below:

Table 1 Study Objectives, 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 Intercurrent Events (ICEs): The principal stratum strategy will be implemented such that an ICE is captured through the population definition. The ICEs 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 ICEs 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

Table 1 Study Objectives, Endpoints, and Estimands

Objectives	Endpoints/Estimands
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
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	Treatment: Ventolin Evohaler and placebo[c] Participant-level outcome: Peak change from baseline in FEV1

Table 1 Study Objectives, Endpoints, and Estimands

Objectives	Endpoints/Estimands
Evohaler compared with placebo on post-dose lung function in adults with asthma	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 timepoint 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

AE = adverse event; AUC0-6 = area under curve from 0 to 6 hours; FEV1 = forced expiratory volume in one second; ICE = intercurrent event; MDI = metered-dose inhaler; PN = predicted normal; Pre-BD = pre-bronchodilator; SAE = serious adverse event.

[a] A participant is considered to have reversibility to Ventolin HFA if the improvement in FEV1 at 30 minutes post-Ventolin HFA is ≥ 12% relative to the predicted value.

Table 1 Study Objectives, Endpoints, and Estimands

Objectives	Endpoints/Estimands

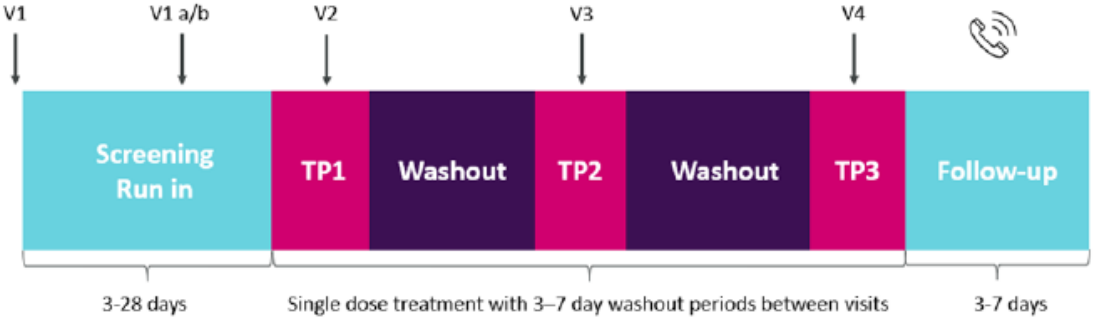
[b] Non-compliance includes taking prohibited medication and lung function data judged to be impacted by important protocol deviations.
[c] Population and strategy for ICEs attributes are the same as the primary estimand specified for the non-inferiority and therapeutic equivalence objectives.

1.2 Study Design

This is a randomised, 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 [pre-BD] forced expiratory volume in one second [FEV1] of ≥ 40% of the predicted normal [PN] value).

For an overview of the study design, see Figure 1.

Figure 1 Study Design



For participants who received their regularly inhaled asthma medications and/or short-acting beta$_2$-adrenoreceptor agonist (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

This study consists of:

- A screening/run-in period

- A treatment phase, which includes 3 randomised 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 informed consent form (ICF). Inclusion/exclusion criteria will be assessed. 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). The maximum screening/run-in period for all participants will be 28 days.

Randomisation will take place at Visit 2. At Visit 2, participants must demonstrate a pre-BD FEV1 of ≥ 40% of the PN value before randomisation. Randomisation will be centralized using interactive response technology (IRT). Randomisation is planned to be stratified by pre-study background asthma maintenance therapy: participants using an inhaled corticosteroid (ICS) and participants not using an ICS (ie, receiving only Short-acting $Beta_2$-adrenoreceptor Agonist [SABA] as needed). Eligible participants will be randomised 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 randomised order, as shown in Table 2.

Table 2 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.

At each treatment visit, bronchodilation activity of the study interventions will be assessed through pulmonary function tests (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 timepoint. 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/withdraw from 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 randomised 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.

1.3 Sample Size Justification

To ensure at least 90 participants complete the study, approximately 102 participants (17 per treatment sequence) will be randomised 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, standard deviation (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.

2 CHANGES TO PROTOCOL PLANNED ANALYSES

The estimand strategy of principal stratum doesn't require missing data following an ICE being imputed, thus the protocol stated imputing missing data following ICE is removed from this plan.

The prior medication is specified in the CSP as any medication with an end date prior to visit 1, while the reference timepoint for analysis purpose is before the first treatment. This changed reference timepoint is consistent with safety analysis objectives.

Pre-study background therapy (Using ICS / Not using ICS) has been added as a covariate in the statistical analyses, as randomisation in the study is based on this stratification factor.

3 DATA ANALYSIS CONSIDERATIONS

3.1 Timing of Analyses

Analyses described in this statistical analysis plan (SAP) will be included in the CSR and produced after final database lock. This will occur when all participants have completed the study or withdrawn from the study early.

3.2 Analysis Populations

Study analysis sets are defined as follows:

Table 3 Study Analysis Sets

Analysis set	Description
Screened Set	All participants who sign the informed consent form (ICF).
Randomised Set	All participants who are randomised to study intervention.
Full Analysis Set (FAS)	Participants who are randomised to study intervention and receive at least one inhalation of the study intervention.
Primary Analysis Set for non-inferiority of a single dose of albuterol delivered from AS MDI compared with Ventolin Evohaler on FEV1 AUC0-6 (PRM1)	Participants who in the FAS, have completed AS MDI and Ventolin Evohaler doses without any ICEs on or before Day 1 of the corresponding AS MDI and Ventolin Evohaler periods, and have AS MDI and Ventolin Evohaler Day 1's pre-dose FEV1 value, at least one FEV1 value post dose 0-3 hours, and at least one FEV1 value post dose 3-6 hours. Participants will be analysed according to the actual intervention received.

Analysis set	Description
Primary Analysis Set for assay sensitivity of a single dose of albuterol delivered from Ventolin Evohaler compared with Placebo on FEV1 AUC0-6 (PRM2)	Participants who in the FAS, have completed Ventolin Evohaler and Placebo doses without any ICEs on or before Day 1 of the corresponding Ventolin Evohaler and Placebo periods, and have Ventolin Evohaler and Placebo Day 1's pre-dose FEV1 value, at least one FEV1 value post dose 0-3 hours, and at least one FEV1 value post dose 3-6 hours. Participants will be analysed according to the actual intervention received.
Primary Analysis Set for equivalence of a single dose of albuterol delivered from AS MDI compared with Ventolin Evohaler on FEV1 AUC0-6	Same as PRM1
Primary Analysis Set for non-inferiority/equivalence of a single dose of albuterol delivered from AS MDI compared with Ventolin Evohaler on FEV1 AUC0-4 (PRM3)	Participants who in the FAS, have completed AS MDI and Ventolin Evohaler doses without any ICEs on or before Day 1 of the corresponding AS MDI and Ventolin Evohaler periods, and have AS MDI and Ventolin Evohaler Day 1's pre-dose FEV1 value, at least one FEV1 value post dose 0-4 hours. Participants will be analysed according to the actual intervention received.
Primary Analysis Set for assay sensitivity of a single dose of albuterol delivered from Ventolin Evohaler compared with Placebo on FEV1 AUC0-4 (PRM4)	Participants who in the FAS, have completed Ventolin Evohaler and Placebo doses without any ICEs on or before Day 1 of the corresponding Ventolin Evohaler and Placebo periods, and have Ventolin Evohaler and Placebo Day 1's pre-dose FEV1 value, at least one FEV1 value post dose 0-4 hours. Participants will be analysed according to the actual intervention received.
Primary Analysis Set for a single dose of albuterol delivered from AS MDI compared with Placebo on FEV1 AUC0-6 (PRM5)	Participants who in the FAS, have completed AS MDI and Placebo doses without any ICEs on or before Day 1 of the corresponding AS MDI and Placebo periods, and have AS MDI and Placebo Day 1's pre-dose FEV1 value, at least one FEV1 value post dose 0-3 hours, and at least one FEV1 value post dose 3-6 hours. Participants will be analysed according to the actual intervention received.
Primary Analysis Set for a single dose of albuterol delivered from AS MDI compared with Placebo on FEV1 AUC0-4 (PRM6)	Participants who in the FAS, have completed AS MDI and Placebo doses without any ICEs on or before Day 1 of the corresponding AS MDI and Placebo periods, and have AS MDI and Placebo Day 1's pre-dose FEV1 value, at least one FEV1 value post dose 0-4 hours. Participants will be analysed according to the actual intervention received.
Primary Analysis Set for a single dose of albuterol delivered from AS MDI compared with Ventolin Evohaler for time to response on	Participants who in the FAS, have completed AS MDI and Ventolin Evohaler doses without any ICEs on or before Day 1 of the corresponding AS MDI and Ventolin Evohaler periods, and have AS MDI and Ventolin Evohaler Day 1's pre-dose FEV1 value, at least one FEV1 value post-dose

