Clinical Study Protocol: PT010018-00

Study Title: A Study to Assess the Pharmacokinetics and Safety of PT010 in Subjects With Moderate to Severe COPD Following Single and Repeat Dose Administration

Study Number: PT010018

Study Phase: I

Product Name: PT010: Budesonide, Glycopyrronium, and Formoterol Fumarate Inhalation Aerosol, Metered Dose Inhaler (BGF MDI)

Indication: Chronic Obstructive Pulmonary Disease

Investigators: Single Center

Sponsor: Pearl Therapeutics, Inc.

[redacted]

Sponsor Contact: [redacted]

	Version Number	Date
Original Protocol:	1.0	14 June 2017

Confidentiality Statement

SYNOPSIS

Sponsor:

Pearl Therapeutics, Inc.

[redacted]

Name of Study Drug:

PT010: Budesonide, Glycopyrronium, and Formoterol Fumarate Inhalation Aerosol, Metered Dose Inhaler (BGF MDI)

Name of Active Ingredients:

Budesonide, Glycopyrronium, and Formoterol Fumarate

Study Title:

A Study to Assess the Pharmacokinetics and Safety of PT010 in Subjects With Moderate to Severe COPD Following Single and Repeat Dose Administration

Study Protocol Number:PT010018-00

Study Phase: I

Primary Objective:

- To assess the pharmacokinetic (PK) profile of BGF MDI in subjects with moderate to severe COPD after single dose administration on the first treatment day and after 7 days of repeat dosing.

Safety Objective:

- To assess the safety and tolerability of BGF MDI in subjects with moderate to severe COPD after single dose administration on the first treatment day and after 7 days of repeat dosing

Study Design:

This is a Phase I open-label, single center study to assess the PK and safety of BGF MDI 320/14.4/9.6 µg in subjects with moderate to severe COPD. Pharmacokinetics will be assessed following a single dose administration on the first treatment day (Day 1) and will be assessed again after 7 days of repeat dosing. This study includes a Screening Period of up to 28 days and a single Treatment Period of 8 days. A follow-up phone call will be conducted at least 5 days but no longer than 7 days after the last dose of study drug.

Subjects who provide informed consent before the conduct of any screening assessments will undergo screening procedures to determine eligibility to participate in the study.

To be considered eligible for the study, subjects must have a documented history (ie, within the past 12 months) of COPD defined as a post-bronchodilator forced expiratory volume in 1 second (FEV_1)/forced vital capacity (FVC) <0.70 and a post-bronchodilator FEV_1 <80% predicted normal. Subjects without historical documentation must meet these criteria at the

Screening Visit. In addition, subjects must have a pre-bronchodilator FEV_1 between ≥50 and <80% predicted normal during Screening after withholding all COPD medications and after withholding the use of albuterol for at least 6 hours prior to the assessment. All eligible subjects will receive Sponsor-provided Ventolin® hydrofluoroalkane (HFA; albuterol sulfate inhalation aerosol) for rescue use throughout the study. During the Screening Period, eligible subjects will continue the use of their regular COPD maintenance therapy. However, any medication containing any one or more of the components of BGF (all formulations of budesonide, glycopyrronium or formoterol fumarate) are prohibited a minimum of 4 weeks before Screening during the study.

Subjects will be admitted to the clinic as an inpatient on Day -1, at which time continuing eligibility will be assessed and subjects will be instructed to discontinue all COPD therapy except study-provided rescue Ventolin HFA after their last dose for the day. Study subjects will use a Placebo MDI for training purposes only to demonstrate proper use of the MDI on Day -1, Day 1, Day 7, and Day 8. The Treatment Period of 8 days will start on Day 1. BGF MDI 320/14.4/9.6 µg will be administered as oral inhalation as follows:

- Single dose administration on the morning of Day 1 (Visit 3) followed by serial blood draws for 24 hours
- Twice daily (BID) dosing every morning and evening on Days 2 through Day 7 approximately 12 hours apart
- Single dose administration on the morning of Day 8 (Visit 5) followed by serial blood draws for 12 hours

Subjects will be discharged on Day 2 of the Treatment Period after performing the last PK blood draw and will continue to administer BGF MDI BID at home on Days 2 through 7. Subjects will return to the clinic for inpatient admission on Day 7 (Visit 4) and administer the evening dose of study drug at the clinic.

