Revised Clinical Study Protocol

Study Code	D6930C00001(PT007001)
NCT #	NCT03364608
Date	12 JAN 2018

A Randomized, Double-blind, Single dose, Placebo-controlled, 5-Period, 5-Treatment, Crossover, Multi-center, Dose-ranging Study to Compare PT007 to Placebo MDI and Open-Label Proventil® HFA in Adult and Adolescent Subjects With Mild to Moderate Asthma

The following Amendment(s) are included in this revised protocol:

Amendment No.	Date of Amendment
Version 1	27 OCT 2017
Version 2, Amendment 1	12 JAN 2018

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Amendment No.	Date of Amendment
Version 1	27 OCT 2017
Version 2, Amendment 1	12 JAN 2018

Clinical Study Protocol	
Drug Substance	PT007
Study Code	D6930C00001 (PT007001)
Version	2.0
Date	12 January 2018

A Randomized, Double-blind, Single dose, Placebo-controlled, 5-Period, 5-Treatment, Crossover, Multi-center, Dose-ranging Study to Compare PT007 to Placebo MDI and Open-Label Proventil® HFA in Adult and Adolescent Subjects With Mild to Moderate Asthma

Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden

VERSION HISTORY

Version 2.0, 12 January 2018
Post-dose spirometry will be collected at 180 and 300 minutes, in addition to the timepoints currently outlined in the protocol. The 180 and 300 minute timepoints were inadvertently not included. Table 2 and the protocol have been updated accordingly. Table 1 was updated to add the superscript "d" to spirometry. This footnote applies to spirometry as well as reversibility testing. Section 4.1.1 and 4.1.2, Visit 1 activities: clarifies that spirometry assessments should be performed only if subjects held their morning doses of asthma medications and SABA for ≥6 hours, per Table 1 and inclusion criteria 5. The previous text was confusing to sites. Section 4.2.2: moved "conducting pre-dose spirometry" from an after randomization activity to a before randomization activity. A pre-bronchodilator FEV_1 ≥40% percent predicted normal value is a randomization criterion.
Version 1.0, 27 October 2017
Initial creation.

This clinical study protocol has been subject to a peer review according to the Sponsor's Standard procedures. The clinical study protocol is publicly registered and the results are disclosed and/or published according to the Sponsor's Global Policy on Bioethics and in compliance with prevailing laws and regulations.

CLINICAL STUDY PROTOCOL SYNOPSIS

A Randomized, Double-blind, Single dose, Placebo-controlled, 5-Period, 5-Treatment, Crossover, Multi-center, Dose-ranging Study to Compare PT007 to Placebo MDI and Open-Label Proventil® HFA in Adult and Adolescent Subjects With Mild to Moderate Asthma

Coordinating Investigator

[redacted]

Study site(s) and number of subjects planned

This study will be conducted at approximately 10 sites in the United States. Across these sites, it is planned that approximately 70 subjects with mild to moderate asthma will be randomized.

Phase of development
II

Study design

This is a randomized, double-blind, single-dose, placebo-controlled, 5-period, 5-treatment, crossover, multi-center study to assess the bronchodilatory effect and safety of 2 dose levels of Albuterol Sulfate Pressurized Inhalation Suspension (hereafter referred to as AS MDI), 90 µg and 180 µg, compared with placebo for AS MDI (hereafter referred to as Placebo MDI) and open-label Proventil® hydrofluoroalkane (HFA; hereafter referred to as Proventil) 90 µg and 180 µg in adult and adolescent subjects with mild to moderate asthma. This study design utilizes 10 treatment sequences.

Objectives

Primary Objective	**Outcome Measures**
To confirm the dose of albuterol delivered from AS MDI that is comparable to Proventil	Primary: Change from baseline in forced expiratory volume in 1 second (FEV_1) area under the curve from 0 to 6 hours (AUC_{0-6}) Secondary efficacy endpoints: • Change from baseline in FEV_1 AUC from 0 to 4 hours (AUC_{0-4}) • Peak change from baseline in FEV_1 Other efficacy endpoints: • Change from baseline in FEV_1 at each post-dose timepoint • Time to peak FEV_1 • Percentage of subjects achieving 12% improvement in FEV_1 from baseline within 30 minutes of dose • Percentage of subjects achieving 15% improvement in FEV_1 from baseline within 30 minutes of dose • Time to onset of response • Duration of response

Secondary Objective	**Outcome Measures**
To assess the dose response of AS MDI versus Placebo MDI	Primary: Change from baseline in FEV_1 AUC_{0-6} Secondary efficacy endpoints: • Change from baseline in FEV_1 AUC_{0-4} • Peak change from baseline in FEV_1 Other efficacy endpoints: • Change from baseline in FEV_1 at each post-dose timepoint • Time to peak FEV_1 • Percentage of subjects achieving 12% improvement in FEV_1 from baseline within 30 minutes of dose • Percentage of subjects achieving 15% improvement in FEV_1 from baseline within 30 minutes of dose • Time to onset of response • Duration of response

Safety Objective	Outcome Measures
To evaluate the safety and tolerability of AS MDI relative to Placebo MDI and Proventil.	Adverse events (AEs)/serious adverse events (SAEs) Vital signs Clinical laboratory parameters Electrocardiograms

Target subject population

Adult and adolescent subjects (≥12 to ≤65 years old) with stable mild to moderate asthma (pre-bronchodilator FEV_1 of ≥40 to <90% predicted normal value), with demonstrated FEV_1 reversibility to Ventolin® HFA (hereafter referred to as Ventolin).

Subjects must be on either a short-acting β-agonist (SABA) as needed as their only asthma therapy or a low to medium inhaled corticosteroid (ICS) dose (either alone or in combination with a long-acting β2-agonist [LABA]) for at least 30 days as a consistent regimen before screening.

Duration of treatment

This is a 5-period crossover study. Each Treatment Period is 1 day. Subjects will receive a single dose of randomized study drug at each of the 5 Treatment Visits (Visits 2, 3, 4, 5, and 6), with a 3- to 7-day Washout Period between Treatment Visits.

All subjects in this study will discontinue their current asthma medications at Visit 1 and initiate Sponsor-provided asthma medication to be used during the Screening Period and throughout the duration of the study. Subjects who were using only SABA as needed before Visit 1 will discontinue their SABA and initiate Sponsor-provided Ventolin, to be used as needed throughout the study, up until 6 hours before each study visit. For these subjects, the minimum Screening Period will be 3 days. Subjects who were receiving regularly scheduled ICS or ICS/LABA before Visit 1 will discontinue their ICS or ICS/LABA and initiate Pulmicort Flexhaler™ 180 µg or 360 µg twice a day, in addition to the Sponsor-provided Ventolin as described above. For these subjects, the minimum Run-in Period will be 14 days. For all subjects, the maximum Screening/Run-in Period will be 28 days.

Each subject will participate for a minimum of 23 days and up to a maximum of 68 days, including the 3- to 28-day Screening Period described above and a telephone call 3 to 7 days after the final dose of study drug.

Investigational product, dosage, and mode of administration

Test product: AS MDI; 45 µg albuterol base (equal to 54 µg albuterol sulfate) or 90 µg albuterol base (equal to 108 µg albuterol sulfate) per actuation

Active comparator: Proventil; 90 µg albuterol base (equal to 108 µg albuterol sulfate) per actuation

Placebo: Placebo MDI manufactured in the image of AS MDI

Each product is taken as follows during 1 of 5 Treatment Visits

- AS MDI 90 µg (2 actuations of 45 µg/actuation)
- AS MDI 180 µg (2 actuations of 90 µg/actuation)
- Placebo MDI (2 actuations)
- Proventil 90 µg (1 actuation of 90 µg/actuation)
- Proventil 180 µg (2 actuations of 90 µg/actuation)

Statistical methods

All efficacy assessments will be compared with Placebo MDI and Proventil, and where appropriate, the AS MDI dose levels will be compared. Efficacy analyses will be performed for the Modified Intent-to-Treat analysis set (defined as subjects who received treatment and have post-treatment efficacy data from at least 2 Treatment Periods). As a sensitivity analysis, the Intent-to-Treat analysis set (defined as subjects who are randomized to treatment and receive at least 1 dose of the study treatment) will also be applied to the primary endpoint, change from baseline in FEV_1 AUC_{0-6}.

The FEV_1 AUC_{0-6} will be analyzed using a linear mixed model with a random subject effect. The fixed effects in the model will include treatment, treatment sequence, baseline FEV_1, and period.

Superiority comparisons of AS MDI relative to Placebo MDI and Proventil versus Placebo MDI will be conducted first using a dose-ordered approach. A 2-sided alpha level of 0.05 will be employed. Estimated treatment differences and 95% confidence intervals will be provided for the superiority comparisons.

The secondary endpoints will be analyzed using a similar approach as that of the primary endpoint.

Adverse events will be tabulated by treatment. No hypothesis tests will be performed.

Sample size

Power calculations were based on the properties of the primary endpoint, the change from baseline in FEV_1 AUC_{0-6}. Randomization of 70 subjects in order to achieve at least 64 subjects completing the study will provide >95% overall probability to demonstrate superiority of each treatment relative to Placebo MDI assuming a minimum detectable difference (active – Placebo MDI) of 100 mL, within-subject standard deviation of 115 mL, and two-sided 5% level test.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study clinical study protocol.

Abbreviation or special term	Explanation
AE	Adverse event
AS MDI	Albuterol Sulfate Pressurized Inhalation Suspension
ATS	American Thoracic Society
AUC	Area under the curve
AUC_{0-6}	Area under the curve from 0 to 6 hours
AUC_{0-4}	Area under the curve from 0 to 4 hours
β-hCG	β-human chorionic gonadotropin
BID	Twice a day
CFR	Code of Federal Regulations
CI	Confidence interval
DBP	Diastolic blood pressure
ECG	Electrocardiogram
eCRF	Case Report Form (electronic/paper)
ERS	European Respiratory Society
FEV_1	Forced expiratory volume in 1 second
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HFA	Hydrofluoroalkane
HR	Heart rate
ICF	Informed consent form
ICH	International Conference for Harmonisation
ICS	Inhaled corticosteroid
ID	Identification
IRB	Institutional Review Board
ITT	Intent-to-Treat
IWRS	Interactive Web Response System
LABA	Long-acting β2-agonist
MedDRA	Medical Dictionary for Regulatory Activities
MDI	Metered dose inhaler

Abbreviation or special term	Explanation
mITT	Modified Intent-to-Treat
PIN	Personal ID number
PFT	Pulmonary function testing
QTcF	Fridericia-corrected QT interval
SABA	Short-acting β-agonist
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure

1. INTRODUCTION

1.1 Background and rationale for conducting this study

Asthma is a heterogeneous disease that is characterized by chronic airway inflammation and bronchial hyperreactivity. It is defined by a history of respiratory symptoms such as wheeze, shortness of breath, chest tightness, and cough that vary over time and in intensity, together with variable expiratory airflow obstruction. Worsening asthma symptoms/airway obstruction can be mild to severe (Global Initiative for Asthma 2017). Albuterol sulfate is a short-acting β-agonist (SABA) that has been used world-wide in the management of asthma symptoms across all severities of asthma for over 40 years (Global Initiative for Asthma 2017).

The test formulation to be evaluated in this study is a metered dose inhaler (MDI) containing albuterol sulfate (Albuterol Sulfate Pressurized Inhalation Suspension; hereafter referred to as AS MDI). This study is designed to support the selection of the albuterol dose by comparing the bronchodilatory effect and safety of 2 dose levels of AS MDI (90 µg and 180 µg) with placebo for AS MDI (hereafter referred to as Placebo MDI) and open-label Proventil® hydrofluoroalkane (HFA; hereafter referred to as Proventil; 90 µg and 180 µg) as the reference product in adult and adolescent subjects with mild to moderate 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 a HFA propellant. When used in MDI products, these particles form strong non-specific associations with the active pharmaceutical ingredient, providing reproducible drug delivery and long-term stability.

All references to doses of AS MDI and Proventil refer to the albuterol base (ie, 90 µg albuterol base, which equals 108 µg albuterol sulfate).

1.2 Rationale for study design, doses and control groups

The primary goal of this study is to confirm the bronchodilatory effect of 2 dose levels of AS MDI relative to Placebo MDI and the active control, Proventil, in subjects with mild to moderate asthma. The study is based on a 5-period Williams (Williams 1949) crossover design to allow the comparison of 2 doses of AS MDI against Placebo MDI and Proventil. The crossover design was selected to ensure acceptable power with a limited subject exposure through within-subject treatment comparisons.

The dose levels of AS MDI to be tested (90 µg and 180 µg) were selected based on over 40 years of clinical experience with inhaled albuterol in asthma patients, and are likely to be efficacious doses with acceptable safety profiles. It is anticipated that the dose of albuterol delivered with AS MDI will be close to the approved dose in Proventil. The doses will allow evaluation of the bronchodilation effect of AS MDI relative to Placebo MDI and Proventil administered at 90 µg and 180 µg. The recommended dose of Proventil for the treatment or prevention of bronchospasm in adults and children aged 4 years and older is 2 actuations of

90 µg every 4 to 6 hours; for some patients, 1 actuation may be sufficient (PROVENTIL HFA package insert).

In this double-blind, placebo-controlled study, AS MDI and Placebo MDI will be blinded to all subjects, study site staff, endpoint assessors, and Sponsor personnel. Proventil 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 drug.

Subjects 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 and adolescents 12 years of age or older currently treated and well controlled with appropriate background standard of care for their asthma severity.

All subjects will use only Sponsor-provided medication for rescue as needed during the study. At Visit 1 (Screening), subjects will discontinue their SABA and initiate Sponsor-provided Ventolin, to be used as needed up until 6 hours before each study visit.

Subjects who were previously on a low to medium dose of an inhaled corticosteroid (ICS) with or without a long-acting β2-agonist (LABA) before study entry will be required to discontinue their previous therapy and initiate Sponsor-supplied Pulmicort Flexhaler™ for at least 14 days to standardize therapy and to confirm asthma is adequately treated prior to randomization; these subjects will also use Sponsor-provided Ventolin as needed for symptoms as described above.

Each dose of AS MDI will be compared with Placebo MDI and Proventil on the primary efficacy endpoint, change from baseline in forced expiratory volume in 1 second (FEV_1) area under the curve (AUC) from 0 to 6 hours (AUC_{0-6}), 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.

1.3 Benefit/risk and ethical assessment

This study has been designed to support the dose selection for a new formulation of albuterol in subjects with mild to moderate asthma. The product being tested in this study, AS MDI, is being compared with an approved inhaled albuterol product to confirm a pharmacologically appropriate dose. The subjects in this study will not gain any therapeutic benefit from the study as it is comprised of only 5 single-dose treatments.

All subjects in this study will be switched at Visit 1 from their current asthma medication to Sponsor-provided asthma medication to be used during the Screening Period and throughout the duration of the study, as described in Section 1.2. Subjects requiring medications other than those specified in Section 1.2 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, subjects must not have used more than 8 actuations per day (ie, 4 doses of 2 actuations per

day) of Sponsor-provided Ventolin for rescue on more than any 3 days during the previous 7 days before randomization.

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

1.4 Study design

This is a randomized, double-blind, single-dose, placebo-controlled, 5-period, 5-treatment, crossover, multi-center study to assess the bronchodilatory effect and safety of 2 dose levels of AS MDI (90 µg and 180 µg) compared with Placebo MDI and open-label Proventil (90 µg and 180 µg) in adult and adolescent subjects with mild to moderate asthma (Figure 1).

This study will be conducted at approximately 10 sites in the US, contributing approximately 7 subjects per site. Across these sites, it is planned that approximately 70 subjects with mild to moderate asthma will be randomized to provide approximately 64 subjects to complete the study. Each subject will participate for a minimum of 23 days and up to a maximum of 68 days, including a 3- to 28-day Screening Period and a telephone call 3 to 7 days after the final dose of study drug. The study is anticipated to run for approximately 4 months, including the recruitment period.

This study consists of a Screening Period, which includes a Run-in Period for those subjects who will be switched from ICS and ICS/LABA to Sponsor-provided Pulmicort Flexhaler, a Treatment Phase, which includes 5 randomized Treatment Periods, and a follow-up telephone call. Each Treatment Period will be 1 day, with a Washout Period of 3 to 7 days between Treatment Periods.

The Screening Period begins at Visit 1. At Visit 1, subjects will sign an informed consent form (ICF). If the subject is a minor, the parent or guardian will sign an ICF and the subject will sign an assent form. Inclusion/exclusion criteria will be assessed. To be eligible, subjects must be on either a SABA as needed as their only asthma therapy or a low to medium ICS dose (either alone or in combination with a LABA) for at least 30 days as a consistent regimen before screening. Subjects must have a pre-bronchodilator FEV_1 between ≥40 and <90% predicted normal value.

All subjects must demonstrate FEV_1 reversibility to Ventolin (defined as improvement in FEV_1 of ≥15% post Ventolin dosing) during the Screening Period; historical reversibility is not acceptable. For subjects who did not administer their morning asthma maintenance medications, as applicable, and/or SABA, reversibility will be measured at Visit 1. For subjects who received their morning asthma maintenance medications, as applicable, and/or SABA, reversibility will be measured at Visit 1a, which will occur within 10 days of Visit 1 and after these medications have been held for the appropriate time period (Table 9). Subjects who do not meet reversibility criteria at Visit 1 or Visit 1a may be retested at a subsequent

Screening Visit (1a or 1b). Only 2 reversibility testing attempts are allowed. Subjects not meeting reversibility criteria after 2 attempts must be screen failed.

Subjects meeting eligibility criteria at Visit 1 will continue in the Screening Period. All subjects in this study will discontinue their current asthma medications at Visit 1 and initiate Sponsor-provided asthma medication to be used during the Screening Period and throughout the duration of the study, as described in Section 1.2. For subjects who were using only SABA as needed before study entry, the minimum Screening Period will be 3 days. For subjects who were receiving regularly scheduled ICS or ICS/LABA before study entry, the minimum Run-in Period (on Pulmicort Flexhaler) will be 14 days. For all subjects, the maximum Screening/Run-in Period will be 28 days.