Analysis set	Description
FEV1 within 30 minutes post-dose (PRM7)	within 30 minutes. Participants will be analysed according to the actual intervention received.
Primary Analysis Set for a single dose of albuterol delivered from AS MDI compared with Ventolin Evohaler and who responded with ≥ 12% improvement in FEV1 from baseline within 30 minutes post-dose (PRM8.1)	Participants who in the FAS, have completed AS MDI and Ventolin Evohaler doses without any ICEs on or before Day 1 of the corresponding AS MDI and Ventolin Evohaler periods, have AS MDI and Ventolin Evohaler Day 1's pre-dose FEV1 value, have achieved with ≥ 12% improvement of FEV1 within 30 minutes post-dose, and have at least one FEV1 value following this improvement. Participants will be analysed according to the actual intervention received.
Primary Analysis Set for a single dose of albuterol delivered from AS MDI compared with Ventolin Evohaler and who responded with ≥ 15% improvement in FEV1 from baseline within 30 minutes post-dose (PRM8.2)	Participants who in the FAS, have completed AS MDI and Ventolin Evohaler doses without any ICEs on or before Day 1 of the corresponding AS MDI and Ventolin Evohaler periods, have AS MDI and Ventolin Evohaler Day 1's pre-dose FEV1 value, have achieved with ≥ 15% improvement of FEV1 within 30 minutes post-dose, and have at least one FEV1 value following this improvement. Participants will be analysed according to the actual intervention received.
Primary Analysis Set for non-inferiority/equivalence of a single dose of albuterol delivered from AS MDI compared with Ventolin Evohaler on Peak FEV1 (PRM9)	Participants who in the FAS, have completed AS MDI and Ventolin Evohaler doses without any ICEs on or before Day 1 of the corresponding AS MDI and Ventolin Evohaler periods, have AS MDI and Ventolin Evohaler Day 1's pre-dose FEV1 value, and have at least one FEV1 value post dose 0-6 hours. Participants will be analysed according to the actual intervention received.
Primary Analysis Set for assay sensitivity of a single dose of albuterol delivered from Ventolin Evohaler compared with Placebo on Peak FEV1 (PRM10)	Participants who in the FAS, have completed Ventolin Evohaler and Placebo doses without any ICEs on or before Day 1 of the corresponding Ventolin Evohaler and Placebo periods, have Ventolin Evohaler and Placebo Day 1's pre-dose FEV1 value, and have at least one FEV1 value post dose 0-6 hours. Participants will be analysed according to the actual intervention received.
Primary Analysis Set for a single dose of albuterol delivered from AS MDI compared with Placebo on Peak FEV1 (PRM11)	Participants who in the FAS, have completed AS MDI and Placebo doses without any ICEs on or before Day 1 of the corresponding AS MDI and Placebo periods, have AS MDI and Placebo Day 1's pre-dose FEV1 value, and have at least one FEV1 value post dose 0-6 hours. Participants will be analysed according to the actual intervention received.
Primary Analysis Set for a single dose of albuterol delivered from AS	Same as PRM9

Analysis set	Description
MDI compared with Ventolin Evohaler on the following: - Change from baseline in FEV1 at each post-dose timepoint - Time to peak FEV1	
Safety Set (SS)	Participants who are randomised to study intervention and receive at least one inhalation of the study intervention. Participants will be classified based on treatment they actually received within each treatment period.

3.3 General Considerations

3.3.1 General Study Level Definitions

3.3.1.1 Study Period Definition

The following study periods are defined for analysis purposes:

- Screening and run-in period: starting on the date of informed consent signed and ending 1 day prior to first dosing. If any participant is re-screened, the latest available informed consent date will be used for this purpose.
- On-treatment period: the day of dose for each period and 1 day after are considered as on-treatment period.
- Post-treatment period/Follow-up period: 2 days after each period's dose until the next period's dose starts, or for the last treatment period, 2 days after the dose until the end of study are considered as post-treatment/follow-up period.
- On-study (on-treatment and post-treatment) period: starting on the date of the first dose of study intervention of TP1 and ending on the study completion or withdrawal date.
- TPx (x = 1, 2, 3) (Figure 1): Each treatment period (TP) consists of on-treatment and post-treatment/follow-up periods as defined above.

3.3.1.2 Baseline Definition

In general, there are 3 definitions of baseline, one is the last non-missing value prior to administration of the first dose of study intervention on TP 1 Day 1. This will be called participant baseline.

Period-specific baseline for FEV1, i.e., is the mean of the 2 pre-dose (60 minutes prior and 30 minutes prior) values taken on Day 1 of each period. When only one pre-dose value is available, that value will be used as baseline FEV1. This is considered as time 0 for FEV1

AUC calculation and is also used for calculation of change from baseline in FEV1 related efficacy endpoints.

In addition, an average baseline for FEV1 is defined as period-specific baseline FEV1 averaged over the treatment periods. This average baseline for FEV1 is used as a covariate in the analyses of change from baseline in FEV1 related efficacy endpoints.

3.3.2 Visit Window

No visit window will be applied for analyses. The scheduled timepoints will be used for the derivation of analysis endpoints.

On-treatment acceptable/borderline FEV1 assessment timepoints are on Day 1 of each period (i.e., Visits 2, 3, and 4). The collection timepoints are at -60 min and -30 min pre-dose, and 5, 15, 30, 45, 60, 120, 180, 240, 300, and 360 minutes post-dose.

Vital signs for Day 1 of each period (i.e., Visits 2, 3, and 4) are to be acquired 60 minutes prior to dosing, and at the end of the study visit (post-dose).

Measurements collected from non-dosing unscheduled visits, repeat assessments, or early study discontinuation visits will be listed and may also be considered in the analysis for safety abnormality summaries.

3.3.3 Handling of Unscheduled Visits

Unscheduled visit, except those where a participant receives treatment, will only be used in the summary of abnormalities.

3.3.4 Multiplicity/Multiple Comparisons

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 hypotheses will be tested in the following sequential order:

1 Non-inferiority: AS MDI versus Ventolin Evohaler for FEV1 AUC0-6
2 Assay sensitivity (Superiority): Ventolin Evohaler versus placebo for FEV1 AUC0-6
3 Upper equivalence limit: AS MDI versus Ventolin Evohaler for FEV1 AUC0-6

Hierarchical testing will continue at the given alpha level until a null hypothesis cannot be rejected; at this time, further testing will stop, and no subsequent null hypotheses in the testing hierarchy will be rejected. Note: Non-inferiority between AS MDI and Ventolin Evohaler can only be declared if superiority of Ventolin Evohaler compared to placebo is also demonstrated.

3.3.5 Handling of Protocol Deviations in Study Analysis

Participants who do not meet eligibility criteria but are still randomised will be analysed according to the analysis sets described in Section 3.2.

3.3.5.1 Important Protocol Deviations

Only important protocol deviations (IPDs) will be listed and tabulated in the CSR. IPDs are a subset of protocol deviations (PDs) that may significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a participant's rights, safety, or well-being.

They may include (but not be limited to):

- Inclusion criteria deviations
- Exclusion criteria deviations
- Participants who met discontinuation criteria for study treatment but were not withdrawn from study treatment
- Participants who developed withdrawal criteria during the study but were not withdrawn
- Investigational product deviations
- Excluded medications taken
- Deviations to study procedure
- Other important deviations (e.g., exceeds the recommended dose of sponsor provided Ventolin/Pulmicort Flexhaler)

All IPDs will be identified and documented by the study team prior to unblinding of the trial. As far as possible, the occurrence of IPDs will be monitored (blinded) during the trial, with emphasis on preventing future IPDs. The process for identification and assessment will be detailed in a separate protocol deviation plan.

4 STATISTICAL ANALYSIS

4.1 Study Population

4.1.1 Participant Disposition and Completion Status

4.1.1.1 Definitions and Derivations

Disposition information can be directly obtained from electronic case report form (eCRF). Participants' completion/discontinuation of study and reason are collected on the Disposition page.

4.1.1.2 Presentation

Participant disposition will be summarized using the Screened set by treatment sequence and in total. The number and percentage (where applicable) of participants will be summarized for the following categories:

- Those who were screened
- Those who were not randomised (and reason)
- Those who were randomised
- Those who were randomised but did not receive any study intervention
- Those who received treatment in period 1
- Those who withdrawn before TP2 (and reason)
- Those who received treatment in period 2
- Those who withdrawn before TP3 (and reason)
- Those who received treatment in period 3
- Those who withdrawn before follow-up TC
- Those who completed the study (have visits 2, 3, 4 and the follow-up TC)
- Those withdrawn from the study (and reason)

In addition, the number and percentage of participants who were not treated (and reasons) as per the planned study intervention will be summarized by treatment using the FAS.

The stratification factor at randomisation (pre-study background therapy, using ICS/not using ICS) will be summarized by treatment sequence and total using the randomized set. Any randomisation stratification errors identified will be documented but not corrected in the IRT.