Subjects will undergo safety assessments and serial blood draws on Day 8 following the morning dose of study drug. After all protocol-specified assessments are completed and safety data have been reviewed by the Principal Investigator or designated staff, the subject will be discharged from the clinic on the evening of Day 8.

Subjects will return to appropriate COPD maintenance medications after the final assessments on Day 8 are completed.

Study Population:

The planned study population will include approximately 30 male and female adult subjects with moderate to severe COPD who will be enrolled to provide approximately 24 subjects who will complete the study.

Study Drug, Dose, and Mode of Administration

Product Name & Dose	Product Strength	Dosage Form/ Fill Count	Administration
BGF MDI 320/14.4/9.6 µg ex-actuator	160/7.2/4.8 µg/actuation	MDI/ 120 inhalations	2 inhalations BID

Duration of Treatment:

It is planned that each subject will receive study drug for 8 days.

Duration of Study:

The entire study period is scheduled to take approximately 7 weeks (expected range between 2.5 to 7 weeks) for each individual subject. The study is anticipated to run for approximately 4 to 6 months.

PK Endpoints

Pharmacokinetics of BGF MDI will be assessed using plasma concentrations of budesonide, glycopyrronium, and formoterol pre-dose and at various times post-dose on Day 1 and Day 8.

Primary PK Endpoints

- Maximum plasma concentration (C_{max})
- Area under the plasma concentration-time curve from 0 to 12 hours (AUC_{0-12})
- Area under the plasma concentration-time curve from 0 to the time of the last measureable plasma concentration ($AUC_{0-tlast}$)

Secondary PK Endpoints

- Time to maximum plasma concentration (t_{max})
- Area under the plasma concentration-time curve from 0 extrapolated to infinity ($AUC_{0-\infty}$)

Safety Endpoints:

- Adverse events (AEs)
- 12-lead electrocardiograms (ECGs)
- Clinical laboratory testing
- Vital sign measurements

Statistical Methods:

Safety Analyses: Descriptive statistics will be provided for ECG, vital signs, and laboratory measurements as appropriate. The frequencies of AEs and the number and percentage of subjects with AEs will also be provided.

PK Analyses: The accumulation ratios for AUC_{0-12} and C_{max} and the linearity ratio $AUC_{0-12}/AUC_{0-\infty}$ between Day 8 and Day 1 for budesonide, glycopyrronium, and formoterol will be analyzed using a mixed model with day as a fixed effect and subject as random effect. Descriptive statistics without model adjustment will be used to describe the other budesonide, glycopyrronium, and formoterol PK parameters after treatment with BGF MDI. The time to steady state for each analyte will be estimated using the effective rate of accumulation.

Sample Size: This study is descriptive in nature. The planned sample size of approximately 30 enrolled subjects is selected to provide approximately 24 completers for assessment of the single- and multiple-dose PK of BGF MDI in subjects with COPD.

Date of Protocol: [redacted]

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

LIST OF APPENDICES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATS	American Thoracic Society
AUC_{0-12}	Area under the plasma concentration-time curve from 0 to 12 hours
$AUC_{0-tlast}$	Area under the plasma concentration-time curve from 0 the time of the last measureable plasma concentration
$AUC_{0-\infty}$	Area under the plasma concentration-time curve from 0 extrapolated to infinity
BFF MDI	Budesonide and Formoterol Fumarate Metered Dose Inhaler
BGF MDI	Budesonide, Glycopyrronium, and Formoterol Fumarate Metered Dose Inhaler
BID	Twice daily
BP	Blood pressure
CI	Confidence interval
CL/F	Apparent total body clearance
C_{max}	Maximum plasma concentration
COPD	Chronic obstructive pulmonary disease
CV%	Coefficient of variation
CYP3A4	Cytochrome P450 3A4
ECG	Electrocardiogram
eCRF	Electronic case report form
ERS	European Respiratory Society
FDA	Food and Drug Administration
FEV_1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
GCP	Good Clinical Practice
GOLD	Global Initiative for Chronic Obstructive Lung Disease