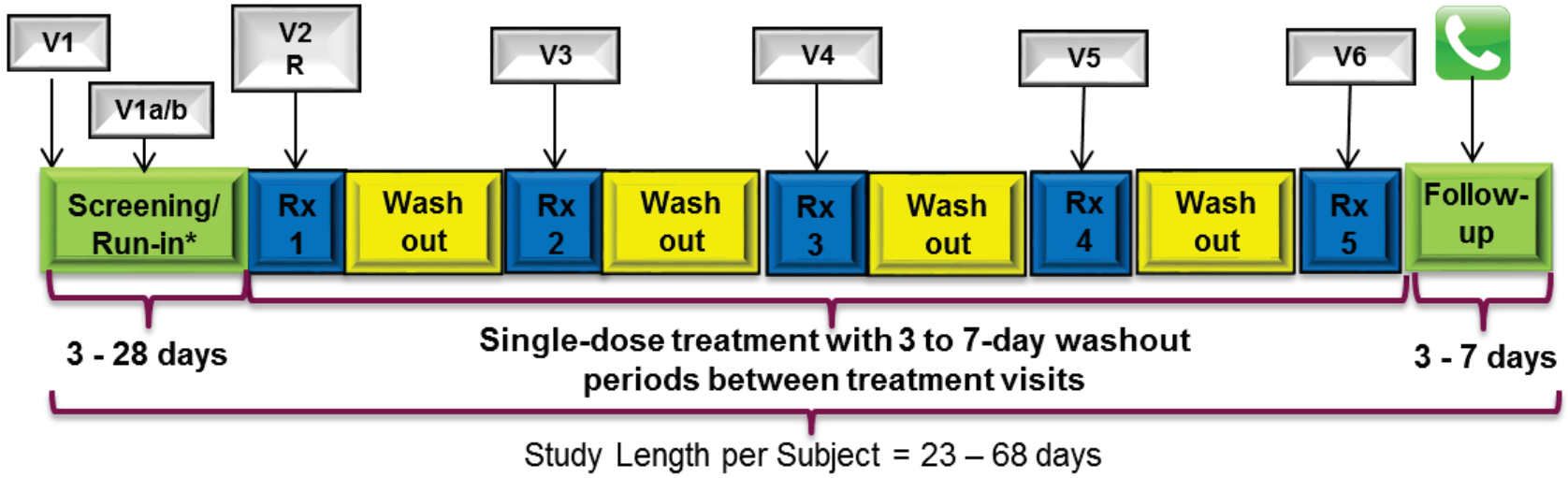
Randomization will take place at Visit 2. At Visit 2, before randomization, subjects must demonstrate a pre-bronchodilator FEV_1 ≥40% predicted normal value (average of 2 pre-bronchodilator assessments). Subjects who do not meet this randomization criterion will be screen failed. Randomization will be centralized through the use of an Interactive Web Response System (IWRS). Eligible subjects will be randomized to 1 of 10 pre-defined treatment sequences. Each sequence will contain AS MDI 90 µg, AS MDI 180 µg, Placebo MDI, Proventil 90 µg, and Proventil 180 µg, in a randomized order. Randomization is planned to be stratified by pre-study background asthma maintenance therapy, with approximately 50% of subjects on an ICS and approximately 50% of subjects who are not on an ICS (receiving only a SABA as needed).

Subjects will receive single doses of randomized study drug at each of the 5 Treatment Visits (Visits 2, 3, 4, 5, and 6), with a 3- to 7-day Washout Period between Treatment Visits. At each Treatment Visit, bronchodilation activity of the study drug will be assessed through pulmonary function testing (PFT). Subjects 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 (Table 1). Safety will be assessed by evaluation of adverse events (AEs), clinical laboratory tests, vital signs, and electrocardiograms (ECGs).

Subjects who prematurely discontinue study drug for any reason before completing all study visits will undergo a Premature Discontinuation Visit. After the last Treatment Period or following a Premature Discontinuation Visit, subjects will be scheduled for a follow-up telephone call to occur 3 to 7 days from the date of the last study drug dose.

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

Figure 1 Study Design Flow Chart



*Subjects on ICS or ICS/LABA prior to Visit 1 will be run-in on Pulmicort Flexhaler 180 or 360 µg BID for a minimum of 14 days.

Abbreviations: BID = twice a day; V=visit; R=randomization; Rx=treatment.

1.5 Study governance and oversight

No study governance or oversight committees will be used in this study.

2. STUDY OBJECTIVES

2.1 Primary objective

Primary Objective	**Outcome Measures**
To confirm the dose of albuterol delivered from AS MDI that is comparable to Proventil	Primary: Change from baseline in FEV_1 AUC_{0-6} Secondary efficacy endpoints: • Change from baseline in FEV_1 AUC from 0 to 4 hours (AUC_{0-4}) • Peak change from baseline in FEV_1 Other efficacy endpoints: • Change from baseline in FEV_1 at each post-dose timepoint • Time to peak FEV_1 • Percentage of subjects achieving 12% improvement in FEV_1 from baseline within 30 minutes of dose • Percentage of subjects achieving 15% improvement in FEV_1 from baseline within 30 minutes of dose • Time to onset of response • Duration of response

2.2 Secondary objectives

Secondary Objective	Outcome Measures
To assess the dose response of AS MDI versus Placebo MDI	Primary: Change from baseline in FEV_1 AUC_{0-6} Secondary efficacy endpoints: • Change from baseline in FEV_1 AUC_{0-4} • Peak change from baseline in FEV_1 Other efficacy endpoints: • Change from baseline in FEV_1 at each post-dose timepoint • Time to peak FEV_1 • Percentage of subjects achieving 12% improvement in FEV_1 from baseline within 30 minutes of dose • Percentage of subjects achieving 15% improvement in FEV_1 from baseline within 30 minutes of dose • Time to onset of response • Duration of response

2.3 Safety objectives

Safety Objective	Outcome Measures
To evaluate the safety and tolerability of AS MDI relative to Placebo MDI and Proventil	AEs/serious adverse events (SAEs) Vital signs Clinical laboratory parameters ECGs

2.4 Exploratory objectives – not applicable

3. SUBJECT SELECTION, ENROLLMENT, RANDOMIZATION, RESTRICTIONS, DISCONTINUATION AND WITHDRAWAL

Each subject must meet all of the inclusion criteria and none of the exclusion criteria for this study. Under no circumstances will there be exceptions to this rule.

3.1 Inclusion criteria

Each subject must meet the following criteria in relationship to Visit 1, unless otherwise noted, to be enrolled in this study:

1. Give their signed written informed consent to participate (and assent, as applicable)

2. Are at least 12 years of age and no older than 65 years

3. Have stable (for 6 months) physician-diagnosed asthma with historical documentation of the diagnosis

4. Must be receiving 1 of the following required inhaled asthma therapies listed below for at least the last 30 days:

    - Only SABA, which is used as needed for rescue
    - Low to medium doses of ICS (alone or in combination with LABA), used regularly as maintenance asthma therapy, with the ICS doses allowed in Table 7, with a stable regimen

5. Pre-bronchodilator FEV_1 of ≥40 to <90% predicted normal value after withholding SABA for ≥6 hours (and/or Visit 1a and/or Visit 1b, if applicable)

6. Confirmed FEV_1 reversibility to Ventolin, defined as a post-Ventolin increase in FEV_1 of ≥15% at either Visit 1, Visit 1a, or Visit 1b; only 2 reversibility testing attempts are allowed

7. Demonstrate acceptable spirometry performance (ie, meet American Thoracic Society [ATS]/European Respiratory Society [ERS] acceptability/repeatability criteria; Appendix A)

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

9. Demonstrate acceptable MDI administration technique
Note: Use of a spacer device during the Screening and randomized Treatment Periods is not permitted.

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

11. If a female of childbearing potential, have a negative serum pregnancy test

12. Women of childbearing potential must agree to 1 of the following to prevent pregnancy:
Note: Women are considered to be of non-childbearing potential if they are physiologically incapable of becoming pregnant, including any female who is 2 years post-menopausal, or surgically sterile, defined as having a bilateral oophorectomy, hysterectomy, or tubal ligation. For purposes of this protocol, menopausal women are defined as women ≥50 years old who are amenorrheic for 12 consecutive months or more following cessation of all exogenous hormonal treatment.

    - Practice abstinence

- If a female of childbearing potential and sexually active, agrees to prevent pregnancy by using 1 of the following methods of birth control from the date the ICF is signed until 2 weeks after the final dose of study drug is taken:
    - Hormonal contraception (eg, oral contraceptive, contraceptive implant, or injectable hormonal contraceptive)
    - Double-barrier birth control (eg, condom plus intrauterine device, diaphragm plus spermicide, condom plus spermicide)
    - Maintenance of a monogamous sexual relationship with a male partner who has been surgically sterilized by vasectomy

13. Male subjects who are sexually active must be surgically sterile or agree to use a double-barrier method of contraception (condom with spermicide) from the first dose of randomized study drug until 2 weeks after their last dose, and must not donate sperm during their study participation period

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

3.2 Exclusion criteria

Subjects who meet any of the following criteria in relationship to Visit 1, unless otherwise stated, will be excluded from the study.

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

2. Oral corticosteroid use (any dose) within 6 weeks

3. 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 (Table 9 and Table 10)

4. Received tiotropium within 2 weeks

5. 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)

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

7. Completed treatment for lower respiratory infection or asthma exacerbation within 6 weeks

8. Upper respiratory infection not resolved within 7 days

9. Hospitalizations for asthma within 6 months

10. Clinically significant laboratory abnormalities or ECG abnormalities, in the opinion of the Investigator
Note: If laboratory tests have to be repeated, the results should be available for review before Visit 2 (Randomization).

11. 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, 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 subject at risk through study participation, or that could affect the efficacy or safety analysis if the disease/condition exacerbated during the study.

12. Cancer not in complete remission for at least 5 years
Note: Subjects with squamous cell carcinoma of the skin, basal cell carcinoma of the skin, in situ carcinoma of the cervix, or localized prostate cancer are eligible, if in the opinion of the Investigator, the condition has been adequately worked up and clinically controlled and the subject's participation in the study would not represent a safety concern.

13. Hospitalized for psychiatric disorder or attempted suicide within 1 year

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

15. Significant, in the opinion of the Investigator, abuse of alcohol or drugs

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

17. Unable to abstain from protocol-defined prohibited medications during the study

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

19. Received a live attenuated vaccination within 7 days

20. Currently pregnant or nursing

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

22. Treatment with investigational study drug (or device) in another clinical study within the last 30 days or 5 half-lives, whichever is longer

23. Randomized in any PT007 study

3.3 Subject enrollment and randomization

3.3.1 Randomization criteria

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

1. Subjects 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 from Visit 1 to Visit 2, except for allowable allergy medications defined in Table 8

3. The last dose of Pulmicort Flexhaler (if applicable) was the previous night (ie, morning dose of Pulmicort Flexhaler was not administered), and the last dose of Sponsor-provided Ventolin was no later than 6 hours before the study visit (if Ventolin is needed in the morning, the visit must be rescheduled)

4. Pre-bronchodilator FEV_1 ≥40% percent predicted normal value

5. Has not used >8 actuations per day (ie, 4 doses of 2 actuations per day) of Sponsor-provided Ventolin for rescue on more than any 3 days during the previous 7 days

6. No upper respiratory infection, lower respiratory infection, or asthma exacerbation during the Screening Period

7. Demonstrate acceptable MDI administration technique

8. Able to comply with all study procedures

For procedures for withdrawal of incorrectly randomized subjects see Section 3.4.

3.3.2 Subject identification

All subjects who undergo screening will be assigned a unique screening identification number (ID) at Visit 1. Only subjects 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 subject randomization number.

3.3.3 Screen failures

Screening failures are subjects who do not fulfil the eligibility criteria for the study and therefore must not be randomized.

3.4 Procedures for handling incorrectly enrolled or randomized subjects

Subjects who fail to meet the eligibility criteria should not, under any circumstances, be enrolled into the Screening Period or receive study drug. There can be no exceptions to this rule. Subjects who are enrolled into the Screening Period but subsequently found not to meet all the eligibility criteria must not be randomized or initiated on study drug.

If a subject does not meet all the eligibility criteria and is randomized in error or is incorrectly started on study drug, the Investigator should inform the Sponsor immediately, and the Sponsor and the Investigator should discuss whether to continue or discontinue the subject from study drug and withdraw the subject from the study. The Sponsor must ensure all decisions are appropriately documented.

3.5 Methods for assigning treatment groups

The randomization scheme will be generated by the Sponsor or designee using computer software incorporating a random number generator. Subjects will be randomly assigned to 1 of 10 treatment sequences based on a Williams design (Williams 1949) using an IWRS. Each sequence will comprise all 5 of the treatments included in this study in a randomized order. All sequences will contain AS MDI 90 µg, AS MDI 180 µg, Placebo MDI, Proventil 90 µg, and Proventil 180 µg.

The 10 treatment sequences are shown below.

Sequence	Period 1	Period 2	Period 3	Period 4	Period 5
1	A	B	E	C	D
2	B	C	A	D	E
3	C	D	B	E	A
4	D	E	C	A	B
5	E	A	D	B	C
6	D	C	E	B	A
7	E	D	A	C	B
8	A	E	B	D	C
9	B	A	C	E	D
10	C	B	D	A	E

Note: A=Placebo; B=AS MDI 90 µg; C=AS MDI 180 µg; D= Proventil 90 µg; E= Proventil 180 µg.

Randomization will be centralized and stratified by pre-study background therapy consisting of either ICS or non-ICS (subjects not previously treated with ICS).

3.6 Methods for ensuring blinding

AS MDI and Placebo MDI will be blinded to all subjects, 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 labeling of AS MDI and Placebo MDI will be designed to ensure blinding.

Randomized Proventil 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 drug.

3.7 Methods for unblinding

Individual treatment codes, indicating the treatment randomization for each randomized subject, will be available to the Investigator(s) or pharmacists from the IWRS. Routines for this will be described in the IWRS user manual that will be provided to each study site.

The IWRS should be used in order to unblind subjects and to unmask drug identity. The Sponsor will not provide a disclosure envelope with the clinical supplies. The Investigator or treating Physician may unblind a subject's treatment assignment only in the case of an emergency, when knowledge of the study drug treatment is essential for the appropriate

clinical management or welfare of the subject. Whenever possible, the Investigator must first discuss options with the Sponsor Medical Monitor or appropriate study personnel before unblinding the subject's treatment assignment. If this is impractical, the Investigator must notify the Sponsor as soon as possible, but without revealing the treatment assignment of the unblinded subject, unless that information is important for the safety of subjects currently in the study. The date and reason for the unblinding must be recorded in the appropriate data collection tool.

The Sponsor retains the right to break the code for SAEs that are unexpected and are suspected to be causally related to a study drug and that potentially require expedited reporting to regulatory authorities. Treatment codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual subject have been made and documented.

3.8 Restrictions

Prohibited concomitant medications are described in Section 7.7.3.

3.8.1 Illicit drugs

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 subject discontinues from the study drug and withdraws from the study. If any illicit drugs or drugs of abuse are used by the subject during the study, the dates of use and the amount will be documented and the subject will be discontinued from study drug and withdrawn from the study at the discretion of the Investigator. 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.

3.8.2 Dietary restrictions

Subjects must not ingest xanthine and/or xanthine analogue (caffeine)-containing foods or beverages or caffeine-containing medications for at least 6 hours before each study visit and throughout the duration of each study visit. Examples of such products include coffee, tea, chocolate, and cola. Decaffeinated beverages are acceptable.

3.9 Discontinuation of study drug

All subjects who discontinue study drug will be withdrawn from the study.

Subjects may be withdrawn from the study at their own request at any time for any reason.

Subjects experiencing any of the changes of concern listed below should be discontinued from randomized study drug and 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

Note: Subjects 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 from study drug and withdrawn from the study.

- [redacted]
- Requirement for any of the prohibited medications listed in Section 7.7.3
- Any safety reason as judged by the Investigator and/or Sponsor
- Pregnancy
- The subject's treatment code is prematurely broken by the Investigator.

Subjects who discontinue study drug and withdraw from the study should be encouraged to complete the Premature Discontinuation Visit (see Section 4.2.5).

Withdrawal of the informed consent

Subjects are free to withdraw from the study at any time without prejudice to further treatment.

A subject who withdraws consent will always be asked about the reason(s) and the presence of any AE. The Investigator will follow up AEs outside of the clinical study.

If a subject withdraws from participation in the study, then his/her enrollment and/or randomization code(s) cannot be reused. Withdrawn subjects will not be replaced.

3.10 Discontinuation of the study

The study may be stopped if, in the judgment of the Sponsor, study subjects are placed at undue risk because of clinically significant findings that:

- meet individual stopping criteria or are otherwise considered significant
- are assessed as causally related to study drug
- are not considered to be consistent with continuation of the study

The Sponsor reserves the right to terminate the study at any time for clinical or administrative reasons. Such a termination must be implemented by the Investigator, if instructed to do so by the Sponsor, in a time frame that is compatible with the subjects' well-being.

Regardless of the reason for termination, all data available for the subject at the time of discontinuation must be recorded in the electronic case report form (eCRF). All reasons for discontinuation of study drug must be documented.

In terminating the study, the Sponsor will ensure that adequate consideration is given to the protection of the subjects' interests.

4. STUDY PLAN AND TIMING OF PROCEDURES

Note: Before conducting any study-related procedures, subjects are required to provide their written informed consent using the Institutional Review Board (IRB)-approved ICF, and assent as appropriate. If the subject is a minor, the parent or guardian will sign an ICF and the subject will sign an assent form. The ICF and assent form should be signed during Visit 1.

A time and events schedule is provided in Table 1. Detailed schedules are provided for timed assessments at Visits 1 through 5 (Table 2) and Visit 6 (Table 3).

When data collection timepoints are concurrent, variables will be collected in the following order: vital signs, ECG, clinical laboratory assessments, and spirometry.