4.1.2 Analysis Sets

4.1.2.1 Definitions and Derivations

Analysis set definitions are as per Table 3 in Section 3.2.

4.1.2.2 Presentation

The number of participants in each treatment sequence and total will be presented for the following categories: included in each analysis set, excluded from each analysis set (and reason for exclusion). Exclusion reason will be presented in the following hierarchical order; ICE, no calculable AUC, no post-dose FEV1 value. The summary will be based on all Randomised participants.

4.1.3 Protocol Deviations

4.1.3.1 Definitions and Derivations

The definition of IPDs and derivations are described in Section 3.3.5.1.

4.1.3.2 Presentation

IPDs will be summarised by sequence and total as well as by the treatment that participants are on when the IPDs happened using the full analysis set (FAS) for the following categories: with at least one important protocol deviation, with each important protocol deviation category.

4.1.4 Demographics

4.1.4.1 Definitions and Derivations

Most demographic information can be directly obtained from eCRF. Age will be derived from the (date of informed consent - date of birth + 1)/365.25, rounded down to the nearest integer. For participants where date of birth is not recorded, the age as recorded in eCRF will be used.

Participants are allowed to report more than one race category on the eCRF. If there are multiple race categories being selected, a category of "Multiple" will be reported in the summary.

4.1.4.2 Presentation

Demographic characteristics including age, age group (≥ 18 to <36, ≥ 36 years), gender, race, ethnicity group (Hispanic or Latino, Not Hispanic or Latino, Not Reported) and country will be summarized by randomised treatment sequence and Total for the FAS, using frequency and percentages for categorical variables and descriptive statistics of n, mean, standard deviation (SD), minimum, 1st quartile (Q1), median, 3rd quartile (Q3), and maximum for continuous variables.

Participant recruitment by country and centre will also be summarized by treatment sequence and Total.

4.1.5 Baseline Characteristics

4.1.5.1 Definitions and Derivations

Baseline characteristics include weight, height, body mass index (BMI).

BMI is calculated as: weight (kg)/height (m)^2.

4.1.5.2 Presentation

Baseline characteristics will be summarised by randomised treatment sequence and total for the FAS in a similar manner to that described for demographics in Section 4.1.4.2.

4.1.6 Disease Characteristics

4.1.6.1 Definitions and Derivations

Disease characteristics will include the following variables.

- Asthma history at study entry:
  - Asthma duration, calculated from the asthma diagnosed date to the date of informed consent (in years) (partial date of asthma diagnosis will be imputed according to the rules described in Appendix 7.1)
  - Previous intensive care unit (ICU) admission for asthma (Yes/No)
  - Requirement of mechanical ventilation in last 5 years (Yes/No)
  - Nicotine use including status of usage (Current, Former, Never) and types of nicotine, alcohol and caffeine use including status of usage (Current, Former, Never)
  - Pre-study background therapy (ICS-containing medications, and SABA only)
- Lung functions at screening (only acceptable/borderline FEV1, FVC values are to be summarised):
  - Last non-missing pre-and post- BD FEV1 (mL), percent predicted normal FEV1 (% PN), forced vital capacity (FVC) (mL), FEV1/FVC (%), percent predicted normal FVC (%PN).
  - Bronchodilator responsiveness calculated by 100× (post-BD FEV1 - pre-BD FEV1)/predicted normal FEV1.
- Lung functions at randomisation (only acceptable/borderline FEV1, FVC values are to be summarised)
  - FEV1 (mL), percent predicted normal FEV1 (% PN), FVC (mL), percent predicted normal FVC (% PN), FEV1/FVC (%). They are calculated as the average of 60 minutes and 30 minutes assessments prior to the first study intervention, or the single timepoint that result is available.

4.1.6.2 Presentation

Asthma disease characteristics and lung functions will be presented by randomised treatment sequence and total for the FAS in a similar manner to that described for demographics in Section 4.1.4.2.

4.1.7 Medical History and Concomitant Disease

4.1.7.1 Definitions and Derivations

Medical and surgical history information can be directly obtained from eCRF.

Past medical history is defined as medical history which was not identified as ongoing at screening. Current medical history is defined as medical history which was identified as ongoing at screening.

4.1.7.2 Presentation

Past and current medical and surgical history will be summarised by randomised treatment sequence and total using the FAS. Medical history will be summarized by system organ class (SOC) and preferred term (PT) assigned to the event by Medical Dictionary for Regulatory Activities (MedDRA). For each PT, the number and percentage of participants reporting at least one occurrence will be presented, i.e., for a participant, multiple occurrences of a medical history will only be counted once.

4.1.8 Prior and Concomitant Medications

4.1.8.1 Definitions and Derivations

Prior and concomitant medications taken by the participant (excluding sponsor-provided background medications) will be coded using the anatomical therapeutic chemical (ATC) classification system within the World Health Organisation (WHO) drug dictionary.

A medication will be regarded as prior if it started prior to the date of first study intervention and was stopped before the date of TP1 study intervention (medication stop date < date of TP1 study intervention).

A medication will be regarded as concomitant if the medication is taken on the day of study intervention or 1 day after. Medications taken during the period of 2 days after study intervention and before next period study intervention starts are considered post-treatment medication. See Section 3.3.1.1 for on-treatment and post-treatment definitions.

The details of handling missing and incomplete medication start and end dates are described in Appendix 7.1.

Prohibited medications are defined in CSP Section 6.9.2.3 and may be considered as non-compliance to the protocol and could be considered as intercurrent events. These medications will be carefully reviewed and protocol non-compliances and ICE status documented prior to unblinding.

4.1.8.2 Presentation

The number and percentage of participants receiving each concomitant medication (by ATC classification system codes and generic name) will be presented by treatment and overall using the FAS. Similarly, the number and percentage of participants receiving prohibited medications will be summarised by treatment as well. Note that, an “Overall” column summarises a participant cross multiple treatment period.

The number and percentage of participants receiving each prior medication (by ATC classification system codes and generic name) will be presented by randomised treatment sequence and total using the FAS.

4.1.9 Study Drug Compliance

4.1.9.1 Definitions and Derivations

Each treatment dose expected consists of 2 puffs, thus the compliance for each treatment is the number of actual puffs / 2 ×100.

4.1.9.2 Presentation

Compliance rate of the study intervention will be summarized descriptively (n and percentage) by treatment for the SS. The compliance categories are discrete, 50%, 100%, > 100%.

4.2 Endpoint Analyses

This section covers details related to efficacy endpoint analyses including primary, secondary, and exploratory analyses.

Summary data will be presented by treatment. Categorical data will be summarised by the number and percentage of participants in each category. Continuous variables will be summarised by descriptive statistics including n, mean, SD, Q1, median, Q3, minimum, and maximum at each visit.

4.2.1 Intercurrent Events

4.2.1.1 Definitions and Derivations

The ICEs identified will include single dose for the affected period was not dosed per-protocol, non-compliance with study protocol that will affect the evaluation of lung function, and treatment period missed.

All ICEs will be identified and documented by the study team prior to unblinding of the trial. Similar with IPDs, the occurrence of ICEs will be monitored (blinded) during the trial, with the emphasis on their future prevention.

4.2.1.2 Presentation

ICEs will be summarized by treatment using FAS.

- Treatment period missed: missing treatment period 2 or 3 due to any reason.
- Non-compliance with study protocol includes taking prohibited medication and lung function data judged to be impacted by important protocol deviations: determined case by case
- Low treatment compliance: Incomplete dosing (i.e., 1 puff for the period)

Two summaries will be provided, one with any type of ICEs per participant summarised by treatment, for which a participant can be counted towards multiple categories of ICEs. The other summary will summarise according to the hierarchy order as above. That is, if a

participant has multiple ICEs, ICE of treatment period missed precedes non-compliance with study protocol, and precedes low treatment compliance.

Table 4 Primary Objectives, Safety Objective, and Exploratory Analyses

Statistical category	Endpoint	Analysis Set	Intercurrent event strategy	Population level summary (analysis)	Details in section
Objective 1: To assess the non-inferiority of a single dose of albuterol delivered from AS MDI relative to Ventolin Evohaler in AUC0-6					
Primary analysis for Primary endpoint	Change from baseline in FEV1 AUC0-6	PRM1	ICEs: 1. Use of prohibited medications 2. IPDs that impact lung function 3. Fail to have both AS MDI and Ventolin Evohaler treatment ICEs will be handled in the analysis set definition following a principal stratum strategy	LSMD in AUC0-6 change from baseline between AS MDI and Ventolin Evohaler (Least squares means and standard errors for each treatment from linear mixed model)	Section 4.2.2
Objective 2: To assess the superiority of a single dose of albuterol delivered from Ventolin Evohaler relative to Placebo in AUC0-6					
Primary analysis for Primary endpoint	Change from baseline in FEV1 AUC0-6	PRM2	ICEs: 1. Use of prohibited medications 2. IPDs that impact lung function 3. Fail to have both Ventolin Evohaler and Placebo treatment ICEs will be handled in the analysis set definition following a principal stratum strategy	LSMD in AUC0-6 change from baseline between Ventolin Evohaler and Placebo (Least squares means and standard errors for each treatment from linear mixed model)	Section 4.2.3
Objective 3: To assess the equivalence of a single dose of albuterol delivered from AS MDI relative to Ventolin Evohaler in AUC0-6					

Statistical category	Endpoint	Analysis Set	Intercurrent event strategy	Population level summary (analysis)	Details in section
Primary analysis for Key secondary endpoint	Change from baseline in FEV1 AUC0-6	PRM1	ICEs: 1. Use of prohibited medications 2. IPDs that impact lung function 3. Fail to have both AS MDI and Ventolin Evohaler treatment ICEs will be handled in the analysis set definition following a principal stratum strategy	LSMD in AUC0-6 change from baseline between AS MDI and Ventolin Evohaler (Least squares means and standard errors for each treatment from linear mixed model)	Section 4.2.4
Objective 4: To assess the non-inferiority of a single dose of albuterol delivered from AS MDI relative to Ventolin Evohaler in AUC0-4					
Analysis for Secondary endpoint	Change from baseline in FEV1 AUC0-4	PRM3	ICEs: 1. Use of prohibited medications 2. IPDs that impact lung function 3. Fail to have both AS MDI and Ventolin Evohaler treatment ICEs will be handled in the analysis set definition following a principal stratum strategy	LSMD in AUC0-4 change from baseline between AS MDI and Ventolin Evohaler (Least squares means and standard errors for each treatment from linear mixed model)	Section 4.2.5
Objective 5: To assess the superiority of a single dose of albuterol delivered from Ventolin Evohaler relative to Placebo in AUC0-4					
Analysis for Secondary endpoint	Change from baseline in FEV1 AUC0-4	PRM4	ICEs: 1. Use of prohibited medications 2. IPDs that impact lung function	LSMD in AUC0-4 change from baseline between Ventolin Evohaler and Placebo (Least squares	Section 4.2.6

Statistical category	Endpoint	Analysis Set	Intercurrent event strategy	Population level summary (analysis)	Details in section
			3. Fail to have both Ventolin Evohaler and Placebo treatment ICEs will be handled in the analysis set definition following a principal stratum strategy	means and standard errors for each treatment from linear mixed model)	
Objective 6: To assess the equivalence of a single dose of albuterol delivered from AS MDI relative to Ventolin Evohaler in AUC0-4					
Analysis for Secondary endpoint	Change from baseline in FEV1 AUC0-4	PRM3	ICEs: 1. Use of prohibited medications 2. IPDs that impact lung function 3. Fail to have both AS MDI and Ventolin Evohaler treatment ICEs will be handled in the analysis set definition following a principal stratum strategy	LSMD in AUC0-4 change from baseline between AS MDI and Ventolin Evohaler (Least squares means and standard errors for each treatment from linear mixed model)	Section 4.2.7
Objective 7: To assess the non-inferiority of a single dose of albuterol delivered from AS MDI relative to Ventolin Evohaler in Peak FEV1					
Analysis for Secondary endpoint	Peak change from baseline in FEV1	PRM9	ICEs: 1. Use of prohibited medications 2. IPDs that impact lung function 3. Fail to have both AS MDI and Ventolin Evohaler treatment ICEs will be handled in the analysis set definition following a principal stratum strategy	LSMD in peak change from baseline in FEV1 between AS MDI and Ventolin Evohaler (Least squares means and standard errors for each treatment from linear mixed model)	Section 4.2.8

Statistical category	Endpoint	Analysis Set	Intercurrent event strategy	Population level summary (analysis)	Details in section
Objective 8: To assess the superiority of a single dose of albuterol delivered from Ventolin Evohaler relative to Placebo in Peak FEV1					
Analysis for Secondary endpoint	Peak change from baseline in FEV1	PRM10	ICEs: 1. Use of prohibited medications 2. IPDs that impact lung function 3. Fail to have both Ventolin Evohaler and Placebo treatment ICEs will be handled in the analysis set definition following a principal stratum strategy	LSMD in peak change from baseline in FEV1 between Ventolin Evohaler and Placebo (Least squares means and standard errors for each treatment from linear mixed model)	Section 4.2.9
Objective 9: To assess the equivalence of a single dose of albuterol delivered from AS MDI relative to Ventolin Evohaler in Peak FEV1					
Analysis for Secondary endpoint	Peak change from baseline in FEV1	PRM9	ICEs: 1. Use of prohibited medications 2. IPDs that impact lung function 3. Fail to have both AS MDI and Ventolin Evohaler treatment ICEs will be handled in the analysis set definition following a principal stratum strategy	LSMD in peak change from baseline in FEV1 between AS MDI and Ventolin Evohaler (Least squares means and standard errors for each treatment from linear mixed model)	Section 4.2.10
Objective 10: To assess the superiority of a single dose of albuterol delivered from AS MDI relative to Placebo in AUC0-6					

Statistical category	Endpoint	Analysis Set	Intercurrent event strategy	Population level summary (analysis)	Details in section
Analysis for Exploratory endpoint	Change from baseline in FEV1 AUC0-6	PRM5	ICEs: 1. Use of prohibited medications 2. IPDs that impact lung function 3. Fail to have both AS MDI and Placebo treatment ICEs will be handled in the analysis set definition following a principal stratum strategy	LSMD in AUC0-6 change from baseline between AS MDI and Placebo (Least squares means and standard errors for each treatment from linear mixed model)	Section 4.2.11
Objective 11: To assess the superiority of a single dose of albuterol delivered from AS MDI relative to Placebo in AUC0-4					
Analysis for Exploratory endpoint	Change from baseline in FEV1 AUC0-4	PRM6	ICEs: 1. Use of prohibited medications 2. IPDs that impact lung function 3. Fail to have both AS MDI and Placebo treatment ICEs will be handled in the analysis set definition following a principal stratum strategy	LSMD in AUC0-4 change from baseline between AS MDI and Placebo (Least squares means and standard errors for each treatment from linear mixed model)	Section 4.2.11
Objective 12: To assess the superiority of a single dose of albuterol delivered from AS MDI relative to Placebo in Peak FEV1					
Analysis for Exploratory endpoint	Peak change from baseline in FEV1	PRM11	ICEs: 1. Use of prohibit medications 2. IPDs that impact lung function	LSMD in peak change from baseline in FEV1 between AS MDI and Placebo (Least squares means and	Section 4.2.11

Statistical category	Endpoint	Analysis Set	Intercurrent event strategy	Population level summary (analysis)	Details in section
			3. Fail to have both AS MDI and Placebo treatment ICEs will be handled in the analysis set definition following a principal stratum strategy	standard errors for each treatment from linear mixed model)	
Objective 13: To further characterize the therapeutic efficacy of a single dose of albuterol delivered from AS MDI relative to Ventolin Evohaler in responders and over post-dose timepoints					
Analysis for Exploratory endpoint	1. Change from baseline in FEV1 at each post-dose timepoint 2. Time when peak FEV1 occurred	PRM9	ICEs: 1. Use of prohibited medications 2. IPDs that impact lung function 3. Fail to have both AS MDI and Ventolin Evohaler treatment ICEs will be handled in the analysis set definition following a principal stratum strategy	1. Descriptive summaries 2. The median differences and corresponding Hodges-Lehmann 95% CIs 3. Endpoints of 3 and 4: Odds ratio between 2 treatments (using generalized mixed effect model) 4. Endpoints of 5 to 8: The median differences and corresponding Hodges-Lehmann 95% CIs	Section 4.2.11
	3. Percentage of participants achieving ≥12% improvement in FEV1 from baseline within 30 minutes of dose 4. Percentage of participants achieving ≥15% improvement in FEV1 from baseline within 30 minutes of dose	PRM7			

Statistical category	Endpoint	Analysis Set	Intercurrent event strategy	Population level summary (analysis)	Details in section
	5. Time to achieve ≥12% improvement in FEV1 from baseline 6. Time to achieve ≥15% improvement in FEV from baseline				
	7. Duration of maintenance of ≥12% improvement	PRM8.1			
	8. Duration of maintenance of ≥15% improvement	PRM8.2			
Safety	• AEs • Asthma-related events	Safety Set	All safety data during on-study period.	Descriptive summaries	Section 4.6

Statistical category	Endpoint	Analysis Set	Intercurrent event strategy	Population level summary (analysis)	Details in section
	• Vital signs (systolic and diastolic blood pressure, pulse rate)				

AE = adverse event; AUC0-4 = Area under curve 0 to 4 hours; AUC0-6 = Area under curve 0 to 6 hours; CI = Confidence interval; FEV1 = Forced expiratory volume in the first second; ICE = Intercurrent event; IPD = Important protocol deviation; LSMD = Least square mean difference.