Table 1 Schedule of Events

	Screening[a]		Treatment Phase[b]					Follow-up	
Procedures	**Visit 1**	**Visit 1a/b**	**Visit 2 Rand. (TP 1) Day 1**	**Visit 3 (TP 2)**	**Visit 4 (TP 3)**	**Visit 5 (TP 4)**	**Visit 6 (TP 5)**	**PDV (if applicable)[c]**	**TC 3 to 7 days after final dose**	**For details see Section**
	Day -28 to Day -1									
Informed consent (and assent, as appropriate)	X									Section 10.4
Eligibility criteria	X									Section 3
Verify randomization criteria			X							Section 3.3.1
Verified continued eligibility		X		X	X	X	X			Section 3
MDI demonstration/training	X		X	X	X	X	X			Section 4.1
Ventolin reversibility test[d]	X	X								Section 5.1.3
Medical/surgical history	X									Section 5.2.1
Demographics	X									Section 4.1
Concomitant medications[e]	X	X	X	X	X	X	X	X		Section 7.7
Spirometry[d]	X	X	X	X	X	X	X			Section 5.1.2
[redacted]	[redacted]									
Physical examination[f]	X						X	X		Section 5.2.1
Vital signs	X		X	X	X	X	X	X		Section 5.2.2
12-lead ECG	X						X	X		Section 5.2.4
Pregnancy test[g]	X		X							Section 5.2.3

Table 1 Schedule of Events

	Screening[a]		Treatment Phase[b]					Follow-up	
Procedures	**Visit 1**	**Visit 1a/b**	**Visit 2 Rand. (TP 1) Day 1**	**Visit 3 (TP 2)**	**Visit 4 (TP 3)**	**Visit 5 (TP 4)**	**Visit 6 (TP 5)**	**PDV (if applicable)[c]**	**TC 3 to 7 days after final dose**	**For details see Section**
	Day -28 to Day -1									
Clinical laboratory testing	X						X	X		Section 5.2.3
Adjust asthma medications per protocol[h]	X	X					X	X		Section 7.2.2
Randomization			X							Section 3.5
Randomized study drug administered			X	X	X	X	X			Section 7.2.1
AEs	X	X	X	X	X	X	X	X	X	Section 6.3
Telephone contact									X	Section 4.3.1

Abbreviations: AE=adverse event; β-hCG= β-human chorionic gonadotropin; ECG=electrocardiogram; FEV_1=forced expiratory volume in 1 second; ICS=inhaled corticosteroid; LABA= long-acting β2-agonist; MDI=metered dose inhaler; PDV=Premature Discontinuation Visit; Rand.=randomization; SABA= short-acting β-agonist; TC=telephone call; TP=Treatment Period.

Note: When data collection timepoints are concurrent, variables will be collected in the following order: vital signs, ECG, clinical laboratory assessments, and spirometry.

[a] Screening Period will be 3 to 28 days for subjects on SABA only before study entry, and 14 to 28 days for subjects on ICS or ICS/LABA before study entry.

[b] Subjects to return to clinic within 3 to 7 days following Visits 2, 3, 4, and 5.

[c] Subjects who prematurely withdraw from the study will undergo a Premature Discontinuation Visit (see Section 4.2.5).

[d] For subjects who received their regularly inhaled asthma medications and/or SABA on the morning of the visit, spirometry and reversibility will be measured at Visit 1a, which will occur within 10 days of Visit 1. For subjects who do not meet reversibility criteria at Visit 1a, Visit 1b will be scheduled for a second reversibility test, to occur within 7 days. Subjects who do not meet reversibility criteria after the second attempt will be screen failed.

[e] At all visits beyond Visit 1, note time of the last dose of asthma medications. The visit must be rescheduled if the last dose of Ventolin was <6 hours before the visit.

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

[g] A serum pregnancy test (β-hCG) will be performed at Visit 1; urine β-hCG test will be performed before randomization at Visit 2 (for women of child-bearing potential only).

[h] At Visit 1, prohibited asthma medications are to be stopped and asthma medications changed as specified in Section 7.2.2. At the end of Visit 6 (or upon premature discontinuation or screen failure, if applicable), subjects will return to pre-study or other appropriate maintenance asthma medications.

Table 2 Timed Assessments at Visits 2, 3, 4 and 5

	Pre-Dose (minutes)		Post-Dose (minutes)										Before leaving clinic	For details see Section
	-60	-30	5	15	30	45	60	120	180	240	300	360		
Vital signs	X												X	Section 5.2.2
Spirometry	X	X	X	X	X	X	X	X	X	X	X	X		Section 5.1.2
AEs	X	X	X	X	X	X	X	X	X	X	X	X	X	Section 6.3

Abbreviations: AE=adverse event.

Table 3. Timed Assessments at Visit 6

	Pre-Dose (minutes)		Post-Dose (minutes)										Before leaving clinic	For details see Section
	-60	-30	5	15	30	45	60	120	180	240	300	360		
Vital signs	**X**												X	Section 5.2.2
12-lead ECG													X	Section 5.2.4
Spirometry	X	X	X	X	X	X	X	X	X	X	X	X		Section 5.1.2
Physical examination													X	Section 5.2.1
Clinical laboratory testing													X	Section 5.2.3
AEs	X	X	X	X	X	X	X	X	X	X	X	X	X	Section 6.3

Abbreviations: AE=adverse event; ECG=electrocardiogram.

4.1 Screening period (Visit 1, and Visits 1a/1b if applicable)

For subjects who were receiving only SABA as needed before study entry, the minimum and maximum Screening Period will be 3 and 28 days, respectively. For subjects who were receiving regularly scheduled ICS or ICS/LABA before study entry, the minimum and maximum Run-in Period will be 14 and 28 days, respectively. The Screening Period should be as short as possible; however, the duration will be determined by the Investigator.

4.1.1 Visit 1

The following activities will be performed at Visit 1:

- Obtain informed consent
- Register subject in IWRS to obtain subject screening number
- Obtain demographic data, including age, race, smoking history, medical/surgical history, and age of onset of asthma
- Obtain medication history, including prior and concomitant medications (see Section 7.7)
- Obtain vital signs (see Section 5.2.2)
- Conduct a complete physical examination (see Section 5.2.1)
- Confirm acceptable MDI device technique and provide training as necessary
- Confirm the subject satisfies inclusion/exclusion criteria (see Section 3.1 and Section 3.2)
- Obtain a 12-lead ECG (see Section 5.2.4)
- Obtain clinical laboratory blood samples, including blood sample for serum β-hCG for all women of child-bearing potential (see Section 5.2.3)
- Discontinue the subject's baseline asthma medications and change to protocol-specified asthma medications as follows for both the Screening and randomized Treatment Periods (see Section 7.7.2.1**)**:
    - For subjects receiving only SABA as needed: switch to Sponsor-provided Ventolin as needed for symptoms
    - For subjects receiving regularly scheduled ICS or ICS/LABA: switch to Sponsor-provided Pulmicort Flexhaler (either 180 µg or 360 µg BID, based on the subject's previous therapy; see Table 7). These

subjects will also receive Sponsor-provided Ventolin as needed for symptoms.

- Record AEs (if any)
  Note: AEs must be recorded during the Screening Period, that is, from the time of signing the ICF (and assent form, as appropriate) to the start of randomized study drug. Adverse events that occur during the Screening Period will be recorded as medical history and not as study AEs unless they meet the definition of an SAE (see definition in Section 6.2).

For subjects who **have not taken** their regular morning doses of asthma maintenance medications and/or SABA within the previous 6 hours, the following activity will also be performed at Visit 1:

- Conduct spirometry assessments (FEV_1) (see Section [redacted]
- Perform Ventolin reversibility test (described in Section 5.1.3).

Note: For subjects who complete this reversibility test at Visit 1 and do not meet Ventolin reversibility criteria, Visit 1a will be scheduled for a second reversibility test.

For subjects who **have taken** their regular morning doses of inhaled asthma maintenance medications and/or SABA within the previous 6 hours before Visit 1 or any of the medications listed in Table 9 within the washout periods listed in Table 9, Visit 1a will be scheduled to allow for washout of asthma medications before spirometry and reversibility testing.

4.1.2 Visit 1a

The following activities will be performed at Visit 1a for subjects who did not complete spirometry at Visit 1 or do not have a reversibility test at Visit 1 or who fail to meet reversibility criteria at Visit 1. Visit 1a will be scheduled to occur within 10 days of Visit 1.

- Review clinical laboratory results from Visit 1
- Review concomitant medications (see Section 7.7)
- Confirm the subject satisfies inclusion/exclusion criteria (see Section 3.1 and Section 3.2)
- Perform Ventolin reversibility test (described in Section 5.1.3)
- Record AEs (if any)

4.1.3 Visit 1b

Visit 1b may only be scheduled for subjects who did not perform Ventolin reversibility testing at Visit 1 and who did not meet Ventolin reversibility criteria at Visit 1a.

For subjects who do not meet reversibility criteria at Visit 1a, Visit 1b will be scheduled to occur within 7 days of Visit 1a for a second reversibility test. Only 2 reversibility attempts will be allowed. Subjects who do not meet reversibility criteria after the second attempt will be screen failed.

The following activities will be performed at Visit 1b for subjects who do not meet reversibility criteria at Visit 1a:

- Review concomitant medications (see Section 7.7)
- Confirm the subject satisfies inclusion/exclusion criteria (see Section 3.1 and Section 3.2)
- Perform Ventolin reversibility test (described in Section 5.1.3)
- Record AEs (if any)

4.2 Treatment periods

4.2.1 General guidance for Treatment Visits 2 through 6 (Treatment Periods 1 through 5)

- At the start of each Treatment Visit, before any study procedures are performed, site personnel must confirm the subject has withheld all asthma medications. The last Pulmicort Flexhaler dose should be no later than the previous night. The last dose of Ventolin should be no later than 6 hours before the visit. Confirm the last time of dosing.
  Note: Subjects who did not withhold their Ventolin as described above before the start of study procedures must have their visit rescheduled as soon as is practical, but within the specified visit window (±2 days).[redacted]
- At Visit 2, the first dose of study drug will be administered before 10 am. At all subsequent Treatment Visits, the first dose of study drug will be administered before 10 am and within 1 hour of the time administered at Visit 2.
- Sites should call the subject on the day before a scheduled visit to remind the subject of the following:
  - Pulmicort Flexhaler and Ventolin should be held for the time periods described above
  - Bring their Sponsor-provided Ventolin and Pulmicort Flexhaler, if assigned, with them to the clinic

- Refrain from ingesting xanthine-containing foods and beverages and caffeine-containing medications for at least 6 hours before each study visit and for the duration of each study visit (see Section 3.8.2)

- Study drug 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 drug on the inner flap of the study day treatment box should be followed

- Refer to Section 7.2.1 for detailed instructions for preparation of treatments for administration. These instructions are to be adhered to and are relevant to all study treatment visits

- Subject will administer the dose of assigned study drug at the clinic

- For doses consisting of 2 inhalations, the in-clinic dosing time will be recorded as the time of administration of the second actuation of study drug

- Site personnel will instruct subjects not to take any non-study asthma medications without site personnel permission during a visit, until all study procedures have been completed and the subject is discharged. Site personnel should take every precaution to prevent use of non-study asthma medications during the test day. Site personnel may request the subject to surrender all non-study asthma medications at the start of the visit before performing any study procedures and return them to the subject at the end of the visit when all study procedures are completed.

- If a subject is experiencing severe symptoms and requires Ventolin for relief of asthma symptoms at any time during a study visit, site personnel must note the time and justification for use in the subject'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.

4.2.2 Visit 2 (Randomization Visit, Treatment Period 1)

The following activities should be performed before randomization:

- Perform a urine pregnancy test

- Confirm randomization criteria (see Section 3.3.1), including pre-dose spirometry assessments (see Section 5.1.2)

- Review concomitant medications

- Review clinical laboratory results from Visit 1

- Record AEs (if any)

  Note: Pre-randomization AEs are to be recorded as part of the medical history unless the event meets the definition of an SAE (see definition in Section 6.2).

- Confirm acceptable MDI device technique

- Register subject in IWRS to obtain subject randomization number. The subject is to be considered randomized after receiving a randomization number from the IWRS.

The following activities are to be performed after randomization:

- Perform all pre-dose vital signs assessments (see Section 5.2.2)

- Dispense study drug (see Section 4.2.1) based on subject treatment assignment information from IWRS

- Perform post-dose spirometry assessments (see Section 5.1.2)

The following will be performed after the final (6-hour post-dose) spirometry test:

- Record AEs (if any)

- Schedule Visit 3, allowing for a Washout Period of 3 to 7 days

- Assure that the subject has enough Sponsor-provided asthma medication to last until the next Treatment Visit (rescue Ventolin for all subjects, Pulmicort Flexhaler 180 µg or 360 µg for those subjects who were on ICS or ICS/LABA before study entry)

- Perform post-dose vital signs assessments (see Section 5.2.2) before the subject leaves the clinic

4.2.3 Visits 3, 4, and 5 (Treatment Periods 2, 3, and 4)

The following should be performed before any other activities:

- Confirm eligibility criteria (see Section 3.1 and Section 3.2)

- Review concomitant medications

- Confirm acceptable MDI device technique

Then the following activities are to be performed:

- Perform pre-dose vital signs assessments (see Section 5.2.2)
- Perform pre-dose spirometry assessments (see Section 5.1.2), [redacted]
- Dispense study drug (see Section 4.2.1) based on subject treatment assignment information from IWRS
- Perform post-dose spirometry assessments (see Section 5.1.2)

The following will be performed after the final (6-hour post-dose) spirometry test:

- Record AEs (if any)
- Schedule the next Treatment Visit, allowing for a Washout Period of 3 to 7 days.
- Assure that the subject has enough Sponsor-provided asthma medication to last until the next Treatment Visit (rescue Ventolin for all subjects, Pulmicort Flexhaler 180 µg or 360 µg for those subjects who were on ICS or ICS/LABA before study entry)
- Perform post-dose vital signs assessments (see Section 5.2.2) before the subject leaves the clinic

4.2.4 Visit 6 (Treatment Period 5)

- Confirm eligibility criteria (see Section 3.1 and Section 3.2)
- Review concomitant medications
- Confirm acceptable MDI device technique
- Perform pre-dose vital signs assessments (see Section 5.2.2)
- Perform pre-dose spirometry assessments (see Section [redacted])
- Dispense study drug (see Section 4.2.1) based on subject treatment assignment information from IWRS
- Perform post-dose spirometry assessments (see Section 5.1.2)

The following will be performed after the final (6-hour post-dose) spirometry test:

- Conduct a complete physical examination (see Section 5.2.1)

- Obtain a 12-lead ECG (see Section 5.2.4)
- Obtain clinical laboratory blood samples (see Section 5.2.3)
- Record AEs (if any)
- Collect all unused Sponsor-provided asthma medication (Sponsor-provided Ventolin and Pulmicort Flexhaler, if applicable)
- Schedule the follow-up telephone call (see Section 4.3.1)
- Perform post-dose vital signs assessments (see Section 5.2.2) before the subject leaves the clinic
- Return subjects to their pre-study asthma maintenance medication regimen or other appropriate asthma medications

4.2.5 Premature Study Withdrawal Visit

See Section 4.3.2. The following activities should occur at the Premature Discontinuation Visit:

- Review concomitant medications
- Perform vital signs assessments (see Section 5.2.2)
- Conduct a complete physical examination (see Section 5.2.1)
- Obtain clinical laboratory blood samples (see Section 5.2.3)
- Obtain a 12-lead ECG (see Section 5.2.4)
- Record AEs (if any)
- Collect all unused Sponsor-provided asthma medication (Sponsor-provided Ventolin and Pulmicort Flexhaler, if applicable)
- Return subjects to their pre-study asthma maintenance medication regimen or other appropriate asthma medications
- Schedule the follow-up telephone call (see Section 4.3.1)

4.3 Follow-up period

4.3.1 Follow-up telephone call

Subjects will be contacted by study personnel through a telephone call 3 to 7 days after the last dose of study drug to assess AEs and SAEs, if any.

4.3.2 Premature withdrawal from the study

Complete the end of treatment form of the eCRF and record the reason for premature study withdrawal. The following categories should be used to describe these events in the eCRF:

- Subject discretion (document reason)
- Investigator considers it to be in the best interest of the subject
- AEs
- Administrative reasons (eg, early termination of the study)
- Subject lost to follow-up
- Major protocol deviation
- Death
- Protocol-specified criteria such as use of prohibited medications (refer to Section 7.7.3).

5. STUDY ASSESSMENTS

The iDatafax system will be used for data collection and query handling. 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.

5.1 Efficacy assessments

Efficacy will be assessed by PFTs. Forced expiratory spirometry for derivation of FEV_1 as defined in ATS/ERS guidelines will be performed in accordance with ATS criteria (Appendix A) using a spirometer that meets or exceeds minimum performance recommendations of the ATS (Appendix B).

5.1.1 Standardization of spirometry collections

To standardize spirometry, all sites will be provided with identical spirometry systems [redacted] with customized, study-specific software. Every effort will be made to provide all sites with standardized spirometry equipment. The volume accuracy of the spirometer is to be checked daily with appropriate documentation in a calibration log prior to the conduct of PFTs on each test day.

The volume accuracy of the spirometer is checked using a 3 L syringe across 3 flow ranges (ie, low, medium, and high flows), with temperature and barometric pressure correction. The calibration syringe must meet ATS specifications and not be used beyond the expiry date. Required accuracy is ±3% (ie, 3.09 L to 2.91 L; ATS/ERS). The results will be printed and maintained in a calibration log, which will be monitored for compliance during the monitoring visits (Appendix B).

All study staff responsible for performing PFTs will receive standardized training at an Investigator meeting. All technicians are required to demonstrate proficiency in the use of the equipment and the ability to perform technically acceptable PFTs (ATS criteria) prior to performing PFTs on study subjects (Miller et al 2005). After each test is performed, the spirometry software will provide immediate feedback to the technician indicating whether the effort meets ATS acceptability and repeatability standards (Appendix B). All PFT testing will be stored electronically. After completion of testing, the study staff will electronically transmit the spirometric measurements for centralized quality assurance review [redacted]. Feedback on the quality of the measurements will be provided to the investigational site and to the Sponsor or designee for central data management.