4.2.2 Primary Endpoint – To Assess the Non-inferiority of AS MDI Relative to Ventolin Evohaler on FEV1 AUC0-6 Hour

4.2.2.1 Definition

To assess the non-inferiority of AS MDI relative to Ventolin Evohaler. The primary endpoint is change from baseline in FEV1 AUC0-6 hour.

The primary estimand for non-inferiority targets participants that are treated with AS MDI and Ventolin Evohaler and do not have any ICEs as defined in Section 4.2.1. The following 5 attributes describe the estimand that will be used to define the treatment effect of interest for the primary non-inferiority analysis:

- Treatment Condition: dosed with AS MDI and Ventolin Evohaler.
- Analysis Set: PRM1 (Section 3.2).
- Participant-level outcomes: change from baseline in FEV1 AUC0-6
- Intercurrent event handling: principal stratum strategy.
- Summary measure: difference in the adjusted means of the participant-level outcomes for the treatment comparison of AS MDI vs Ventolin Evohaler.

4.2.2.2 Derivations

AUC0-6 will be calculated using the trapezoidal rule and will be normalised by dividing by the time in minutes from dosing to the last measurement included (i.e., ~360 minutes).

That is,

$$(FEV_1)AUC_{0-6} = \frac{\frac{1}{2}\sum_1^k[(FEV_1)_{(i)} + (FEV_1)_{(i-1)}] \times (t_i - t_{(i-1)})}{(t_k)}$$

Where $t_i = t_{5\,min}, t_{15\,min}, t_{30\,min}, t_{45\,min}, \ldots, t_{300\,min}, t_{360\,min}$, $t_0 = 0$, $(FEV_1)_{(i)} = FEV_1\ at\ t_i$, and $(FEV_1)_{(0)} = trough\ FEV_1$. Note that t_i is referring to the actual relative collection timepoints. FEV1 is acceptable/borderline FEV1 assessment. Trough is referring to the average value of -60 min, and -30 min timepoints' FEV1 values for that period. If only one timepoint FEV1 value is available, it will be used as the trough value.

Change from baseline in AUC0-6 is calculated by subtracting AUC0-6 from the trough value (i.e., period-specific baseline FEV1 value) as described in Section 3.3.1.2.

4.2.2.3 Handling of Dropouts and Missing Data

Trough value can only be calculated if at least one valid pre-dose FEV1 value is available; also, for post-dose timepoints, it is required to have at least one valid FEV1 value between 0 and 3 hours, and at least one valid FEV1 value between 3 and 6 hours.

No imputation of missing assessments will be performed for the principal stratum strategy.

4.2.2.4 Primary Analysis – Principal Stratum Strategy Estimand

For the primary endpoint of change from baseline in FEV1 AUC0-6, the null hypothesis to be tested is that the AS MDI is inferior to Ventolin Evohaler in FEV1 AUC0-6. Let μ_D stand for the difference in change from baseline FEV1 AUC0-6 between AS MDI and Ventolin Evohaler.

Non-inferiority

- H0: $\mu_D \leq$ -100 mL
- HA: $\mu_D >$ -100 mL

where H0 is the null hypothesis, and HA is the alternative hypothesis. The null hypothesis will be rejected when the lower limit of the 90% confidence interval (CI) bound for the estimated mean treatment difference is > -100 mL.

Change from baseline in FEV1 AUC0-6 will be analysed using a linear mixed model with participant as a random effect using the PRM1 analysis set. The fixed effects in the model will include treatment, treatment period, and stratum of ICS use. 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). Adjusted treatment means, standard errors, and 90% CIs will be presented. In addition, sensitivity analyses will be conducted replacing the stratum of ICS use by the actual pre-study background therapy (i.e., ICS containing medication, SABA only) as collected in the eCRF in the model.

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

4.2.2.5 Subgroup Analyses

Not Applicable.

4.2.3 Primary Endpoint – To Assess the Superiority of Ventolin Evohaler Relative to Placebo on FEV1 AUC0-6 Hour

4.2.3.1 Definition

The endpoint of the change from baseline in FEV1 AUC0-6 is the subsequent endpoint after test of non-inferiority between AS MDI and Ventolin Evohaler.

The primary estimand is defined similarly as in Section 4.2.2.1 with treatment being changed to Ventolin Evohaler and Placebo. The following 5 attributes describe the estimand that will be used to define the treatment effect of interest for the primary superiority analysis:

- Treatment Condition: dosed with Ventolin Evohaler and Placebo.
- Analysis Set: PRM2 (Section 3.2).
- Participant-level outcomes: change from baseline in FEV1 AUC0-6
- Intercurrent event handling: principal stratum strategy.
- Summary measure: difference in the adjusted means of the participant-level outcomes for the treatment comparison of Ventolin Evohaler versus Placebo.

4.2.3.2 Derivations

Baseline FEV1 is the period-specific baseline as defined in Section 3.3.1.2. AUC0-6 calculation is as defined in Section 4.2.2.2.

4.2.3.3 Handling of Dropouts and Missing Data

The endpoints missing data and handling rules described in Section 4.2.2.3 will be applied.

4.2.3.4 Primary Analysis – Principal Stratum Strategy Estimand

The objective to establish assay sensitivity (superiority) of a single dose of albuterol delivered from Ventolin Evohaler compared with placebo on FEV1 AUC0-6 is using the following 2-sided hypotheses. Let μ_D stands for the difference in change from baseline FEV1 AUC0-6 between Ventolin Evohaler and Placebo.

Assay Sensitivity

- H0: $\mu_D = 0$
- HA: $\mu_D \neq 0$

where the H0 and HA are the null hypothesis and alternative hypothesis, respectively.

The null hypothesis will be rejected at the 5% significance level (i.e., p-value < 0.05).

Change from baseline in FEV1 AUC0-6 will be analysed using a linear mixed model similar as specified in Section 4.2.2.4 using PRM2 analysis set. Adjusted treatment means, standard errors, 95% CIs, and p-value will be obtained. In addition, sensitivity analyses will be conducted replacing the stratum of ICS use by the actual pre-study background therapy (i.e., ICS containing medication, SABA only) in the model.

4.2.3.5 Subgroup Analyses

Not Applicable.

4.2.4 Key Secondary Endpoint – To demonstrate equivalence of AS MDI relative to Ventolin Evohaler on FEV1 AUC0-6 hour

4.2.4.1 Definition

Estimand is defined same as in Section 4.2.2.1.

4.2.4.2 Derivations

The derivation rules mentioned in Section 4.2.2.2 will be applied.

4.2.4.3 Handling of Dropouts and Missing Data

The endpoints missing data and handling rules described in Section 4.2.2.3 will be applied.

4.2.4.4 Primary Analysis – Principal Stratum Strategy Estimand

To test for equivalence, the non-inferiority null hypothesis must be tested first (see Section 4.2.2.4), 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

- H0: $\mu_D \geq 100$ mL
- HA: $\mu_D < 100$ 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.

Change from baseline in FEV1 AUC0-6 will be analysed using a linear mixed model similar as specified in Section 4.2.2.4 using PRM1 analysis set. Adjusted treatment means, standard errors, 90% CIs will be obtained. In addition, sensitivity analyses will be conducted replacing the stratum of ICS use by the actual pre-study background therapy (i.e., ICS containing medication, SABA only) in the model.

4.2.4.5 Subgroup Analyses

Not Applicable.

4.2.5 Secondary Endpoint – To Demonstrate Non-inferiority of AS MDI Relative to Ventolin Evohaler on FEV1 AUC0-4 Hour

4.2.5.1 Definition

Similar to the primary endpoint, the estimand for non-inferiority targets participants that are treated with AS MDI and Ventolin Evohaler and do not have any ICEs as defined in Section 4.2.1. The following 5 attributes describe the estimand that will be used to define the treatment effect of interest for the non-inferiority analysis:

- Treatment Condition: dosed with AS MDI and Ventolin Evohaler.
- Analysis Set: PRM3 (Section 3.2).
- Participant-level outcomes: change from baseline in FEV1 AUC0-4
- Intercurrent event handling: principal stratum strategy.
- Summary measure: difference in the adjusted means of the participant-level outcomes for the treatment comparison of AS MDI vs Ventolin Evohaler.

4.2.5.2 Derivations

The derivation rules mentioned in Section 4.2.2.2 will be applied with AUC calculation up to timepoint of 240 minutes (i.e., 4 hour).

4.2.5.3 Handling of Dropouts and Missing Data

Trough value can only be calculated if at least one valid pre-dose FEV1 value is available; also, for post-dose timepoints, it is required to have at least one valid FEV1 value post-dose from 0 to 4 hour timepoint. No imputation of missing assessments will be performed.

4.2.5.4 Analysis of Secondary Endpoint – Principal Stratum Strategy Estimand

Same method as described in Section 4.2.2.4 will be used for PRM3 analysis set.

4.2.5.5 Subgroup Analyses

Not applicable.