5.1.2 Assessment of FEV_1

Spirometry will be conducted at all visits except the Premature Discontinuation Visit (when applicable).

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) will be performed and the 2 best efforts that meet the ATS/ERS acceptability and reproducibility criteria will be recorded. The best efforts will be based on the highest FEV_1. The average of these 2 assessments will be used to calculate the screening FEV_1.

[redacted]At all Treatment Visits (Visits 2, 3, 4, 5, and 6), spirometry will be conducted 60 minutes and 30 minutes before study drug administration. The average of these 2 assessments will be used to calculate morning pre-dose FEV_1.

Following study drug administration at each visit, spirometry will be obtained at 5, 15, 30, 45, 60, 120, 180, 240, 300, and 360 minutes post-dose. Three tests will be performed at each timepoint. The highest value at each timepoint will be used for these post-dose assessments.

5.1.3 Characterization of reversibility

Reversibility to Ventolin will be evaluated at Visit 1, 1a, and/or 1b. Subjects must demonstrate reversibility to Ventolin to be randomized in 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 and that short-acting bronchodilators were not administered within 6 hours of testing

2. Perform pre-bronchodilator PFTs at 30 minutes before administration of Ventolin

3. Administer 2 actuations of Ventolin (90 µg per actuation; total 180 µg)

4. Perform post-bronchodilator PFTs 30 minutes after the administration of Ventolin.

Reversibility will be a comparison of the best FEV_1 effort obtained at 30 minutes pre-bronchodilator to the best FEV_1 effort obtained at 30 minutes post-bronchodilator following administration of Ventolin. A subject is considered reversible to Ventolin if the improvement in FEV_1 at 30 minutes post-Ventolin is ≥15%.

[redacted]

5.2 Safety assessments

Safety will be assessed by vital signs, ECGs, and clinical laboratory tests, in addition to recording AEs.

5.2.1 Medical/surgical history and physical examination

Medical and surgical history will be collected at Visit 1. A complete physical examination will be performed at Visits 1 and 6 or the Premature Discontinuation Visit, as applicable.

A complete physical examination will include the following: general appearance, skin, head, eyes, ears, nose, throat, neck (including thyroid), lymph nodes, chest, heart, abdomen, extremities, and nervous system. Additionally, weight, assessed in ordinary indoor clothing with shoes off, and height will be recorded at Visit 1 only (Table 1).

5.2.2 Vital signs

At all study visits (Visits 1 to 6 and the Premature Discontinuation Visit, if applicable), heart rate (HR), systolic blood pressure (SBP), and diastolic blood pressure (DBP) will be assessed. At all Treatment Visits, vital signs will be assessed pre-dose and post-dose before the subject

leaves the clinic. Heart rate, SBP and DBP will be assessed after the subject is supine or seated for 5 minutes. If, in the opinion of the Investigator, a clinically significant vital sign 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 (see Section 6.1).

5.2.3 Clinical laboratory safety assessments

Blood will be collected for clinical laboratory testing at Visit 1, Visit 6 (post-dose), and during the Premature Discontinuation Visit, if applicable.

Subjects will be in a seated or supine position during blood collection. Clinical laboratory tests for this study are listed in Table 4.

Approximately 10 mL of blood will be collected per subject during the study. The exact blood volume collected may vary depending on laboratory procedures. However, it will not exceed 15 mL per subject during the study.

Clinical safety laboratory tests will be analyzed by a central laboratory according to standardized, validated assays. The laboratory will supply detailed procedures for the preparation and collection of blood samples along with all containers needed for their collection. Blood sample volumes will meet the laboratory's specification. Sites must evaluate clinical laboratory data before the subject is randomized.

Table 4. List of Laboratory Tests

Hematology	
Hemoglobin	Platelet count
Hematocrit	Mean corpuscular hemoglobin
White blood cell count with differential	Mean corpuscular hemoglobin concentration
Red blood cell count	Mean corpuscular volume
Clinical chemistry	
Liver enzyme and other liver function tests	**Other clinical chemistry**
Alanine aminotransferase	Albumin
Aspartate aminotransferase	Blood urea nitrogen
Alkaline phosphatase	Calcium
Bilirubin, total	Chloride
Gamma-glutamyl transferase	Cholesterol
	Bicarbonate
	Creatinine
	Glucose
	Magnesium
	Potassium
	Phosphate
	Protein, total
	Sodium
	Triglycerides
	Urea
Other tests:	
β-hCG test for pregnancy[a]	
Creatinine clearance will be estimated at Screening only. The CKD-EPI formula will be used for subjects >18 years old, and the Schwartz equation will be used for subjects ≤18 years old (Schwartz et al 1976).	

Abbreviations: CKD-EPI=Chronic Kidney Disease Epidemiology Collaboration.

[a] Serum β-hCG will be assessed in all women of childbearing potential at Visit 1. Urine β-hCG test will be performed at Visit 2 before randomization.

5.2.4 12-lead ECG

A single 12-lead ECG will be obtained at Visit 1, post-study drug dosing at Visit 6, and during the Premature Discontinuation Visit, if applicable.

To standardize ECG collection, all sites will be provided with identical ECG equipment [redacted] with customized study-specific software on a laptop. All study staff responsible for performing ECG collection will receive identical, detailed training at the Investigator meeting as well as site-phone training sessions. Each site is required to demonstrate proficiency in the use of the equipment and the ability to perform technically acceptable ECGs before performing testing on study subjects. After each test is performed, the site will electronically transfer the ECG data for centralized quality assurance review [redacted] Feedback on the quality of the ECGs will be provided to the investigational site via a site qualification form. Sites must evaluate a subject's ECG data before the subject is randomized.

The ECG parameters to be assessed include HR, PR interval, QRS axis, QRS interval, and QT/Fridericia-corrected QT (QTcF) interval. The QT intervals and calculated QTcF intervals will be reviewed and checked for gross inaccuracies by the Investigator or designated ECG reviewer.

5.3 Other assessments – not applicable

5.4 Pharmacokinetics – not applicable

5.5 Pharmacodynamics – not applicable

5.6 Genetics – not applicable

5.7 Biomarker analysis - not applicable

6. SAFETY REPORTING AND MEDICAL MANAGEMENT

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

6.1 Definition of AEs

The following definitions of terms are guided by the International Conference for Harmonisation (ICH) and the US Code of Federal Regulations (CFR) (21 CFR 312.32) and are included herein.

An AE is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An AE (also referred to as an adverse experience) can be any unfavorable and unintended sign (eg, an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, without any judgment about causality. An AE can arise from any use of the drug (eg, off label use, use in combination with another drug) and from any route of administration, formulation, or dose, including an overdose.

Adverse events include, but are not limited to:

- any symptom or condition not previously reported by the subject (medical history)
- an exacerbation of a pre-existing symptom or condition
- a significant increase in frequency or intensity of a pre-existing episodic event or condition
- a drug interaction
- a condition first detected or diagnosed after study drug administration even though it may have been present prior to the start of the study

An AE does not include:

- medical or surgical procedures (eg, surgery, endoscopy, tooth extraction, blood transfusion); the condition that led to the procedure is an AE (eg, bleeding esophageal varices, dental caries)
- overdose of either study drug or concurrent medication without any clinical signs or symptoms
- non-clinically significant abnormal laboratory values (if accompanied by signs/symptoms, the signs or symptoms are considered an AE)

6.2 Definitions of SAE

An AE is considered "serious" if, in the view of the Investigator or Sponsor, it results in any of the following outcomes:

- death
- a life-threatening AE
- inpatient hospitalization or prolongation of existing hospitalization
- a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- a congenital anomaly/birth defect

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood

dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Hospitalization for a pre-existing condition, including an elective procedure, which has not worsened, does not constitute an SAE.

An AE is considered "life-threatening" if, in the view of the Investigator or Sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse reaction or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

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

6.3 Recording of AEs

6.3.1 Performing AE assessments

The Investigator is responsible for promptly documenting and reporting all AEs observed during the study in the subject's eCRF and on the AE Reporting Form. If the AE is unexpected, the Investigator should report the AE immediately to the Sponsor. In addition, certain AEs (as described in Section 6.2) are classified as 'serious' and must be reported no later than 24 hours after the Investigator recognizes/classifies the event as an SAE to the Sponsor or its designee.

In the case of SAEs, after discussing the details of the event, the Investigator and the Medical Monitor may discontinue the subject from randomized study drug.

6.3.2 Pre-randomization AEs

Adverse events occurring from the time the subject signs informed consent until the subject is randomized will be summarized as medical history and not as an AE unless the event meets the definition of an SAE as defined in Section 6.2.

6.3.3 AEs based on signs and symptoms

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.

6.3.4 AEs based on examinations and tests

Many laboratory abnormalities observed during the course of a study will be included under a reported AE describing a clinical syndrome (eg, elevated blood urea nitrogen and creatinine in the setting of an AE of renal failure, or decreased hemoglobin in a case of bleeding esophageal varices). Isolated laboratory abnormalities should be reported as AEs if they are considered to be clinically significant by the Investigator.

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

Criteria for a "clinically significant" laboratory abnormality are:

- a laboratory abnormality that leads to study drug dose suspension or discontinuation
- a laboratory abnormality that results in any therapeutic intervention (ie, concomitant medication or therapy)
- Any other laboratory abnormality judged by the Investigator to be of any particular clinical concern (eg, significant fall in hemoglobin not requiring transfusion)

For laboratory abnormalities that do not meet the above criteria but are outside of the normal reference range, the Investigator should indicate whether the value is clinically significant or not clinically significant for the subject.

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.

Paradoxical bronchospasm will be monitored [redacted].

6.3.5 Disease under study

Symptoms of the disease under study are those which might be expected to occur as a direct result of the subject's asthmatic condition (eg, wheeze, breathlessness, cough). Events that are unequivocally due to the disease under study should not be reported as an AE during the study unless they meet SAE criteria or lead to discontinuation of study drug.

6.3.6 Severity

The Investigator must categorize the severity of each AE according to the following guidelines:

Mild: Associated with no limitation of usual activities or only slight discomfort; generally not requiring alteration or cessation of study drug administration; and/or not needing therapeutic intervention.

Moderate: Associated with limitation of usual activities or significant discomfort; generally requiring alteration or cessation of study drug administration; and/or requiring therapeutic intervention.

Severe: Associated with inability of subject to carry out usual activities or very marked discomfort; considered to be life-threatening; resulting in significant disability or incapacity; and requiring therapeutic intervention.

6.3.7 Relationship to study drug

The Investigator will assess causal relationship between the study drug and each AE, and answer 'yes' or 'no' to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by the study drug?'

For SAEs causal relationship will also be assessed for other medication and study procedures. 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 C.

6.4 Reporting of SAEs

In agreeing to the provisions of this protocol, the Investigator accepts all legal responsibilities for AE identification, documentation, grading, assignment of causality, and prompt notification of SAEs to the Sponsor or designee. All SAEs must be reported to the Sponsor or designee no later than 24 hours after the Investigator recognizes/classifies the event as an SAE. All SAEs should be documented and reported using the eCRF. At a minimum, a description of the event and the Investigator's judgment of causality must be provided at the time of the initial report using the appropriate form (eg, SAE Report Form). After the initial report, as necessary, the Investigator must provide any additional information on an SAE to the Sponsor or designee within 2 working days after receiving the information. Follow up information will be a detailed written report that may include copies of hospital records, case reports, autopsy reports, and other pertinent documents.

For subjects discontinuing study drug, all AEs/SAEs will be collected through the follow-up telephone call.

Post-treatment SAEs following the last dose of study drug must be reported to the Sponsor as described in Section 6.4.3.

The Investigator is responsible for continuing to report any new or relevant follow-up information that s/he learns about the SAE.

6.4.1 Supplemental investigations of SAEs

The Investigator and supporting personnel responsible for subject care should discuss with the Sponsor Medical Monitor or designee any need for supplemental investigations of SAEs. If additional assessments are conducted, results must be reported to the Sponsor. If a subject dies during study participation and if a post mortem examination is performed, a copy of the autopsy report should be submitted to the Sponsor.

6.4.2 Post-study follow-up of AEs

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

6.4.3 Notification of post-treatment SAEs

Investigators are not obligated to actively follow subjects after completion of the study. However, if the Investigator becomes aware of a post-treatment SAE occurring within 3 to 7 days following the last dose of study drug, the SAE must be reported to the Sponsor, whether or not the event is attributable to study drug. All SAEs must be reported to the Sponsor no later than 24 hours after the Investigator recognizes/classifies the event as an SAE.

6.4.4 IRB notification of SAEs

The Investigator is responsible for promptly notifying her/his IRB of all SAEs, including any follow-up information, occurring at their site and any SAE regulatory report, including any follow-up reports, received from the Sponsor. Documentation of IRB submission must be retained for each safety report. The Investigator is also responsible for notifying the Sponsor if their IRB requires revisions to the ICF or other measures based on its review of an SAE Report.

6.4.5 Health Authority Safety Reports

The Sponsor or its representatives will submit a safety report to the appropriate regulatory agencies for any suspected adverse reaction that is both serious and unexpected within the timeframe specified by each regulatory agency.

The Sponsor or its representatives will send copies of each submitted safety report to Investigators actively participating in the Sponsor's clinical studies. Safety reports must also be submitted to the appropriate IRBs as soon as possible. Documentation of submission to the IRB must be retained for each safety report.

6.5 Overdose

An overdose is defined as any dose greater than the highest dose investigated in this study that results in clinical signs and symptoms. In the event of a study drug overdose, the Investigator should use their best clinical judgment in treating the overdose, and the Sponsor's Medical Monitor should also be contacted. Investigators should refer to the relevant document(s) for detailed information regarding warnings, precautions, contraindications, AEs, and other significant data pertaining to the study drug(s) being administered. Such document(s) may include but are not limited to the Investigator's Brochure for AS MDI and approved product labeling for open-label products.

6.6 Pregnancy

Any pregnancy that occurs from Visit 1 until study completion must be reported to the Sponsor. The pregnancy must be followed up to determine the outcome (including premature termination) and status of mother and child.

6.6.1 Maternal exposure

If a subject becomes pregnant during the course of the study, the study drug should be discontinued immediately.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/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 abnormality) should be followed up and documented even if the subject was withdrawn from the study.

If any pregnancy occurs in the course of the study, then the Investigator or other site personnel should inform the appropriate Sponsor representatives immediately but **no later than 24 hours** of when he or she becomes aware of it.

Pregnancy should be recorded on a paper Pregnancy Report Form and reported by the Investigator to the Sponsor or designee. Pregnancy follow-up should be recorded on the same Pregnancy Report Form and should include possible relationship to the study drug in response to the pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

The same timelines apply when outcome information is available.

6.6.2 Paternal exposure

Male subjects who are sexually active must agree to use a double barrier method of contraception (condom with spermicide) from the first dose of randomized treatment until 2 weeks after their last dose, and must not donate sperm during their study participation period. If a male subject's partner becomes pregnant during the course of the study, it must be reported to the Sponsor within 24 hours of the Investigator learning of its occurrence.

6.7 Medication Error

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

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 subject.

Medication error includes situations where an error:

- occurred
- was identified and intercepted before the subject 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 subject
- drug not administered as indicated, for example, 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 subject received the medication (excluding IWRS errors)
- wrong drug administered to subject (excluding IWRS errors)

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

- errors related to or resulting from IWRS, including those which lead to one of the above listed events that would otherwise have been a medication error
- subject accidentally missed drug dose(s) (eg, forgot to take medication)
- accidental overdose (will be captured as an overdose)
- subject failed to return unused medication or empty packaging
- errors related to background and rescue medication, or standard of care medication in open label studies

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

If a medication error occurs in the course of the study, then the Investigator or other site personnel informs the appropriate Sponsor representatives immediately but **no later than 24 hours** of when he or she becomes aware of it.

6.8 Management of study drug-related toxicities – not applicable

7. INVESTIGATIONAL PRODUCT AND OTHER TREATMENTS

7.1 Identity of investigational products

In this protocol, "study drug" refers to an active ingredient or placebo being tested or used as a reference in this study. Study drugs used in this study are summarized in Table 5. Instructions for priming and use are provided in Appendix D.

AS MDI and Placebo MDI are manufactured and supplied by the Sponsor. Placebo MDI is manufactured in the image of the active test product. For open-label Proventil (active control), MDIs will be provided from commercial supplies. Manufacturer's instructions for study drug administration will be provided.

Table 5. Randomized Study Drugs

Product Name and Dose	Product Strength	Manufacturer	Dosage Form/ Fill Count	Administration
AS MDI 90 µg	AS MDI 45 µg/ actuation[a]	Pearl	MDI/ 120 actuations	Taken as 2 actuations
AS MDI 180 µg	AS MDI 90 µg/ actuation[b]	Pearl	MDI/ 120 actuations	Taken as 2 actuations
Placebo MDI	Formulation does not contain an active ingredient	Pearl	MDI/ 120 actuations	Taken as 2 actuations
Proventil 90 µg	Albuterol 90 µg/actuation[b]	Merck Sharp & Dohme Corp.	MDI/ 200 actuations	Taken as 1 actuation
Proventil 180 µg	Albuterol 90 µg/actuation[b]	Merck Sharp & Dohme Corp.	MDI/ 200 actuations	Taken as 2 actuations

Note: All study drugs will be administered by oral inhalation.
[a] Each inhalation contains 54 µg albuterol sulfate corresponding to 45 µg albuterol base per actuation
[b] Each inhalation contains 108 µg albuterol sulfate corresponding to 90 µg albuterol base per actuation

For the Sponsor-provided background asthma medication (Ventolin and Pulmicort Flexhaler) and Ventolin for reversibility testing, commercial dry powder inhalers/MDIs with dose counters and manufacturer's instructions for use will be provided. These medications are listed in Table 6.

Table 6. Other Sponsor-provided Study Medications

Product Name	Product Strength	Manufacturer	Dosage Form/ Fill Count	Administration
Pulmicort Flexhaler	Budesonide 180 µg	AstraZeneca	DPI/ 120 actuations	1 or 2 inhalations BID, as directed at Visit 1
Ventolin	Albuterol 90 µg/actuation[a]	GlaxoSmithKline	MDI/ 200 actuations	Taken as directed for reversibility testing (Visits 1, 1a, or 1b) and as needed for symptoms during the Screening and randomized Treatment Periods

Abbreviation: DPI=dry powder inhaler.
Note: All study drugs will be administered by oral inhalation.
[a] Each inhalation contains 108 µg albuterol sulfate corresponding to 90 µg albuterol base per actuation.

7.2 Dose and treatment regimens

Each of the 5 Treatment Visits will include 1 of the following single-dose treatments, based on the subject's randomized treatment assignment:

- AS MDI 90 µg (2 actuations of 45 µg/actuation)
- AS MDI 180 µg (2 actuations of 90 µg/actuation)
- Placebo MDI (2 actuations)
- Proventil 90 µg (1 actuation of 90 µg/actuation)
- Proventil 180 µg (2 actuations of 90 µg/actuation)

7.2.1 Randomized study drug

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 component ID number. Confirm that the identifier given by IWRS and the ID number written on the label are the same. The foil overwrap is labeled with a 2-part label. Write the subject number and treatment visit number on each part of the 2-part label. The tear-off part of the label is to be placed onto the IWRS confirmation report.

All MDIs must be primed by study personnel before the first use. Priming involves 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.

AS MDI must be primed in a separate room from the subject 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, and therefore to ensure consistency in the administration for all subjects, the MDIs are to be gently shaken (5 to 10 seconds) immediately before each actuation (inhalation).

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.

Each dose will consist of 2 actuations from the MDI. See Appendix D for instructions on the administration of AS MDI and Placebo MDIs.

Open-label Proventil

Individual Proventil MDIs will be contained in an individual visit treatment box. The visit treatment box will have a 2-part label with a component ID number. Confirm that the identifier given by IWRS and the component ID number written on the label are the same. Write the subject number and treatment visit number on each part of the 2-part label. The tear-off part of the label is to be placed onto the IWRS confirmation report.

Proventil should be primed by study personnel (in a separate room from the subject treatment area) per manufacturer's instructions before administering to subject. Since Proventil is primed in a separate room before dosing, there is a possibility that there may be a delay between priming and dosing, and therefore to ensure consistency in the administration for all subjects, the MDIs are to be gently shaken (5 to 10 seconds) immediately before each actuation (inhalation).

Each dose will consist of 1 or 2 actuations from the MDI. See Appendix D for the manufacturer's instructions on the administration of Proventil.

7.2.2 Sponsor-provided background asthma therapies

Ventolin

Open-label Ventolin will be provided by the Sponsor and stored in a secured location within the clinic or pharmacy facilities. Ventolin should be stored at room temperature by the subject. Ventolin should be primed per manufacturer's instructions before dispensing to subject. See Appendix D for the manufacturer's instructions on the administration of Ventolin. Study personnel will record the number on the dose counter at the time of dispensing (following priming) and upon return.

Pulmicort Flexhaler

Open-label Pulmicort Flexhaler 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 subject. Pulmicort Flexhaler should be primed per manufacturer's

instructions before dispensing to subject. See Appendix D for the manufacturer's instructions on the administration of Pulmicort Flexhaler. Study personnel will record the number on the dose counter at the time of dispensing (following priming) and upon return.

7.3 Labeling

AS MDI and Placebo MDI will be packaged by the Sponsor. Open-label Proventil (randomized study drug), Ventolin for rescue and reversibility testing, and Pulmicort Flexhaler will be supplied as commercially sourced open-label MDIs.

7.3.1 Primary packaging and labeling

Labels will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines. The labels will fulfil GMP Annex 13 requirements for labeling.

Blinded supplies (AS MDI and Placebo MDI)

Each MDI will be labeled with a 1-part label. The foil pouch will be labeled with a 1-part label. A 2-part label will be affixed to the carton holding the foil.

Open-label supplies (Proventil)

Open-label Proventil will be provided as individually labeled MDIs. Each MDI will contain a single label.

Both single and 2-part labels will be printed with black ink and may include the following text:

• Packaging Lot Trace ID #	• Dosing Instructions
• Space for entry of screening #	• Storage Conditions
• Component ID #	• Compound ID - Protocol #
• Space for entry of randomization #	• Country regulatory requirements
• Fill Count & Dosage Form	• Sponsor address (if applicable)
• Space for entry of Interval ID (Visit # only)	• Translation Key (if applicable)
• Re-evaluation/Expiration date (if applicable)	

7.3.2 Secondary packaging and labeling information (box)

AS MDI, Placebo MDI, open-label Proventil, open-label Ventolin, and open-label Pulmicort Flexhaler supplies will be provided as 1 MDI per box. Box configuration is subject to change due to packaging constraints.

Each box will be labeled with a 2-part panel label printed with black ink and may include the following text:

- Packaging Lot ID #
- Space for entry of screening #
- Component ID #
- Space for entry of randomization #
- Kit Contents (1 MDI)
- Space for entry of Interval ID
- Re-evaluation date (if applicable)
- Dosing Instructions (if applicable)
- Storage Conditions
- Compound ID - Protocol #
- Country regulatory requirements
- Sponsor address (If applicable)
- Translation Key (If applicable)

7.4 Storage

All study drugs and Sponsor-provided medication should be kept in a secure place under appropriate storage conditions. The investigational product label specifies the appropriate storage. Commercially sourced medications (Proventil, Ventolin, and Pulmicort Flexhaler) should be stored as indicated on the respective product label.

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.

7.5 Compliance

The time of administration of randomized study drug will be recorded in the appropriate sections of the eCRF.

7.6 Accountability

Study personnel will have access to an IWRS to allocate subjects, to assign drug to subjects, and to manage the distribution of clinical supplies. Clinical supplies will be packaged according to a component schedule generated by the Sponsor or designee. Each person accessing the IWRS must be assigned an individual unique personal ID number (PIN). They must use only their assigned PIN to access the system and they must not share their assigned PIN with anyone.

The study drug provided for this study will be used only as directed in the clinical study protocol. Under no circumstances will the Investigator(s) allow the study drug to be used other than as directed by this protocol.

Investigational clinical supplies must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the Investigator and designated assistants have access. Storage conditions for the clinical supplies

should be observed, monitored, and documented. Clinical supplies are to be dispensed only in accordance with the protocol. The Investigator is responsible for keeping accurate records of the clinical supplies received from the Sponsor, the amount dispensed to and returned by the subjects, and the amount remaining at the conclusion of the study. Study drug should be handled in accordance with Good Pharmacy Practices. The Clinical Monitor should be contacted with any questions concerning investigational products where special or protective handling is indicated. At the end of the study, all clinical supplies including partial and empty containers must be returned as directed by the Sponsor.

Sites should check with the Sponsor representative for appropriate documentation that must be completed for drug accountability.

The Investigator or designated assistant should not open individual clinical supply containers until all pre-dose assessments have been completed and the subject is eligible to be randomized/continue with the study. Any deviation from this must be discussed with the Clinical Monitor.

For each subject, all used study drug materials will be collected. Used subject supplies will be kept at room temperature in a secure and locked cabinet until returned to the Sponsor or designee. **Note:** Used study drug will be stored separately from unused study drug.

7.7 Concomitant and other treatments

7.7.1 Prior medications

All prescription and over-the-counter medications, as well as any herbal or vitamin supplements, taken by the subject 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 subject's and site's ability.

Some subjects eligible for this study will be on regular inhaled asthma maintenance therapy defined as an ICS with or without a LABA with a stable dose for at least 30 days prior to Visit 1. The permitted total daily ICS dosage to qualify ICS usage for the 30 days prior to Visit 1, along with the assigned dose for Sponsor-provided Pulmicort Flexhaler, is defined in Table 7.

Table 7 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	100 to ≤200	360
Beclomethasone	>200 to ≤400	720
Budesonide	200 to ≤400	360
Budesonide	>400 to ≤800	720
Ciclesonide	80 to ≤160	360
Ciclesonide	>160 to ≤320	720
Fluticasone furoate	100	360
Fluticasone furoate	200	720
Fluticasone propionate	100 to ≤250	360
Fluticasone propionate	>250 to ≤500	720
Mometasone furoate	110 to ≤220	360
Mometasone furoate	>220 to ≤440	720
Triamcinolone acetonide	400 to ≤1000	360
Triamcinolone acetonide	>1000 to ≤2000	720

7.7.2 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 9 or Table 10). All concomitant medications taken during the study will be recorded on the Concomitant Medications eCRF page with indication, total daily dose, route of administration, and dates of drug administration. Any additions, deletions, or changes in the dose of these medications while in the study should be entered in the eCRF. Subjects should also be instructed to contact the Investigator if they develop any illnesses, especially those requiring medicinal intervention.

7.7.2.1 Required concomitant medications

Subjects who were receiving a regularly scheduled ICS or ICS/LABA before study entry will be switched to Pulmicort Flexhaler 180 µg or 360 µg BID, and LABA (if applicable) will be discontinued (Table 7). These subjects will continue to use Sponsor-provided Pulmicort Flexhaler 180 µg or 360 µg BID, as assigned at Visit 1, throughout the Screening Period and for the remainder of the study during both the randomized Treatment Periods and Washout Periods.

No other asthma medications are allowed for the remainder of the study, except for Sponsor-provided Ventolin to be used as needed for rescue.

7.7.2.2 Allowed allergy medications

Table 8 lists allergy medications that are allowed as long as the subject has been on a stable dose for at least 30 days before Visit 1 and remains on a stable dose throughout the study.

Table 8 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.

7.7.3 Prohibited medications

7.7.3.1 Prohibited asthma and allergy medications and washout periods

Specific prohibited asthma and allergy medications are listed in Table 9. Subjects taking any of these prohibited medications are required to stop taking them at Visit 1 and are required to attend Visit 1a for reversibility testing. The required washout period for each medication before reversibility testing is shown in Table 9.

Table 9 Prohibited Asthma and Allergy Medications That Must be Discontinued at Visit 1 and Required Washout Period Prior to Visit 1a

Medication	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[c]	
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.

[c] In combination with an ICS.

7.7.3.2 Prohibited non-asthma and non-respiratory medications

Subjects requiring medications presented in Table 10 are prohibited from participating in this study. Subjects 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 course of the study. If subjects require any of the prohibited medications listed in Table 10, the Investigator should discuss with the monitor the suitability of the subject continuing study drug.

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 subject requires a systemic corticosteroid to treat an asthma worsening or asthma exacerbation, the subject will be discontinued from study drug and withdrawn from the study.

Table 10 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
Cardiac anti-arrhythmics (Class Ia, III)	7 days, unless amiodarone, then 3 months
Anticonvulsants for seizure disorder[c]	Allowed if stable dose for 12 months and free of seizures for 1 year
Antipsychotic drugs[d]	30 days
Tricyclic antidepressants[d]	14 days
Monoamine oxidase inhibitors	14 days
Antitumor necrosis factor α antibodies (eg, infliximab and any other members of this class of drugs)	30 days or 5 half-lives, whichever is longer
Monoclonal antibodies[e]	30 days or 5 half-lives, whichever is longer
Protease inhibitors (eg, ritonavir)	30 days

Note: Benzodiazepines are not exclusionary. Serotonin norepinephrine reuptake inhibitors and selective serotonin reuptake inhibitors are not excluded as long as the subject has been on a stable dose for at least 30 days before Visit 1 and throughout the Screening and Treatment Phase, and the dose does not exceed the maximum recommended.

[a] Subjects 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 subject meets all of the ECG inclusion criteria and none of the ECG exclusion criteria, and if, in the opinion of the Investigator, there are no safety concerns for the subject 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] 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 subject has been on a stable dose for at least 6 weeks.

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

7.7.4 Other concomitant treatment

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

8. STATISTICAL ANALYSES

This study will be conducted as a 5-period, 5-treatment Williams (Williams 1949) crossover design evaluating the following 5 treatments:

- AS MDI 90 µg (2 actuations of 45 µg/actuation)
- AS MDI 180 µg (2 actuations of 90 µg/actuation)
- Placebo MDI (2 actuations)
- Proventil 90 µg (1 actuation of 90 µg/actuation)
- Proventil 180 µg (2 actuations of 90 µg/actuation)

The primary objective of this study is to determine the dose of albuterol delivered from AS MDI that is comparable to Proventil. This design utilizes 10 treatment sequences.

8.1 Statistical considerations

Analyses will be performed by the Sponsor or its representatives. All analyses will be specified in a detailed statistical analysis plan (SAP) that will include table and data listing shells with mock graphical representations. The SAP will be signed before database lock and unblinding.

8.2 Sample size estimate

Power calculations were based on the properties of the primary endpoint, the change from baseline in FEV_1 AUC_{0-6}. Randomization of 70 subjects in order to achieve at least 64 subjects completing the study will provide >95% overall probability to demonstrate superiority of each treatment relative to Placebo MDI assuming a minimum detectable difference (active–Placebo MDI) of 100 mL, within-subject standard deviation of 115 mL, and 2-sided 5% level test. The estimate of the within-subject standard deviation was obtained from a 5-treatment, 5-period dose-ranging study to evaluate albuterol dry powder inhaler and HFA in subjects ages 12 and older with persistent asthma (NCT01058863).

8.3 Definitions of analysis sets

The following analysis sets are defined in this study:

- The **Intent-To-Treat (ITT) analysis set** is defined as all subjects who are randomized to treatment and receive at least 1 dose of the study treatment. Subjects will be analyzed in each period according to the treatment they were assigned to per the randomization scheme (Note that a subject who used a study treatment but took less than 1 full dose of treatment will qualify for this analysis set).

- A **Modified ITT (mITT) analysis set** is a subset of the ITT analysis set including subjects who received treatment and have post-treatment efficacy data from at least 2 Treatment Periods. Data judged to be impacted by major protocol deviations will be determined prior to unblinding and excluded per the statistical protocol deviation plan. Statistical tabulations and analyses will be by randomized treatment, but data obtained after subjects receive an incorrect treatment will be excluded from the affected periods.

- The **Safety analysis set** is defined as all subjects who are randomized to treatment and receive at least 1 dose of the study treatment. Subjects will be analyzed according to treatment received rather than per the randomization scheme.

- The **Not Randomized analysis set** is defined as subjects who did not receive a randomization number and therefore did not receive a dose of study treatment (eg, subjects who were screen failures or stopped participation before being randomized).

Demographics and baseline characteristics will be summarized for the ITT, mITT, and Safety analysis sets. Extent of exposure will be summarized for the Safety analysis set. The Safety analysis set will be used to summarize safety.

Efficacy analyses will be performed for the mITT analysis set. As a sensitivity analysis, the primary endpoint, change from baseline in FEV_1 AUC_{0-6}, will also be analysed using the ITT analysis set.

8.4 Outcome measures for analyses

All efficacy assessments are relative to baseline and will be compared with Placebo MDI and Proventil, and where appropriate, the AS MDI dose levels will be compared. Since pre-dose values are known to be variable and an isolated timepoint may not accurately reflect the true baseline, the following baseline will be used for the statistical analyses of study assessments unless otherwise specified: the mean of available pre-dose values on the first day of each treatment cycle, ie., the mean of pre-dose values at Visits 2, 3, 4, 5, and 6, where the mean of the 60- and 30-minute pre-dose value for each visit is obtained and then the visit means are averaged.

Refer to Section 2 for a complete delineation of efficacy and safety endpoints.

8.5 Methods for statistical analyses

8.5.1 Primary efficacy analysis

The FEV_1 AUC_{0-6} is the area under the curve for the change from baseline in FEV_1 calculated using the trapezoidal rule. 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 FEV_1 AUC_{0-6} will be analyzed using a linear mixed model with a random subject effect. The fixed effects in the model will include treatment, treatment sequence, baseline FEV_1, and period. Analyses will be conducted on the overall study population, and may also be conducted separately within each of the 2 ICS use subgroups (previous ICS use and no previous ICS use before Visit 1).

Superiority comparisons of AS MDI relative to Placebo MDI and Proventil versus Placebo MDI will be conducted first using a dose-ordered approach. A 2-sided alpha level of 0.05 will be employed. Estimated treatment differences and 95% confidence intervals (CIs) will be provided for the superiority comparisons.

If both AS MDI 180 µg and Proventil 180 µg are statistically superior to Placebo MDI, as an exploratory endpoint, the non-inferiority of AS MDI 180 µg versus Proventil 180 µg for FEV_1 AUC_{0-6} will be assessed using a non-inferiority margin of 100 mL. If both AS MDI 90 µg and Proventil 90 µg are statistically superior to Placebo MDI, the non-inferiority of AS MDI 90 µg versus Proventil 90 µg for FEV_1 AUC_{0-6} will also be tested.

Comparisons among the dose levels within a product will also be conducted for exploratory purposes. Estimated treatment differences and 95% CIs will be provided.

8.5.2 Secondary efficacy analysis

The secondary endpoints will be analyzed using a similar approach as that of the primary endpoint. Linear mixed models will be fit with a random subject effect. The fixed effects will include baseline FEV_1, treatment, treatment sequence, and period.

The peak change from baseline in FEV_1 will be calculated using the largest FEV_1 value measured during the 6 hours post-dosing.

The FEV_1 AUC_{0-4} will be calculated in a similar manner as FEV_1 AUC_{0-6}; however, the trapezoidal rule will only be implemented through the 4-hour nominal timepoint. The AUC values will be normalized accordingly.

8.5.3 Other efficacy analysis

Responders will be defined as subjects achieving ≥15% improvement in FEV_1 within 30 minutes after dosing.

The time to onset of response for each individual subject will be defined as the first timepoint for which an increase from baseline FEV_1 of at least 15% is observed within the first 30 minutes post dose.

The duration of response for each subject will be defined as the time from onset of a 15% or greater increase in FEV_1 to the offset of the 15% increase in FEV_1 relative to baseline.

Change from baseline in FEV_1 at each post-dose timepoint will be presented graphically by treatment.

The median values for time to peak FEV_1, time to onset of response, and duration of response will be reported by treatment. The median differences and corresponding Hodges-Lehmann CIs will be presented for pairwise comparisons among the treatments.