4.2.6 Secondary Endpoint – To Demonstrate Superiority of Ventolin Evohaler Relative to Placebo on FEV1 AUC0-4 Hour

4.2.6.1 Definition

Similar to the primary endpoint, the estimand for superiority targets participants that are treated with Ventolin Evohaler and Placebo and do not have any ICEs as defined in Section 4.2.1. The following 5 attributes describe the estimand that will be used to define the treatment effect of interest for the superiority analysis:

- Treatment Condition: dosed with Ventolin Evohaler and Placebo.

- Analysis Set: PRM4 (Section 3.2).
- Participant-level outcomes: change from baseline in FEV1 AUC0-4
- Intercurrent event handling: principal stratum strategy.
- Summary measure: difference in the adjusted means of the participant-level outcomes for the treatment comparison of Ventolin Evohaler vs Placebo.

4.2.6.2 Derivations

The derivation rules mentioned in Section 4.2.2.2 will be applied with AUC calculation up to timepoint of 240 minutes (i.e., 4 hour).

4.2.6.3 Handling of Dropouts and Missing Data

The handling of dropouts and missing data as described in Section 4.2.5.3 will be applied.

4.2.6.4 Analysis of Secondary Endpoint – Principal Stratum Strategy Estimand

Same method as described in Section 4.2.3.4 will be used for PRM4 analysis set.

4.2.6.5 Subgroup Analyses

Not Applicable.

4.2.7 Secondary Endpoint – To Demonstrate Equivalence of AS MDI Relative to Ventolin Evohaler on FEV1 AUC0-4 Hour

4.2.7.1 Definition

Estimand is defined same as in Section 4.2.5.1.

4.2.7.2 Derivations

The derivation rules mentioned in Section 4.2.2.2 will be applied with AUC calculation up to timepoint of 240 minutes (i.e., 4 hour).

4.2.7.3 Handling of Dropouts and Missing Data

The handling of dropouts and missing data as described in Section 4.2.5.3 will be applied.

4.2.7.4 Primary Analysis – Principal Stratum Strategy Estimand

Same method as described in Section 4.2.4.4 will be applied to PRM3 analysis set.

4.2.8 Secondary Endpoint – To demonstrate non-inferiority of AS MDI relative to Ventolin Evohaler on Peak FEV1

4.2.8.1 Definition

Similar to the primary endpoint, the estimand for non-inferiority targets participants that are treated with AS MDI and Ventolin Evohaler and do not have any ICEs as defined in

Section 4.2.1. The following 5 attributes describe the estimand that will be used to define the treatment effect of interest for the non-inferiority analysis:

- Treatment Condition: dosed with AS MDI and Ventolin Evohaler.
- Analysis Set: PRM9 (Section 3.2).
- Participant-level outcomes: peak change from baseline in FEV1
- Intercurrent event handling: principal stratum strategy.
- Summary measure: difference in the adjusted means of the participant-level outcomes for the treatment comparison of AS MDI vs Ventolin Evohaler.

4.2.8.2 Derivations

Baseline FEV1 is the period-specific baseline as defined in Section 3.3.1.2. The peak change from baseline in FEV1 will be calculated using the largest FEV1 value measured during the 6-hour post-dosing period (i.e., up through the 6-hour nominal timepoint) and subtract the period-specific baseline.

4.2.8.3 Handling of Dropouts and Missing Data

The handling of dropouts and missing data as described in Section 4.2.5.3 will be applied.

4.2.8.4 Analysis of Secondary Endpoint – Principal Stratum Strategy Estimand

Same method as described in Section 4.2.2.4 will be used for PRM9 analysis set with the change of endpoint to the peak change from baseline in FEV1.

4.2.8.5 Subgroup Analyses

Not Applicable.

4.2.9 Secondary Endpoint – To Demonstrate Superiority of Ventolin Evohaler Relative to Placebo on Peak FEV1

4.2.9.1 Definition

Similar to the primary endpoint, the estimand for superiority targets participants that are treated with Ventolin Evohaler and Placebo and do not have any ICEs as defined in Section 4.2.1. The following 5 attributes describe the estimand that will be used to define the treatment effect of interest for the superiority analysis:

- Treatment Condition: dosed with Ventolin Evohaler and Placebo.
- Analysis Set: PRM10 (Section 3.2).
- Participant-level outcomes: peak change from baseline in FEV1
- Intercurrent event handling: principal stratum strategy.

- Summary measure: difference in the adjusted means of the participant-level outcomes for the treatment comparison of Ventolin Evohaler vs Placebo.

4.2.9.2 Derivations

Period-specific baseline as mentioned in Section 4.2.2.2 will be used. The peak change from baseline in FEV1 will be calculated using the largest FEV1 value measured during the 6-hour post-dosing period (i.e., up through the 6-hour nominal timepoint).

4.2.9.3 Handling of Dropouts and Missing Data

The handling of dropouts and missing data as described in Section 4.2.5.3 will be applied.

4.2.9.4 Analysis of Secondary Endpoint – Principal Stratum Strategy Estimand

Same method as described in Section 4.2.3.4 will be used for PRM10 analysis set with the change of endpoint to the peak change from baseline in FEV1.

4.2.9.5 Subgroup Analyses

Not Applicable.

4.2.10 Secondary Endpoint – To Demonstrate Equivalence of AS MDI Relative to Ventolin Evohaler on Peak FEV1

4.2.10.1 Definition

Estimand is defined same as in Section 4.2.8.1.

4.2.10.2 Derivations

Period-specific baseline as mentioned in Section 4.2.2.2 will be used. The peak change from baseline in FEV1 will be calculated using the largest FEV1 value measured during the 6-hour post-dosing period (i.e., up through the 6-hour nominal timepoint).

4.2.10.3 Handling of Dropouts and Missing Data

The handling of dropouts and missing data as described in Section 4.2.5.3 will be applied.

4.2.10.4 Primary Analysis – Principal Stratum Strategy Estimand

Same method as described in Section 4.2.4.4 will be applied to PRM9 analysis set with the change of endpoint to the peak change from baseline in FEV1.

4.2.11 Exploratory Endpoints

4.2.11.1 Definition

To assess superiority of AS MDI relative to Placebo using following endpoints:

- Change from baseline in FEV1 AUC0-6

- Change from baseline in FEV1 AUC0-4
- Peak change from baseline in FEV1

The principal stratum strategy estimand is defined similar to the primary endpoint, the estimand for superiority targets participants that are treated with AS MDI and Placebo and do not have any ICEs as defined in Section 4.2.1. The following 5 attributes describe the estimand that will be used to define the treatment effect of interest for the superiority analysis:

- Treatment Condition: dosed with AS MDI and Placebo.
- Analysis Set: PRM5, PRM6, PRM11 (Section 3.2).
- Participant-level outcomes: change from baseline in FEV1 AUC0-6, FEV1 AUC0-4, and peak change from baseline in FEV1
- Intercurrent event handling: principal stratum strategy.
- Summary measure: difference in the adjusted means of the participant-level outcomes for the treatment comparison of AS MDI vs Placebo.

To characterize the therapeutic efficacy of AS MDI relative to Ventolin Evohaler using following endpoints:

- Change from baseline in FEV1 at each post-dose timepoint
- 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 of ≥12% improvement in FEV1
- Time to onset of response of ≥15% improvement in FEV1
- Duration of response of ≥12% improvement in FEV1
- Duration of response of ≥15% improvement in FEV1

Responder is defined by at least 12% (or 15%) improvement in FEV1 from baseline within 30 minutes post-dose. The time to onset of response for each individual participant is defined as the first timepoint for which an increase from baseline FEV1 of at least 12% (or 15%) is observed within the first 30 minutes post dose. Time to onset of response is only applicable to participants who responded. Duration of response is calculated from the onset of response followed up to the last occurrence of the response. If offset of response (i.e.

<12% or <15% increase in FEV1) was not achieved during the assessment period, the last available time of assessment will be used as the offset. If a participant had a 2nd onset of response subsequent to achievement of offset, their data for that period will be excluded from the duration of response analysis.

4.2.11.2 Derivations

Period-specific baseline will be used for the calculation of change from baseline in FEV1 value. AUC0-6 and AUC0-4 calculation, as well as Peak FEV1 definition can be found in Sections 4.2.2.2, 4.2.5.2, and 4.2.8.2. These calculations are for AS MDI and Placebo treatment periods.

Responders are defined for treatment of AS MDI and Ventolin Evohaler for the following 2 criteria:

1. Achieving ≥12% improvement in FEV1 from baseline within 30 minutes post-dose.
2. Achieving ≥15% improvement in FEV1 from baseline within 30 minutes post-dose

Baseline FEV1 is the period-specific baseline as defined in Section 3.3.1.2.

Duration (in minutes) of the corresponding ≥12% improvement-responder is the time from the first occurrence of ≥12% improvement within 30 minutes post-dose to the last occurrence of FEV1 value ≥12% improvement from baseline. The duration is only applicable for the responders. For participants maintaining ≥12% improvement until the last timepoint assessment (i.e., 360 minutes), the duration is calculated to the last FEV1 assessment time. Duration of ≥15% improvement-responder will be calculated in the similar manner.