The percentages of subjects achieving a 12% and 15% improvement from baseline within 30 minutes post dose will be tabulated by treatment. The odds of being a responder may also be estimated using a generalized mixed effects model.

8.5.4 Type 1 error control

The Type I error rate will be controlled at the 5% level across the superiority comparisons of the primary endpoint, FEV_1 AUC_{0-6}. In general, the superiority of Proventil relative to Placebo MDI will be tested first using a dose-ordered approach. If Proventil 180 µg is superior to Placebo MDI, AS MDI 180 µg will be compared to Placebo MDI. If AS MDI 180 µg is superior to Placebo MDI, the superiority of the 90-µg dose relative to Placebo MDI will be tested. Full details of the procedure will be specified in the statistical analysis plan; however, the totality of the data including comparisons among AS MDI dose levels will be used to select an appropriate dose for AS MDI.

8.5.5 Data validation and transformation

In general, the distribution of spirometry measures is well approximated by a normal distribution. Under some circumstances, however (eg, during an exacerbation unrelated to treatment), extreme and atypical values can arise. Such values have high influence on estimation of variance parameters and on standard errors of fixed effect estimates. The distribution of scaled marginal residuals, and influence statistics will be examined to identify such cases. In the event that a single or small number of such outlying values are found to exist and found to be highly influential, the effects may be ameliorated by either transformation or removal of the outlier. Transformations to be considered may include the logarithmic transformation or normal rank transformations. Where outliers are removed, sensitivity analyses including those values will be reported.

Changes in spirometry measures from baseline, and from timepoint to timepoint will be examined graphically before database lock, and before unblinding, as part of data quality management.

8.5.6 Safety analyses

No formal statistical analysis of safety data is planned. Safety data will be summarized by treatment and listed.

8.5.6.1 AEs

Adverse events occurring during each Treatment Period will be summarized by the number of subjects experiencing an event and tabulated at the level of the Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term. The version of MedDRA current at the time of database lock will be used for the final analysis of data. Tabulations will be broken down by severity, seriousness, AEs leading to discontinuation, and

by relationship to study drug. No hypothesis tests will be performed. Tables will show the overall incidence of AEs and the incidence for each treatment.

8.5.6.2 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.

8.5.6.3 Clinical laboratory measurements

Subjects with out-of-range values will be listed.

8.5.6.4 12-Lead ECGs

Subjects with out-of-range values will be listed.

8.5.7 Handling of missing data

Pre-dose spirometry values will use the average of the non-missing -60 minute and -30 minute values.

For the mITT analyses, FEV_1 AUC_{0-6}, FEV_1 AUC_{0-4}, and peak FEV_1 will be calculated if there is at least 1 non-missing data point during the first 2 hours post-dose.

8.5.8 Statistical software

Data processing, statistical screening, descriptive reporting, and analysis of the efficacy and safety data will be performed using SAS (SAS Institute, Cary, NC, US; Version 9.3 or higher).

9. STUDY AND DATA MANAGMENT BY THE SPONSOR

9.1 Training of study site staff

Before the first subject is entered into the study, a Sponsor representative will review and discuss the requirements of the clinical study protocol and related documents with the investigational staff and train them in any study specific-procedures and study system(s) used.

The Principal Investigator will ensure that appropriate training relevant to the study is given to all of these staff, and that any new information relevant to the performance of this study is forwarded to the staff involved.

The Principal Investigator will maintain a record of all individuals involved in the study (medical, nursing and other staff).

9.2 Monitoring of the study

During the study, a Sponsor representative will have regular contacts with the study site, including visits to:

- provide information and support to the Investigator(s)
- confirm that facilities remain acceptable
- confirm that the Clinical Study Team is adhering to the clinical study protocol, that data are being accurately and timely recorded in the eCRFs, that biological samples are handled in accordance with the laboratory manual, and that study drug accountability checks are being performed
- perform source data verification (a comparison of the data in the eCRFs with the subject's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating subjects. This will require direct access to all original records for each subject (eg, clinic charts)

The Sponsor representative will be available between visits if the Investigator(s) or other staff at the site needs information and advice about the study conduct.

9.2.1 Source data

Refer to the Clinical Study Agreement for location of source data.

9.2.2 Study agreements

The Principal Investigator at each site should comply with all the terms, conditions, and obligations of the Clinical Study Agreement, or equivalent, for this study. In the event of any inconsistency between this clinical study protocol and the Clinical Study Agreement, the terms of clinical study protocol shall prevail with respect to the conduct of the study and the treatment of subjects and in all other respects, not relating to study conduct or treatment of subjects, the terms of the Clinical Study Agreement shall prevail.

Agreements between the Sponsor and the Principal Investigator should be in place before any study-related procedures can take place, or subjects are enrolled.

9.2.3 Archiving of study documents

The Investigator should follow the principles outlined in the Clinical Study Agreement.

9.3 Study timetable and end of study

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

The study may be terminated at individual study sites if the study procedures are not being performed according to Good Clinical Practice (GCP), or if recruitment is slow.

9.4 Data management

Data management of the study will be performed by the Sponsor or designee, and supervised by the Sponsor.

10. ETHICAL AND REGULATORY REQUIREMENTS

10.1 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/GCP, applicable regulatory requirements and the Sponsor's policy on Bioethics and Human Biological Samples.

10.2 Subject data protection

The ICF will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation.

10.3 Ethics and regulatory review

An IRB should approve the final clinical study protocol, the final version of the ICF, the assent form, and any other written information and/or materials to be provided to the subjects. The opinion of the IRB should be given in writing.

The IRB should approve all advertising used to recruit subjects for the study.

The Sponsor will approve any modifications to the ICF that are needed to meet local requirements.

If required by local regulations, the clinical study protocol should be re-approved by the IRB annually.

Before enrollment of any subject into the study, the final clinical study protocol, including the final version of the ICF and assent form, is approved by the national regulatory authority or a notification to the national regulatory authority is done, according to local regulations.

Each Principal Investigator is responsible for providing the IRB with reports of any serious and unexpected adverse drug reactions from any other study conducted with the investigational product. The Sponsor will provide this information to the Principal Investigator so that he/she can meet these reporting requirements.

The head of the study site should seek the opinion of the IRB with respect to the appropriateness of continuing the study at the study site at least once a year when the duration of the study exceeds 1 year. The Principal Investigator should submit progress reports to the IRB via the head of the study site at the time of the clinical study protocol re-approval.

Before enrollment of any subject into the study, the final clinical study protocol, including the final version of the ICF, should be approved by the national regulatory authority with notification provided, according to local regulations. The Sponsor will handle the distribution of any of these documents to the national regulatory authorities.

The Sponsor will provide regulatory authorities, IRB, the head of the study site, and the Principal Investigator with safety updates/reports according to local requirements.

10.4 Informed consent

The Principal Investigator(s) at each study site will:

- ensure each subject is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study
- ensure each subject is notified that they are free to discontinue from the study at any time
- ensure that each subject is given the opportunity to ask questions and allowed time to consider the information provided
- ensure each subject provides signed and dated informed consent before conducting any procedure specifically for the study. If the subject is a minor, the parent or guardian will sign an ICF and the subject will sign an assent form.
- ensure the original, signed ICF (and assent form, as appropriate) is/are stored in the Investigator's study file
- ensure a copy of the signed ICF (and assent form, as appropriate) is/are given to the subject (and the subject's parent or guardian if the subject is a minor)
- ensure that any incentives for subjects who participate in the study as well as any provisions for subjects harmed as a consequence of study participation are described in the ICF that is approved by an IRB

10.5 Changes to the clinical study protocol and ICF/assent form

Study procedures will not be changed without the mutual agreement of the Coordinating Investigator and the Sponsor.

If there are any substantial changes to the clinical study protocol, then these changes will be documented in a new version of the study protocol.

The new version of the clinical study protocol is to be approved by the relevant IRB and if applicable, also the national regulatory authority approval, before implementation. Local requirements are to be followed for new versions of clinical study protocols.

The Sponsor will distribute any new versions of the clinical study protocol to each Principal Investigator(s). For distribution to the IRBs see Section 10.3.

If a change to a clinical study protocol requires a change to a site's ICF and assent form, the Sponsor and the site's IRB are to approve the revised ICF and assent form before the revised forms are used.

10.6 Audits and inspections

Authorized representatives of the Sponsor, a regulatory authority, or an IRB may perform audits or inspections at the study site, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities were conducted, and data were recorded, analysed, and accurately reported according to the clinical study protocol, GCP, guidelines of the ICH, and any applicable regulatory requirements. The Investigator will contact the Sponsor immediately if contacted by a regulatory agency about an inspection at the site.

11. LIST OF REFERENCES

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Appendix A Spirometry Assessment Criteria

Spirometry Assessment Criteria
Acceptable Versus Usable Tests

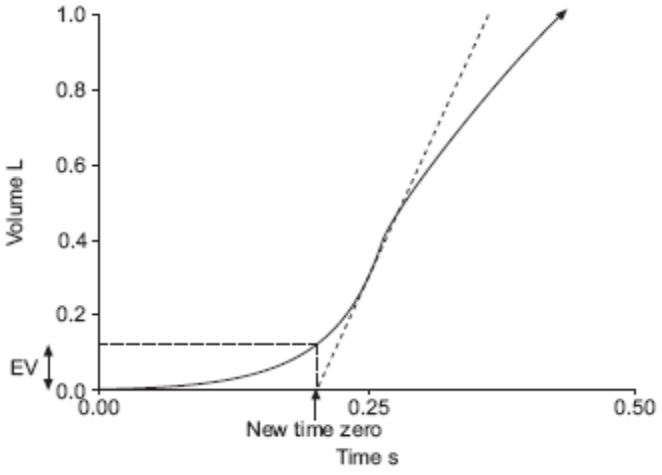
***Acceptable* Tests must meet the following Criteria:**

1. Acceptable start of exhalation with brisk upstroke, no hesitation or false start, and EV < 5% of FVC or 0.150 L, whichever is the greater (see example in Figure A2-1)
2. No cough during the first second
3. No valsalva maneuver
4. No leak
5. No obstruction of mouthpiece
6. No extra breaths
7. Plateau achieved, ie., the volume-time curve shows no change in volume (<0.025 L) for ≥ 1s, and the subject has tried to exhale for at least 6 seconds

An acceptable test meets all seven criteria listed. This is to be considered the "gold standard".

Usable spirometry tracings are those that only meet criteria 1 and 2. When this occurs, repeat testing up to eight attempts for pre-dose and five attempts for post-dose assessments, in an effort to obtain three acceptable spirograms. If only usable tests are obtained, report results based on the three best usable trials with observed limitations.

Figure A2-1 Example of a Usable Spirogram



EV=back extrapolation volume

The expanded version of the early part of a subject's volume-time spirogram, illustrating back extrapolation through the steepest part of the curve, where flow is PEFR, to determine the new "time zero". Forced vital capacity -4.291 L; EV – 0.123 L (2.9% FVC): back extrapolation line through PEF.

Between-Maneuver Reproducibility Criteria

Pre-dose Assessments

After **three** acceptable spirograms have been obtained, apply the following tests:

- The two largest values of FVC must be within 0.150 L of each other
- The two largest values of FEV_1 must be within 0.150 L of each other

If these criteria are met, the spirometry testing for that timepoint may conclude. The highest FEV_1 and the highest FVC obtained at each testing timepoint (even if from different reproducible tracings), will be collected.

If acceptability criteria are not met, continue testing until they are met or the subject cannot/ should not continue (maximum of eight attempts).

Post-dose Assessments

After **two** acceptable spirograms have been obtained, apply the following tests:

- The two largest values of FVC are within 0.150 L of each other and/or
- The two largest values of FEV_1 are within 0.150 L of each other

If these criteria are met, the spirometry testing for that timepoint may conclude. The highest FEV_1 and the highest FVC obtained at each testing timepoint (even if from different reproducible tracings), will be collected.

If acceptability/reproducibility criteria are not met, continue testing until they are met or the subject cannot/ should not continue (maximum of five attempts).

Appendix B Spirometry Performance Recommendations

Spirometry Performance Recommendations

Spirometry data of the highest quality must be obtained for proper interpretation of the results of this protocol. To these ends, a standard spirometer will be used (provided by Pearl Therapeutics), central training provided, qualification will be required, and specific operating instruction will also be provided.

Source: ATS/ERS Task Force 2005.

FEV_1, FVC, FEF_{25-75} MANEUVERS

Equipment Requirements

The spirometer must be capable of accumulating volume for ≥15 s (longer times are recommended) and measuring volumes of ≥8 L (body temperature (ie, 37°C), ambient pressure saturated with water vapor, BTPS) with an accuracy of at least ±3% of reading or ±0.050 L, whichever is greater, with flows between 0 and 14 $L\text{-}s^{-1}$. The total resistance to airflow at 14.0 $L\text{-}s^{-1}$ must be <1.5 $cmH_2O\ L^{-1}s^{-1}$ (0.15 $kPa\ L^{-1}s^{-1}$). The total resistance must be measured with any tubing, valves, pre-filter, etc. included that may be inserted between the subject and the spirometer. Some devices may exhibit changes in resistance due to water vapor condensation, and accuracy requirements must be met under BTPS conditions for up to 8 successive FVC maneuvers performed in a 10-minute period without inspiration from the instrument.

Display

For optimal quality control, both flow–volume and volume–time displays are useful, and test operators should visually inspect the performance of each maneuver for quality assurance before proceeding with another maneuver. This inspection requires tracings to meet the minimum size and resolution requirements set forth in this standard. Displays of flow versus volume provide more detail for the initial portion (first 1 s) of the FVC maneuver. Since this portion of the maneuver, particularly the peak expiratory flow rate (PEFR), is correlated with the pleural pressure during the maneuver, the flow–volume display is useful to assess the magnitude of effort during the initial portions of the maneuver. The ability to overlay a series of flow–volume curves registered at the point of maximal inhalation may be helpful in evaluating repeatability and detecting sub-maximal efforts. However, if the point of maximal inhalation varies between blows, then the interpretation of these results is difficult because the flows at identical measured volumes are being achieved at different absolute lung volumes. In contrast, display of the FVC maneuver as a volume–time graph provides more detail for the latter part of the maneuver. A volume–time tracing of sufficient size also allows independent measurement and calculation of parameters from the FVC maneuvers. In a display of multiple trials, the sequencing of the blows should be apparent to the user. For the start of test display, the volume–time display should include ≥0.25 s, and preferably 1 s, before exhalation starts (zero volume). This time period before there is any change in volume is needed to calculate the back extrapolated volume (EV) and to evaluate effort during the initial portion of the

maneuver. Time zero, as defined by EV, must be presented as the zero point on the graphical output. The last 2 s of the maneuver should be displayed to indicate a satisfactory end of test.

When a volume–time curve is plotted as hardcopy, the volume scale must be ≥10 mm L^{-1} (BTPS). For a screen display, 5 mm L^{-1} is satisfactory (Table A1-1).

Table A1-1. Recommended Minimal Scale Factors for Time, Volume and Flow on Graphical Output

Parameter	Instrument Display		Hardcopy Graphical Output
	Resolution Required	Scale Factor	Resolution Required
Volume*	0.050 L	5 mm-L^{-1}	0.050 L
Flow*	0.200 L-s^{-1}	2.5 mm L^{-1} s^{-1}	0.200 L-s^{-1}
Time	0.2 s	10 mm-s^{-1}	0.2 s

*The correct aspect ratio for flow versus volume display is 2 units of flow per 1 unit of volume

The time scale should be ≥20 mm-s^{-1}, and larger time scales are preferred (≥30 mm-s^{-1}) when manual measurements are made. When the volume–time plot is used in conjunction with a flow–volume curve (ie., both display methods are provided for interpretations and no hand measurements are performed), the time scale requirement is reduced to 10 mm-s^{-1} from the usually required minimum of 20 mm-s^{-1} (Table A1-1). The rationale for this exception is that the flow–volume curve can provide the means for quality assessment during the initial portion of the FVC maneuver. The volume–time curve can be used to evaluate the latter part of the FVC maneuver, making the time scale less critical.

Validation

It is strongly recommended that spirometry systems should be evaluated using a computer-driven mechanical syringe or its equivalent, in order to test the range of exhalations that are likely to be encountered in the test population. Testing the performance of equipment is not part of the usual laboratory procedures.

Quality Control

Attention to equipment quality control and calibration is an important part of good laboratory practice. At a minimum, the requirements are as follows: 1) a log of calibration results is maintained; 2) the documentation of repairs or other alterations which return the equipment to acceptable operation; 3) the dates of computer software and hardware updates or changes; and 4) if equipment is changed or relocated (eg, industrial surveys), calibration checks and quality-control procedures must be repeated before further testing begins.

Key aspects of equipment quality control are summarized in Table A1-2.

Table A1-2. Summary of Equipment Quality Control

Test	Minimal Interval	Action
Volume	Daily	Calibration check with a 3 L syringe
Leak	Daily	2 cm H_2O (0.3 kPa) constant pressure for 1 minute
Volume Linearity	Quarterly	1 L increments with a calibrating syringe measured over the entire volume range
Flow Linearity	Weekly	Test at least 3 different flow ranges
Time	Quarterly	Mechanical recorder check with stop watch
Software	New versions	Log installation date and perform test using "known" subject

Calibration is the procedure for establishing the relationship between sensor-determined values of flow or volume and the actual flow or volume. A calibration check is different from calibration and is the procedure used to validate that the device is within calibration limits, eg, ±3% of true. If a device fails its calibration check then new calibration procedure or equipment maintenance is required. Calibration checks must be undertaken daily, or more frequently, if specified by the manufacturer. The syringe used to check the volume calibration of spirometers must have an accuracy of ±15 mL or ±0.5% of the full scale (15 mL for a 3-L syringe), and the manufacturer must provide recommendations concerning appropriate intervals between syringe calibration checks. Users should be aware that a syringe with an adjustable or variable stop may be out of calibration if the stop is reset or accidentally moved. Calibration syringes should be periodically (eg, monthly) leak tested at more than 1 volume up to their maximum; this can be done by attempting to empty them with the outlet corked. A dropped or damaged syringe should be considered out of calibration until it is checked.