4.2.11.3 Handling of Dropouts and Missing Data

The endpoints missing data and handling rules described in Section 4.2.5.3 will be applied.

4.2.11.4 Analysis of Exploratory Endpoint

For endpoint of change from baseline in FEV1 AUC0-6, AUC0-4, and peak change from baseline FEV1 for AS MDI and Placebo treatment periods, a linear mixed model with participant as a random effect using the PRM5 (change from baseline in FEV1 AUC0-6), PRM6 (change from baseline in FEV1 AUC0-4), or PRM11 (peak change from baseline in FEV1) analysis sets. The fixed effects in the model will include treatment, treatment period, and stratum of ICS use. An additional covariate for average baseline (period-specific baseline FEV1 averaged over the treatment periods) will also be included. Adjusted treatment means, standard errors, 95% CIs, and p-values will be obtained.

For participants with treatments of AS MDI and Ventolin Evohaler, following summaries will be provided by treatment for each exploratory endpoint.

- FEV1 value for pre-dose timepoints, period-specific baseline (i.e., trough FEV1), each post-dose timepoint, and change from baseline to each post-dose timepoint will be descriptively summarised. (PRM9 analysis set)
- The median values for time to peak FEV1 will be reported. The median difference and corresponding Hodge-Lehmann 95% CI will be presented. (PRM9 analysis set)
- The percentages of participants achieving a ≥12% and ≥15% improvement from baseline within 30 minutes post dose will be tabulated. The odds ratio of being a responder will be estimated using a generalized mixed effects model with fixed effects of treatment, period and stratum of ICS use, and random participant effect. (PRM7 analysis set)
- The median time to onset of responses (≥12% and ≥15% separately) will be reported. The median difference in the paired observations (non-missing time of onset values for both AS MDI and Ventolin Evohaler) and the corresponding Hodges-Lehmann 95% CI will be presented. (PRM7 analysis set)
- The median duration of ≥12% response will be reported. The median difference in the paired observations (non-missing duration of response for both AS MDI and Ventolin Evohaler) and the corresponding Hodges-Lehmann 95% CI will be presented. (PRM8.1 analysis set)
- Similarly the median duration of ≥15% response will be reported. The median difference in the paired observations (non-missing duration of response for both AS MDI and Ventolin Evohaler) and the corresponding Hodges-Lehmann 95% CI will be presented. (PRM8.2 analysis set)

In addition, line plots will be generated to show the mean change from baseline in FEV1 over time, with time 0 being the trough FEV1 i.e. the period specific baseline value for each treatment.

4.3 Pharmacodynamic Endpoint(s)

Efficacy endpoints are also considered as pharmacodynamic endpoints. Detailed analyses are described in Sections 4.2.

4.4 Pharmacokinetics

Not applicable.

4.5 Immunogenicity

Not applicable.

4.6 Safety Analyses

All safety variables will be summarised using the Safety Set.

All safety measurements will use all available data for analyses, including data from unscheduled visits and repeated measurements unless otherwise specified.

No safety data will be imputed. The handling of partial/missing dates for AEs and prior/concomitant medications is detailed in Appendix 7.1. Duration of AEs and prior/concomitant medications will not be calculated using imputed dates.

Listings are provided for all participants or the Safety Analysis Set as applicable.

4.6.1 Exposure

Not applicable. Single dose is given for each treatment.

4.6.2 Adverse Events

4.6.2.1 Definitions and Derivations

All AEs will be collected from randomisation throughout the treatment period and the follow-up period. SAEs will be recorded from the time of signing of the ICF. They will be coded using the latest version of the MedDRA available at the time of clinical data base lock for the study.

On-treatment Adverse events include adverse events with an onset date on or 1 day after the dose of study intervention. This includes worsening of pre-existing events before randomisation.

Post-treatment AEs include adverse events with an onset date 2 or more days after the dose of study intervention. These events include those that arise either between two treatment periods (from Day 3 following the initial treatment up to the next treatment), or from Day 3 following the final treatment until the end of the study.

AE data will be categorized according to their onset date into the following study periods:

- AEs in screening/run-in period: All AEs with a start date/time on or after Visit 1 and prior to the date of the administration of study intervention of TP 1 Day 1.
- AEs in on-treatment period of TP x: All AEs with a start date/time at the time of or 1 day after the administration of TP 1 study intervention.
- AEs in post-treatment/follow-up period of TP x: All AEs with a start date/time on 2 or more days after the study intervention for the period.
- AEs in on-study period: All AEs with a start date/time after randomisation until study completion or withdrawal date.

The timing of AEs will be assigned to the period in which they first occurred. If an AE has a missing onset date, then unless the stop date of the AE indicates otherwise, this will be considered an on-treatment event and belonging to all TPs provided the participant was treated for that TP. Similarly, if an AE has a partial onset date, then unless the partial onset date or the stop date indicates otherwise, this will be considered an on-treatment AE and assigned to a TP depending on the partial onset date and/or stop date by comparing with start date/time of each TP. The details of handling missing, and incomplete AE dates are described in Appendix 7.1.

Intensity

Intensity will be classified as mild, moderate, and severe. Intensity for AEs will be collected on "Adverse Events" form of eCRF. Should a participant experience multiple events within a SOC or PT, only the participant's maximum intensity will be counted for that SOC or PT. If the AE record is missing intensity, no imputation of intensity will be performed.

Relationship to study interventions

Relationship to study interventions/other medication/study procedure, as indicated by the Investigator, will be classified as not related or related. Should a participant experience multiple events within a SOC or PT, the participant will be counted as related for that SOC or PT if one of those is related. If the relationship for the AE record is missing, no imputation of the relationship will be performed.

4.6.2.2 Presentation

On-treatment AEs will be presented by the actual treatment the participant is on when the AE starts. Post-treatment AEs will be presented by the last treatment the participant is on before the AE starts. Summaries will be separated by study periods (on-treatment periods and post-treatment periods) as defined in Section 4.6.2.1 and by treatment. Note that, an "Overall" column summarises a participant cross multiple treatment period.

An overall summary table will be produced showing the number and percentage of participants with at least one AE in each of the following categories: any AEs, SAEs, SAEs with outcome of death, any AEs leading to discontinuation of study, any related AEs (per investigator's causality assessment), and any related SAEs (per investigator's causality assessment).

AEs, SAEs, SAEs with outcome of death, AEs leading to study discontinuation, possibly related AEs (per investigator's causality assessment), and possibly related SAEs (per investigator's causality assessment) will be summarized by SOC and PT according to

MedDRA. At each SOC and PT level, the number and percentage of participants who had at least one AE at that level will be presented. A participant with multiple AEs at the same SOC and PT level will only be counted once for that level of summarisation. SOC will be sorted by international order and PT within the SOC will be sorted by alphabetical order.

AEs will also be summarised by SOC, PT, and maximum intensity. A participant with multiple AE occurrences at the same SOC and PT level will only be counted once for that level using the highest recorded intensity among these occurrences (the order being severe, moderate, and mild).

Non-serious AE that has >5% participants will be summarised for the number and percentage of participants as well as the total number of events. Individual terms by SOC and PT will be presented as well.

Key participant information will be presented for participants with AEs with outcome of death, SAEs, and AEs leading to discontinuation of study. All AEs (including during screening/run-in period) will be included in the listing for safety set.

Summaries as described above are presented for on-treatment periods. In addition, overall summary, AEs by SOC and PT, and SAEs by SOC and PT will be summarised for post-treatment periods.

4.6.3 Asthma-Related Event

4.6.3.1 Definitions and Derivations

Asthma-related events are collected in eCRF at Visits 2, 3, 4, and PDV. It includes information as below:

- Number of ambulance transports, hospital admission or emergence department > 24 hours, days hospitalization intensive care, days hospitalization coronary care, days hospitalization general care, number of emergency room visits, and number of urgent care visits
- Number of visits to specialist, visits of primary health care physician and other health care visits, home visits physician, home visits nurse, home visits other health care
- Number of telephone calls to physician, nurse, specialist, and other physician/health care provider
- Number of spirometry assessments, advanced pulmonary function tests, plain chest x-ray assessments, computed tomography assessments, and oxygen initiation.

4.6.3.2 Presentation

The number and percentage of participants for each category of asthma-related events will be summarised by treatment using the SS. Events that occurred in the PDV will be counted towards the last treatment that the participant received. For the "Overall" column, the total number of events cross multiple treatment periods will be summed together for a participant.

4.6.4 Vital Signs

4.6.4.1 Definitions and Derivations

Vital signs (sitting pulse rate, systolic blood pressure [BP], and diastolic BP) will be obtained in accordance with the schedule provided in the CSP.

Changes in vital signs parameters between pre-dose timepoint and each post-baseline assessment will be calculated. Pre-dose timepoint for vital signs is the measurement taken 60 minutes prior to administration of the study intervention for the period. There will be no imputation for missing values.