With regard to time, assessing mechanical recorder time scale accuracy with a stopwatch must be performed at least quarterly. An accuracy of within 2% must be achieved.

Quality Control for Volume-Measuring Devices

The volume accuracy of the spirometer must be checked at least daily, with a single discharge of a 3-L calibrated syringe. Daily calibration checking is highly recommended so that the onset of a problem can be determined within 1 day and also to help define day-to-day laboratory variability. More frequent checks may be required in special circumstances, such as: 1) during industrial surveys or other studies in which a large number of subject maneuvers

are carried out, the equipment's calibration should be checked more frequently than daily; and 2) when the ambient temperature is changing (eg, field studies), volume accuracy must be checked more frequently than daily and the BTPS correction factor appropriately updated.

The accuracy of the syringe volume must be considered in determining whether the measured volume is within acceptable limits. For example, if the syringe has an accuracy of 0.5%, a reading of ±3.5% is appropriate.

The calibration syringe should be stored and used in such a way as to maintain the same temperature and humidity of the testing site. This is best accomplished by keeping the syringe in close proximity to the spirometer, but out of direct sunlight and away from heat sources.

Volume-type spirometer systems must be evaluated for leaks every day. The importance of undertaking this daily test cannot be overstressed. Leaks can be detected by applying a constant positive pressure of ≥3.0 cmH2O (0.3 kPa) with the spirometer outlet occluded (preferably at or including the mouthpiece). Any observed volume loss of .30 mL after 1 minute indicates a leak and needs to be corrected.

At least quarterly, volume spirometers must have their calibration checked over their entire volume range using a calibrated syringe or an equivalent volume standard. The measured volume should be within ±3.5% of the reading or 65 mL, whichever is greater. This limit includes the 0.5% accuracy limit for a 3-L syringe. The linearity check procedure provided by the manufacturer can be used if it is equivalent to 1 of the following procedures: 1) consecutive injections of 1-L volume increments while comparing observed volume with the corresponding cumulative measured volume, eg, 0–1,1–2, 2–3,…6–7 and 7–8 L, for an 8-L spirometer; and 2) injection of a 3-L volume starting at a minimal spirometer volume, then repeating this with a 1-L increment in the start position, eg, 0–3, 1–4, 2–5, 3–6, 4–7 and 5–8 L, for an 8-L spirometer. The linearity check is considered acceptable if the spirometer meets the volume accuracy requirements for all volumes tested.

Quality Control for Flow-Measuring Devices

With regards to volume accuracy, calibration checks must be undertaken at least daily, using a 3-L syringe discharged at least 3 times to give a range of flows varying between 0.5 and 12 L-s^{-1} (with 3-L injection times of 6 s and 0.5 s). The volume at each flow should meet the accuracy requirement of ±3.5%. For devices using disposable flow sensors, a new sensor from the supply used for patient tests should be tested each day.

For linearity, a volume calibration check should be performed weekly with a 3-L syringe to deliver 3 relatively constant flows at a low flow, then 3 at a mid-range flow, and finally 3 at a high flow. The volumes achieved at each of these flows should each meet the accuracy requirement of ±3.5%.

Equipment

For measurements of VC and IC, the spirometer or flow meter must comply with the requirements for FVC (as described previously) and be capable of accumulating volume for ≥30 s. Expiratory maneuvers or, ideally, both inspiratory and expiratory maneuvers should be included in the display of VC maneuver. Regardless of whether the inspiratory or expiratory maneuver is used for deriving measurements, a display of the entire recorded VC maneuver must be provided. The maximal expiratory volume must be assessed to determine whether the subject has obtained a plateau in the expiratory effort. For display of the slow VC, the time scale may be reduced to 5 mm-s^{-1}.

Technical Considerations

Minimal recommendations for spirometry systems

Accurate results require accurate equipment. Spirometer equipment recommendations apply to all spirometers and are minimal requirements. In some circumstances, it may be appropriate to exceed these requirements (ie., in some research/surveillance applications). Instrumentation recommendations should be followed to provide accurate spirometric data and information that is comparable from laboratory to laboratory and from 1 time period to another. The accuracy of a spirometry system depends on characteristics of the entire system, from the volume or flow transducer and the use of an in-line filter, to the recorder, display or processor. Changes in any aspect of the equipment or errors at any step in the process can affect the accuracy of the results. For example, if the BTPS correction factor is wrong, an accurately measured FVC will be incorrectly reported. Spirometers are not required to measure all of the indices in Table A1-3, but must meet the recommendations for those that are measured. Accuracy and repeatability recommendations apply over the entire volume range of the instrument.

Table A1-3. Range and Accuracy Recommendations Specified for Forced Expiratory Maneuvers

Test	Range/Accuracy (BTPS)	Flow Range ($L\text{-}s^{-1}$)	Time (s)	Resistance and Back Pressure	Test Signal
VC	0.5–8 L, ± 3% of reading or ± 0.050 L, whichever is greater	0-14	30		3-L Calibration syringe
FVC	0.5–8 L, ± 3% of reading or ±0.050 L, whichever is greater	0-14	15	<1.5 cm H_2O L^{-1} s^{-1} (0.15 kPa $L^{-1}s^{-1}$)	24 ATS waveforms, 3-L Cal Syringe

Table A1-3. Range and Accuracy Recommendations Specified for Forced Expiratory Maneuvers

Test	Range/Accuracy (BTPS)	Flow Range ($L\text{-}s^{-1}$)	Time (s)	Resistance and Back Pressure	Test Signal
FEV_1	0.5–8 L, ± 3% of reading or ± 0.050 L, whichever is greater	0-14	1	<1.5 cm H_2O L^{-1} s^{-1} (0.15 kPa $L^{-1}s^{-1}$)	24 ATS waveforms
Time Zero	The timepoint from which all FEV_t measurements are taken.			Back extrapolation	

FEVt: forced expiratory volume in t seconds

Body temperature, ambient pressure, saturated with water vapor correction

All spirometry values should be reported at BTPS by any method (measuring temperature and barometric pressure) proven effective by the manufacturer. For volume-type spirometers, the temperature inside the spirometer should be measured for each breathing maneuver. Regardless of the BTPS correction technique used, the ambient temperature must always be recorded with an accuracy of ±1°C. In situations where the ambient air temperature is changing rapidly (>3°C in <30 min), continuous temperature corrections may be necessary. Spirometer users should be aware of potential problems with testing performed at lower ambient temperatures: 17°C is the lower limit for ambient temperature, unless a manufacturer states that their spirometer will operate accurately at lower ambient temperatures. If barometric pressure is not used in calculating the BTPS correction factor, the range of barometric pressures over which the BTPS correction factor is valid must be published.

Appendix C Additional Safety Information

Additional Safety Information
Further Guidance on the Definition of a Serious Adverse Event (SAE)

Life threatening

'Life-threatening' means that the subject was at immediate risk of death from the AE as it occurred or it is suspected that use or continued use of the product would result in the subject'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 a serious AE, 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 subject was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important medical event or medical intervention

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

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

- Angioedema not severe enough to require intubation but requiring iv 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

A Guide to Interpreting the Causality Question

When making an assessment of causality consider the following factors when deciding if there is a 'reasonable possibility' that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the subject actually 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? The Sponsor 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 limited or insufficient information in the case, it is likely that the event(s) will be assessed as 'not related'.

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

Appendix D Instructions for Use of Inhaled Medications

Instructions for Use of Inhaled Medications

Instructions for Use of the AS MDI and Placebo for AS MDI

1. How do I store the inhaler?

- The inhaler should be stored between 20°C-25°C (68°-77°F) as directed by the label.

2. Preparation of the inhaler

- Take the inhaler out of the pouch. Safely throw away the pouch and the desiccant packet that comes inside the pouch.
- Take the cap off the inhaler by gently squeezing the sides of the dust-cap and pulling off.
- Inspect the front of the inhaler and make sure there is nothing inside the mouthpiece of the inhaler. Make sure the canister is fully and firmly inserted into the actuator.
- The inhaler must be primed before first use. Priming involves releasing a certain number of sprays (4) into the air before 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 the inhaler is ready to use.
- To prime the inhaler, gently shake the inhaler for 5-10 seconds and then spray once into the air away from yourself and others.
  NOTE: an audible "click" may be heard which is advancement of the dose counter and considered normal.
- Wait approximately 5-10 seconds and then repeat step #2.2.5, three more times.

3. Using the inhaler

- The inhaler should be held upright with the mouthpiece at the bottom and the canister at the top as pictured in Figure 1.
- Shake the inhaler for 5 to 10 seconds.
- Breathe out fully through your mouth, expelling as much air from your lungs as possible. Tilt your head back slightly, place the mouthpiece into your mouth, holding the inhaler with the mouthpiece down, and closing

your lips around it. To allow the medication to enter your lungs, keep your tongue flat on the bottom of your mouth.

- While breathing in deeply and slowly through your mouth, fully depress the top of the dose counter with your index finger. Immediately after the spray is delivered, release your finger from the canister. When you have breathed in fully, remove the inhaler from your mouth and close your mouth.
- Hold your breath as long as possible, up to 10 seconds, and then breathe normally.
- If more than one spray is necessary, repeat steps 2.3.2 to 2.3.5 the necessary number of times.
- If the device will be used again, place the dust-cap back onto the device.

Figure 1. Metered Dose Inhaler Diagram

Instructions for Use of the PROVENTIL HFA

Attention Health Care Professional:
Detach Patient's Instructions for Use from package insert and dispense with the product
PROVENTIL® HFA
(albuterol sulfate)
Inhalation Aerosol
FOR ORAL INHALATION ONLY
Patient's Instructions for Use

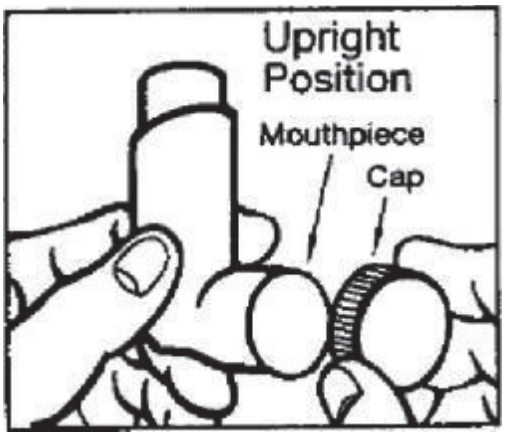


Figure 1

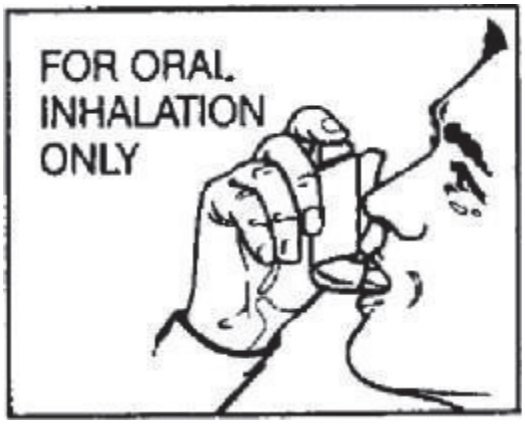


Figure 2

Before using your PROVENTIL® HFA (albuterol sulfate) Inhalation Aerosol, read complete instructions carefully. Children should use PROVENTIL HFA Inhalation Aerosol under adult supervision, as instructed by the patient's doctor

Please note that indicates that this inhalation aerosol does not contain chlorofluorocarbons (CFCs) as the propellant.

1. SHAKE THE INHALER WELL immediately before each use. **Then remove the cap from the mouthpiece** (see Figure 1). **Check mouthpiece for foreign objects prior to use.** Make sure the canister is fully inserted into the actuator.

2. As with all aerosol medications, it is recommended to prime the inhaler before using for the first time and in cases where the inhaler has not been used for more than 2 weeks. Prime by releasing four “test sprays” into the air, away from your face.
3. BREATHE OUT FULLY THROUGH THE MOUTH, expelling as much air from your lungs as possible. Place the mouthpiece fully into the mouth, holding the inhaler in its upright position (see Figure 2) and closing the lips around it.
4. WHILE BREATHING IN DEEPLY AND SLOWLY THROUGH THE MOUTH, FULLY DEPRESS THE TOP OF THE METAL CANISTER with your index finger (see Figure 2).
5. HOLD YOUR BREATH AS LONG AS POSSIBLE, up to 10 seconds. Before breathing out, remove the inhaler from your mouth and release your finger from the canister.
6. If your physician has prescribed additional puffs, wait 1 minute, shake the inhaler again, and repeat steps 3 through 5. Replace the cap after use.
7. KEEPING THE PLASTIC MOUTHPIECE CLEAN IS EXTREMELY IMPORTANT TO PREVENT MEDICATION BUILDUP AND BLOCKAGE. THE MOUTHPIECE SHOULD BE WASHED, SHAKEN TO REMOVE EXCESS WATER, AND AIR DRIED THOROUGHLY AT LEAST ONCE A WEEK. INHALER MAY STOP SPRAYING IF NOT PROPERLY CLEANED. **Routine cleaning instructions:** Step 1. To clean, remove the canister and mouthpiece cap. Wash the mouthpiece through the top and bottom with warm running water for 30 seconds at least once a week (see Figure A). **Never immerse the metal canister in water.**

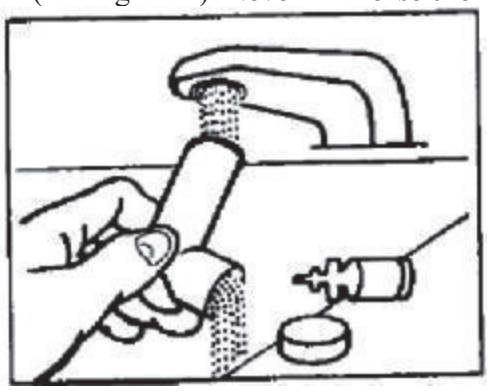


Figure A

Wash mouthpiece under warm running water.

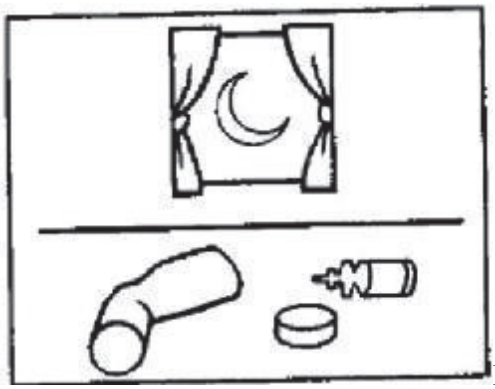


Figure B

Allow mouthpiece to air dry, such as overnight.

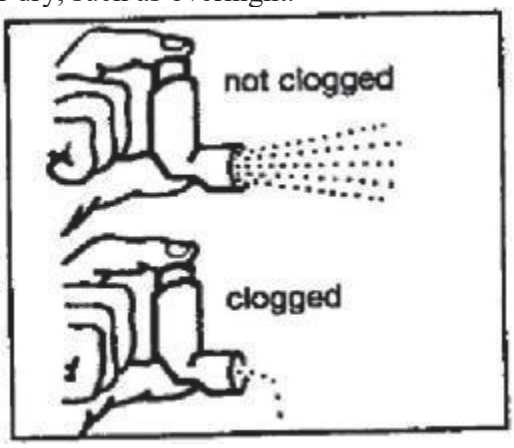


Figure C

When blocked, little or no medicine comes out. Step 2. To dry, shake off excess water and let the mouthpiece air dry thoroughly, such as overnight (see Figure B). When the mouthpiece is dry, replace the canister and the mouthpiece cap. Blockage from medication buildup is more likely to occur if the mouthpiece is not allowed to air dry thoroughly. **IF YOUR INHALER HAS BECOME BLOCKED** (little or no medication coming out of the mouthpiece, see Figure C), wash the mouthpiece as described in Step 1 and air dry thoroughly as described in Step 2. **IF YOU NEED TO USE YOUR INHALER BEFORE IT IS COMPLETELY DRY, SHAKE OFF EXCESS WATER,** replace the canister, and test spray twice into the air, away from your face, to remove most of the water remaining in the mouthpiece. Then take your dose as prescribed. **After such use, rewash and air dry thoroughly as described in Steps 1 and 2.**

8. The correct amount of medication in each inhalation cannot be assured after 200 actuations, even though the canister is not completely empty. The canister should be

discarded when the labeled number of actuations have been used. Before you reach the specific number of actuations, you should consult your physician to determine whether a refill is needed. Just as you should not take extra doses without consulting your physician, you also should not stop using PROVENTIL HFA Inhalation Aerosol without consulting your physician.

You may notice a slightly different taste or spray force than you are used to with PROVENTIL HFA Inhalation Aerosol, compared to other albuterol inhalation aerosol products.

DOSAGE:

Use only as directed by your physician.

WARNINGS:

The action of PROVENTIL® HFA Inhalation Aerosol should last up to 4 to 6 hours. PROVENTIL HFA Inhalation Aerosol should not be used more frequently than recommended. Do not increase the number of puffs or frequency of doses of PROVENTIL HFA Inhalation Aerosol without consulting your physician. If you find that treatment with PROVENTIL HFA Inhalation Aerosol becomes less effective for symptomatic relief, your symptoms become worse, and/or you need to use the product more frequently than usual, medical attention should be sought immediately. While you are taking PROVENTIL HFA Inhalation Aerosol, other inhaled drugs should be taken only as directed by your physician. If you are pregnant or nursing, contact your physician about the use of PROVENTIL HFA Inhalation Aerosol.

Common adverse effects of treatment with PROVENTIL HFA Inhalation Aerosol include palpitations, chest pain, rapid heart rate, tremor, or nervousness. Effective and safe use of PROVENTIL HFA Inhalation Aerosol includes an understanding of the way that it should be administered. Use PROVENTIL HFA Inhalation Aerosol only with the yellow actuator supplied with the product. The PROVENTIL HFA Inhalation Aerosol actuator should not be used with other aerosol medications.

For best results, use at room temperature. Avoid exposing product to extreme heat and cold.

Shake well before use.

Contents Under Pressure.

Do not puncture. Do not store near heat or open flame. Exposure to temperatures above 120°F may cause bursting. Never throw container into fire or incinerator. Store between 15° - 25°C (59° - 77°F). **Store the inhaler with the mouthpiece down.** Avoid spraying in eyes. Keep out of reach of children.

Further Information: Your PROVENTIL® HFA (albuterol sulfate) Inhalation Aerosol does not contain chlorofluorocarbons (CFCs) as the propellant. Instead, the inhaler contains a hydrofluoroalkane (HFA-134a) as the propellant.

Developed and Manufactured by: 3M Health Care Limited
Loughborough UK or 3M Drug Delivery Systems Northridge, CA 91324, USA Rev. 12/14 **653300**

Instructions for Use of the VENTOLIN HFA

This Patient Information leaflet summarizes the most important information about VENTOLIN HFA. If you would like more information, talk with your healthcare provider or pharmacist. You can ask your healthcare provider or pharmacist for information about VENTOLIN HFA that was written for healthcare professionals.

For more information about VENTOLIN HFA, call 1-888-825-5249 or visit our website at www.ventolin.com.

What are the ingredients in VENTOLIN HFA?

Active ingredient: albuterol sulfate
Inactive ingredient: propellant HFA-134a

Instructions for Use

For Oral Inhalation Only

Your VENTOLIN HFA inhaler

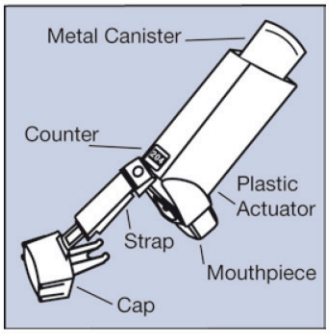


Figure A

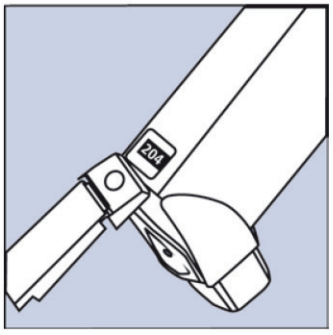


Figure B

- The metal canister holds the medicine. **See Figure A.**
- The canister has a counter to show how many sprays of medicine you have left. The number shows through a window in the back of the actuator. **See Figure B.**
- The counter starts at either **204** or **064**, depending on which size inhaler you have. The number will count down by 1 each time you spray the inhaler. The counter will stop counting at **000**.
- **Do not try to change the numbers or take the counter off the metal canister.** The counter cannot be reset, and it is permanently attached to the canister.
- The blue plastic actuator sprays the medicine from the canister. The actuator has a protective cap that covers the mouthpiece. **See Figure A.** Keep the protective cap on the mouthpiece when the canister is not in use. The strap keeps the cap attached to the actuator.

- **Do not** use the actuator with a canister of medicine from any other inhaler.
- **Do not** use a VENTOLIN HFA canister with an actuator from any other inhaler.

Before using your VENTOLIN HFA inhaler

- Take VENTOLIN HFA out of the foil pouch just before you use it for the first time. Safely throw away the pouch and the drying packet that comes inside the pouch.
- The inhaler should be at room temperature before you use it.
- If your child needs to use VENTOLIN HFA, watch your child closely to make sure your child uses the inhaler correctly. Your healthcare provider will show you how your child should use VENTOLIN HFA.

Priming your VENTOLIN HFA inhaler

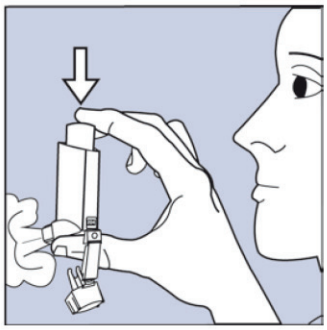


Figure C

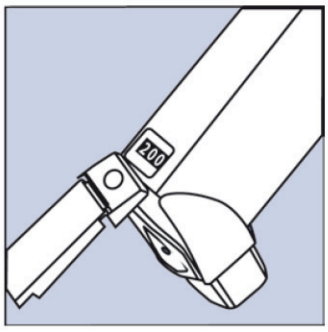


Figure D

- **Before you use VENTOLIN HFA for the first time, you must prime the inhaler so that you will get the right amount of medicine when you use it.**
- To prime the inhaler, take the cap off the mouthpiece and shake the inhaler well. Then spray the inhaler 1 time into the air away from your face. **See Figure C. Avoid spraying in eyes.**
- Shake and spray the inhaler like this 3 more times to finish priming it. The counter should now read **200** or **060**, depending on which size inhaler you have. **See Figure D.**
- You must prime your inhaler again if you have not used it in more than 14 days or if you drop it. Take the cap off the mouthpiece and shake and spray the inhaler 4 times into the air away from your face.

How to use your VENTOLIN HFA inhaler

Follow these steps every time you use VENTOLIN HFA.

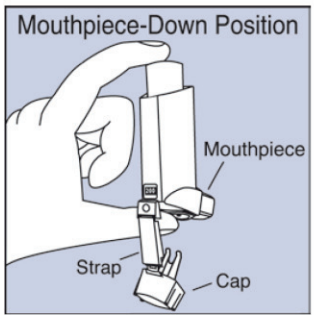


Figure E

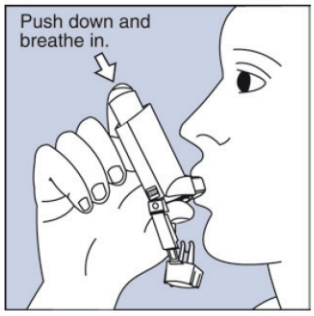


Figure F

Step 1. Make sure the canister fits firmly in the actuator. The counter should show through the window in the actuator.

Shake the inhaler well before each spray.

Take the cap off the mouthpiece of the actuator. Look inside the mouthpiece for foreign objects, and take out any you see.

Step 2. Hold the inhaler with the mouthpiece down. **See Figure E.**

Step 3. Breathe out through your mouth and push as much air from your lungs as you can. Put the mouthpiece in your mouth and close your lips around it. **See Figure F.**

Step 4. Push the top of the canister **all the way down** while you breathe in deeply and slowly through your mouth. **See Figure F.**

Step 5. After the spray comes out, take your finger off the canister. After you have breathed in all the way, take the inhaler out of your mouth and close your mouth.

Step 6. **Hold your breath for about 10 seconds,** or for as long as is comfortable. **Breathe out slowly as long as you can.**

If your healthcare provider has told you to use more sprays, wait 1 minute and shake the inhaler again. Repeat Steps 2 through Step 6.

Step 7. Put the cap back on the mouthpiece after every time you use the inhaler. Make sure it snaps firmly into place.

Cleaning your VENTOLIN HFA inhaler

If you need to use your inhaler before the actuator is completely dry:

- Shake as much water off the actuator as you can.
- Put the cap on the mouthpiece and then put the canister in the actuator and make sure it fits firmly.
- Shake the inhaler well and spray it 1 time into the air away from your face.
- Take your VENTOLIN HFA dose as prescribed.
- Follow cleaning Steps 8 through 13 above.

Replacing your VENTOLIN HFA inhaler

- **When the counter reads 020**, you should refill your prescription or ask your healthcare provider if you need another prescription for VENTOLIN HFA.
- **Throw the inhaler away** when the counter reads **000** or 12 months after you opened the foil pouch, whichever comes first. You should not keep using the inhaler when the counter reads **000** because you will not receive the right amount of medicine.
- **Do not use the inhaler** after the expiration date, which is on the packaging it comes in.

For correct use of your VENTOLIN HFA inhaler, remember:

- The canister should always fit firmly in the actuator.
- Breathe in deeply and slowly to make sure you get all the medicine.
- Hold your breath for about 10 seconds after breathing in the medicine. Then breathe out fully.
- Always keep the protective cap on the mouthpiece when your inhaler is not in use.
- Always store your inhaler with the mouthpiece pointing down.
- Clean your inhaler at least 1 time each week.

If you have questions about VENTOLIN HFA or how to use your inhaler, call GlaxoSmithKline (GSK) at 1-888-825-5249 or visit www.ventolin.com.

This Patient Information and Instructions for Use have been approved by the U.S. Food and Drug Administration.

Instructions for Use of PULMICORT FLEXHALER

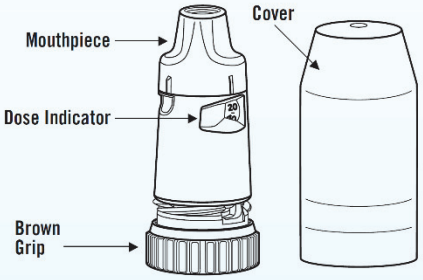
How to Get Started Using Your PULMICORT FLEXHALER® (budesonide inhalation powder, 90 mcg & 180 mcg)

Please read these instructions carefully before you start to take your medicine, and use only as directed by a health care professional.

Priming Your PULMICORT FLEXHALER

Before you use a new PULMICORT FLEXHALER for the first time, you must prime it.

Figure 1- **Parts of your PULMICORT FLEXHALER**



To prime your PULMICORT FLEXHALER follow the steps below:

1. 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 (see Figure 2).
2. Continue to hold your PULMICORT FLEXHALER upright as shown in Figure 1. Use your other hand to hold the inhaler in the middle. Do not hold the inhaler at the top of the mouthpiece.
3. 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 which way you turn it first). You will hear a "click" during one of the twisting movements (see Figure 3 and 4).
4. Repeat Step 3. Your PULMICORT FLEXHALER is now primed. You are ready to load your first dose.

You do not have to prime your PULMICORT FLEXHALER again after this even if you do not use it for a period of time.

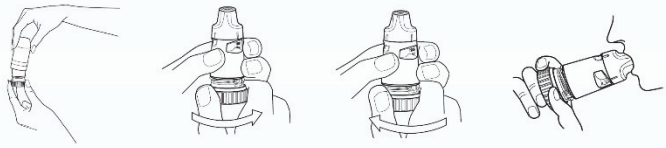


Figure 2 - **Load** Figure 3 - **Twist** Figure 4 - **Click** Figure 5 - **Inhale**

Loading a Dose

1. Hold your PULMICORT FLEXHALER upright as described above. With your other hand, twist the white cover and lift it off (see Figure 2).
2. Continue to hold your PULMICORT FLEXHALER upright to be sure that the right dose of medicine is loaded.
3. Use your other hand to hold the inhaler in the middle. Do not hold the mouthpiece when you load the inhaler.
4. Twist the brown grip fully in one direction as far as it will go. Twist it fully back again in the other direction as far as it will go (it does not matter which way you turn it first) [see Figure 3].
   - You will hear a "click" during one of the twisting movements (see Figure 4)
   - PULMICORT FLEXHALER will only give one dose at a time, no matter how often you click the brown grip, but the dose indicator will continue to move (advance). This means that if you continue to move the brown grip, it is possible for the indicator to show fewer doses or zero doses even if more doses are left in the inhaler
   - **Do not shake the inhaler after loading it**

Inhaling a Dose

1. Turn your head away from the inhaler and breathe out (exhale). If you accidentally blow into your inhaler after loading a dose, follow the instructions for loading a new dose.
2. Place the mouthpiece in your mouth and close your lips around the mouthpiece. Breathe in (inhale) deeply and forcefully through the inhaler (see Figure 5).
3. You may not sense the presence of any medication entering your lungs when inhaling from PULMICORT FLEXHALER. This lack of sensation does not mean that you did not get the medication. You should not repeat your inhalations even if you did not feel the medication when inhaling.
4. Do not chew or bite on the mouthpiece.
5. Remove the inhaler from your mouth and exhale. **Do not blow or exhale into the mouthpiece.**
6. If more than one dose is prescribed repeat the steps above.
7. When you are finished taking your dose, place the white cover back on the inhaler and twist shut.
8. **Rinse your mouth with water after each dose to decrease your risk of getting thrush. Do not swallow the water.**

Pulmicort Flexhaler®
(budesonide inhalation powder, 90 mcg & 180 mcg)

Reading the Dose Indicator Window

- The label on the box or cover will tell you how many doses are in your PULMICORT FLEXHALER
- Your PULMICORT FLEXHALER has a dose indicator window just below the mouthpiece. The dose indicator tells you about how many doses are left in the inhaler. Look at the middle of the window to find out about how many doses are left in your inhaler (see Figure 6)
- The dose indicator is connected to the turning grip and moves (counts down) every time a dose is loaded. **It is not likely that you will see the dose indicator move with each dose.** You can usually see the indicator move each time you use about 5 doses
- The dose indicator starts with either the number 60 or 120 when full, depending upon the strength of the inhaler. The indicator is marked in intervals of 10 doses. Markings are either with numbers or dashes (alternating), counting down to "0"

60-Dose Inhaler	120-Dose Inhaler	
20 —	80 —	Dose indicator starts at 60 or 120 depending on strength (90 mcg or 180 mcg) of the inhaler and counts down to 0.
40 —	100 —	
60	120	

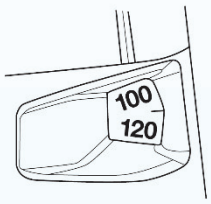


Figure 6 - **Dose Indicator**

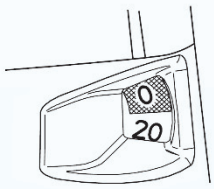


Figure 7 - **Empty**

- The dose indicator will tell you about how many doses are left in your PULMICORT FLEXHALER
- **If you complete the instructions for loading the dose more than one time before you inhale the dose, you will only receive one dose.** The dose indicator will move a small amount but it is not likely that you will see the dose indicator move with each dose
- **Your inhaler is empty when the number 0 on the red background reaches the middle of the dose indicator window. Throw away this inhaler. The inhaler may not give you the right amount of medicine, even though it may not feel completely empty and may seem like it continues to work** (see Figure 7)
- **Do not put your PULMICORT FLEXHALER in water (do not immerse it) to find out if it is empty. Check the dose indicator window to see how many doses are left**
- Refill your PULMICORT FLEXHALER prescription before your medicine runs out. You will get a new inhaler each time you refill your prescription

Cleaning your PULMICORT FLEXHALER

- Keep your PULMICORT FLEXHALER clean and dry at all times. Do not immerse it in water
- Wipe the outside of the mouthpiece one time each week with a dry tissue
- Do not use water or liquids when cleaning the mouthpiece
- Do not try to remove the mouthpiece or twist it

Do not use your PULMICORT FLEXHALER if it has been damaged or if the mouthpiece has become detached. Talk to your doctor or pharmacist if you have any problems with your PULMICORT FLEXHALER.

IMPORTANT INFORMATION ABOUT PULMICORT FLEXHALER

Important Safety Information

PULMICORT FLEXHALER is not a bronchodilator and should NOT be used to treat an acute asthma attack. If you are switching to PULMICORT FLEXHALER from an oral corticosteroid, follow your doctor's instructions to avoid serious health risks when you stop using oral corticosteroids.

Avoid exposure to infections such as chicken pox and measles. Tell your doctor immediately if exposed. Inhaled corticosteroids may cause a reduction in growth rate. The long-term effect on final adult height is unknown.

Rare instances of glaucoma, increased intraocular pressure, cataracts have been reported following the inhaled administration of corticosteroids.

Please see last page for continued Important Safety Information on PULMICORT FLEXHALER

Pulmicort Flexhaler®
(budesonide inhalation powder, 90 mcg & 180 mcg)

Appendix E Sponsor Signatory

Sponsor Signatory

Study Title: A Randomized, Double-blind, Single dose, Placebo-controlled, 5-Period, 5-Treatment, Crossover, Multi-center, Dose-ranging Study to Compare PT007 to Placebo MDI and Open-Label Proventil® HFA in Adult and Adolescent Subjects With Mild to Moderate Asthma

Study Number: D6930C00001 (PT007001)

Final Date: 12 January 2018

Signature: [redacted]

Name: [redacted]

Title: [redacted]

Appendix F Investigator's Agreement and Signature Page

Investigator's Agreement and Signature Page

Study Title:	A Randomized, Double-blind, Single dose, Placebo-controlled, 5-Period, 5-Treatment, Crossover, Multi-center, Dose-ranging Study to Compare PT007 to Placebo MDI and Open-Label Proventil® HFA in Adult and Adolescent Subjects With Mild to Moderate Asthma
Study Number:	D6930C00001 (PT007001)
Final Date:	12 January 2018

I agree:

a. To assume responsibility for the proper conduct of the study at this site.

b. To conduct the study in compliance with the protocol and with any other study conduct procedures provided by Pearl Therapeutics, Inc. (hereafter referred to as Pearl).

c. Not to implement any changes to the protocol without agreement from the Sponsor and prior review and written approval from the IRB/IEC, except where necessary to eliminate an immediate hazard to the subjects, or for administrative aspects of the study (where permitted by all applicable regulatory requirements).

d. That I am aware of, and will fully comply with GCP and all applicable regulatory requirements.

e. That I am thoroughly familiar with the appropriate use of the investigational product(s), and other information provided by the Sponsor including, but not limited to, the following: the protocol and the current Investigator Brochure (IB).

f. To ensure that all persons assisting me with the study are qualified, adequately informed about the investigational product(s) and of their study-related duties and functions.

g. To supply Pearl with any necessary information regarding ownership interest and financial ties; to promptly update this information if any relevant changes occur during the course of the study and for 1 year following completion of the study; and agree that Pearl may disclose any information it has about such ownership interests and financial ties to regulatory authorities.

h. I agree to report all information or data in accordance with the protocol and any other study conduct procedures provided by Pearl.

i. That since the information in this protocol and IB is confidential, I understand that its disclosure to any third parties, other than those involved in approval, supervision or conduct of the study is prohibited.

j. To accurately transfer all required data from each subject's source document to the eCRFs. The eCRFs will be provided to the Sponsor in a timely manner at the completion of the study, or as otherwise specified by the Sponsor.

k. To allow authorized representatives of Pearl or regulatory authority representatives to conduct on-site visits to review, audit and copy study documents. I will personally meet with these representatives to answer any study-related questions.

Signature:_____ Date:_____

Name:_____

Site Name:_____