Absolute values and changes from pre-dose (where applicable) will be compared to the relevant reference range tabulated below, and classified as low (below range), normal (within range or on the limits), or high (above range). All values falling outside the reference ranges will be flagged. Treatment-emergent abnormalities (i.e., vital signed collected on the day of study intervention or 1 day after) will also be flagged based on a combination of the criteria of low value, high value, and decrease and increase from baseline described in the tabulation below.

Table 5 Vital Signs Reference Ranges and Treatment Emergent Change

Parameter	Unit	Low value	Low decrease	High value	High increase
Pulse	Beats per minute	≤50	NA	≥120	NA
		≤50 and decrease from BL ≥20		≥120 and increase from BL ≥20	
Systolic blood pressure	mmHg	≤90	NA	≥160	NA
		≤90 and decrease from BL ≥20		≥160 and increase from BL ≥20	
Diastolic blood pressure	mmHg	≤50	NA	≥100	NA
		≤50 and decrease from BL ≥10		≥100 and increase from BL ≥10	

BL=baseline.

4.6.4.2 Presentations

Vital sign parameters will be presented for each treatment. Summary statistics for continuous variables include n, mean, SD, minimum, Q1, median, Q3, and maximum. Frequency tables include number and percentage of participants in the respective category.

These summaries will be produced for the on-treatment period, as defined in Section 3.3.1.1.

For post-dose visit, descriptive statistics for all vital sign parameters will be presented for absolute value, together with the corresponding changes from pre-dose.

AZ-defined reference ranges (see Table 5 in Section 4.6.4.1) will be used for the identification of individual abnormalities. Frequency table presents the number of participants reporting at least one on-treatment abnormality. Participants who have treatment-emergent changes from baseline outside the pre-defined AZ clinically important change criteria will also be summarised.

A shift table will be produced for each vital signs variable to display low, normal, and high values. The shift table will present pre-dose and post-dose values for each variable by treatment.

Key participant information will be presented for participants with values outside range and treatment-emergent changes in vital sign parameters outside of predefined criteria.

5 INTERIM ANALYSIS

Not Applicable.

6 REFERENCES

Kenward and Roger, 2010

Kenward MG, Roger JH. The use of baseline covariates in crossover studies. Biostatistics. 2010;11(1):1-17.

Williams, 1949

Williams EJ. Experimental designs balanced for the estimation of residual effects of treatments. Australian J of Sci Res. 1949;2:149-68. Available from https://doi.org/10.1071/CH9490149.

Wang et al, 2009

Wang BS, Wang XJ, Gong LK. The construction of a Williams design and randomization in cross-over clinical trials using SAS. J. Stat. Soft. Code Snippets 2009;29(1):1-10. Available from https://doi.org/10.18637/jss.v029.c01.

7 APPENDIX

7.1 Partial Dates for Adverse Events, Prior/Concomitant Medications, and Asthma Diagnosis

Dates missing the day or both the day and month of the year will adhere to the following conventions in order to classify AEs and to classify prior/concomitant medications:

Adverse Events

- The missing start day will be set to:
  - First day of the month of occurrence, if the start YYYY-MM is after the YYYY-MM of first study intervention.
  - The day of the first study intervention, if the start YYYY-MM is the same as YYYY-MM of the first study intervention.
  - The date of informed consent, if the start YYYY-MM is before the YYYY-MM of the first study intervention.
- The missing end day will be set to:
  - The last day of the month of the occurrence, if the end YYYY-MM is after the YYYY-MM of the first study intervention.
  - Date of death if the participant died in the same month.
  - The day of last study treatment if the YYYY-MM of occurrence is the same as the last study intervention.
- If the start date is missing both the day and month, the date will be set to:
  - January 1 of the year of occurrence.
  - The date of the first study intervention, if the start year is the same as the year of the first study intervention.
- If the end date is missing both the day and month, the date will be set to:
  - December 31 of the year of occurrence.
  - Date of death if the participant died in the same year.
  - Last study intervention date if the year of occurrence is the same as the last study intervention date.
- If the start date is null, the date will be set to:
  - The date of first study intervention.
  - January 1 of the same year as the end date, if the end date suggests that the start date could be prior to the date of first study intervention.
- If the end date is null and not recorded as ongoing, the date will be set to:
  - The date of the first study intervention, if the start date is prior to the date of first study intervention.
  - The date of last visit, if the start date is on or after the date of first study intervention.

- If the end date is null and recorded as ongoing, the end date will not be imputed.

Prior/concomitant medication

- The missing day of start date of a therapy will be set to the first day of the month that the event occurred.
- The missing day of end date of a therapy will be set to the last day of the month of the occurrence.
- If the start date of a therapy is missing both the day and month, the onset date will be set to January 1 of the year of onset.
- If the end date of a therapy is missing both the day and month, the date will be set to December 31 of the year of occurrence.
- If the start date of a therapy is null and the end date is not a complete date then the start date will be set to the earliest of the imputed partial end date and the date of the first study visit.
- If the start date of a therapy is null and the end date is a complete date
    - and the end date is after the date of the first study visit then the start date will be set to the date of the first study visit.
    - otherwise the start date will be set to the end date of the therapy.
- If the end date of a therapy is null and the start date is not a complete date then the end date will be set to the study end date.
- If the end date of a therapy is null and the start date is a complete date
    - and the start date is prior to the study end date then the end date will be set to the study end date.
    - Otherwise, the end date will be set to the start date of the therapy.

Asthma Diagnosis

- Missing only day of the diagnosis, then will be set to 1st of the month.
- Missing day and month of the diagnosis, then will be set to Jan 1st of the year.

7.2 SAS Code for Statistical Analyses

- Linear Mixed Model for change from baseline in FEV1 AUC or peak change from baseline in FEV1:

```
proc mixed data=eff method=REML noclprint plots=all;
  class SUBJID APERIODC TRTA(ref="VER") STRATARN;
  model CHG = BASE APERIODC TRTA STRATARN/ DDFM=KR residual;
  random SUBJID;
  lsmeans TRTA / diff cl alpha=0.05 cov;
run;
```

- Generalized mixed effects model for percentages of participants achieving a 12% and 15% improvement from baseline within 30 minutes post dose:

```
proc glimmix data=tte method=QUAD;
  class SUBJID APERIOD TRTA(REF="VER") STRATARN;
  model RESP(event='1')=TRTA APERIODC STRATARN/ dist=bin link=logit;
  random INT / SUBJECT=SUBJID;
  lsmeans TRTA / diff cl or;
run;
```

- Non-parametric descriptive statistics and CI's of the treatment differences using Hodges-Lehmann's median for paired data:

```
%macro HL_paired(dsn=, trt1=, trt2=, alpha=);
*** STEP 1: Calculate the differences between each pair of treatments
for each subject and record the sample size as a macro variable for
later use. Note that the macro only calculates differences for 2
treatments so repeat this macro as needed.;
DATA ONE; SET &DSN;
CALL SYMPUT('SIZE',TRIM(LEFT(_N_)));
DIFF=&TRT1-&TRT2;
RUN;

*** STEP 2: Use ARRAY to form all possible ordered pairs of
differences and average values;
PROC TRANSPOSE DATA=ONE OUT=TWO(DROP=_NAME_);
VAR DIFF;
RUN;
DATA THREE; SET TWO;
ARRAY X{&SIZE} COL1-COL&SIZE;
DO I=1 TO &SIZE;
DO J= I TO &SIZE;
STAT=(X{I}+X{J})/2;
OUTPUT;
END;
END;

*** STEP 3: Calculate the point estimate of the Hodges-Lehmann
median difference;
PROC SORT DATA=THREE;
BY STAT;
RUN;
PROC MEANS MEDIAN NOPRINT;
VAR STAT;
OUTPUT OUT=EST(DROP=_FREQ_ _TYPE_)
MEDIAN=ESTIMATE;
RUN;
```

```
*** STEP 4: Calculate the confidence interval of the Hodges-Lehmann
median difference;
DATA FOUR;
LOWORD=1+INT(&SIZE*(&SIZE+1)/4 +
PROBIT(&ALPHA/2)*SQRT(&SIZE*(&SIZE+1)*(2*&SIZE+1)/24));
UPPORD= CEIL(&SIZE*(&SIZE+1)/4 + PROBIT(1-
&ALPHA/2)*SQRT(&SIZE*(&SIZE+1)*(2*&SIZE+1)/24));
RUN;

DATA FIVE; SET THREE END=LAST;
IF _N_=1 THEN SET FOUR;
RETAIN LOWER UPPER;
IF _N_=LOWORD THEN LOWER=STAT;
IF _N_=UPPORD THEN UPPER=STAT;
IF LAST THEN OUTPUT;
KEEP LOWER UPPER;
RUN;

*** STEP 5: Put the point estimate and confidence into one dataset;
DATA HL_EST; MERGE EST FIVE;
RUN;
%MEND HL_PAIRED;
```

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