hCG	Human chorionic gonadotropin
HFA	Hydrofluoroalkane
ICF	Informed consent form
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
ICS	Inhaled corticosteroid
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ISMPP	International Society for Medical Publication Professionals
LABA	Long-acting β2-agonist
LAMA	Long-acting muscarinic antagonist
λ_z	Terminal elimination rate constant
LSM	Least square mean
MDI	Metered dose inhaler
NHANES	National Health and Nutrition Examination Survey
PFT	Pulmonary function test
PK	Pharmacokinetics
PT009	Budesonide and Formoterol Fumarate Inhalation Aerosol
PT010	Budesonide, Glycopyrronium, and Formoterol Fumarate Inhalation Aerosol
QTcF	Fridericia-corrected QT interval
RAC(C_{max})	Accumulation ratio for C_{max}
RAC(AUC_{0-12})	Accumulation ratio for AUC_{0-12}
Rlin	Linearity ratio
SABA	Short-acting β2-agonist
SAE	Serious adverse event
SAMA	Short-acting muscarinic antagonist
SAP	Statistical analysis plan
$t_{1/2}$	Apparent terminal elimination half-life

TEAE	Treatment-emergent adverse event
t_{max}	Time to maximum plasma concentration
US	United States
Vd/F	Apparent volume of distribution

TRADEMARK INFORMATION

Trademarks not owned by the Sponsor:

Foradil
Perforomist
Pulmicort
Rhinocort
Robinul
Seebri
Symbicort
Turbuhaler
Xolair

1 INTRODUCTION AND STUDY RATIONALE

Chronic obstructive pulmonary disease (COPD) is a common preventable and treatable disease characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases, the most common of which is cigarette smoke. Exacerbations and co-morbidities contribute to the overall severity in individual patients. Chronic obstructive pulmonary disease is a leading cause of morbidity and mortality worldwide and results in a significant economic and social burden that is both substantial and increasing. Pharmacologic therapy in COPD is used to reduce symptoms, reduce the frequency and severity of exacerbations, and improve health status and exercise tolerance (Global Initiative for Chronic Obstructive Lung Disease [GOLD 2017]).

Bronchodilator medications are central to the symptomatic management of COPD. The principal bronchodilator treatments are β_2-agonists, anticholinergics, and methylxanthines used as monotherapy or in combination. Treatment with long-acting bronchodilators is more convenient and more effective at producing maintained symptom relief than treatment with short-acting bronchodilators.

Regular treatment with inhaled corticosteroids (ICS) improves symptoms, lung function, and quality of life and reduces the frequency of exacerbations in subjects with COPD with a forced expiratory volume in 1 second (FEV_1) value of <60% of predicted. Withdrawal from treatment of ICS may lead to exacerbations in some patients. When combined with a long-acting β_2-agonist (LABA), an ICS is more effective than the individual components in improving lung function and quality of life and reducing exacerbations in subjects with moderate to very severe COPD (GOLD 2017).

Pearl Therapeutics, Inc. (hereinafter referred to as Pearl) is developing a fixed-dose ICS/long-acting muscarinic antagonist (LAMA)/LABA triple combination product, Budesonide, Glycopyrronium, and Formoterol Fumarate Inhalation Aerosol (PT010), hereafter referred to as Budesonide, Glycopyrronium, and Formoterol Fumarate Metered Dose Inhaler (BGF MDI), for the treatment of patients with COPD. Budesonide and Formoterol Fumarate Inhalation Aerosol (PT009), hereinafter referred to as Budesonide and Formoterol Fumarate (BFF) MDI is also being developed as a twice daily (BID) fixed dose ICS/LABA treatment for patients with COPD. Glycopyrronium, and Formoterol Fumarate Inhalation Aerosol MDI is approved in the United States (US) as a BID maintenance bronchodilator treatment in patients with COPD under the tradename Bevespi Aerosphere®.

Budesonide is a well-established corticosteroid approved worldwide in monotherapy and combination therapies for the treatment of asthma and allergic rhinitis. It is available in both intranasal and orally inhaled formulations. Inhaled budesonide in combination with formoterol fumarate dihydrate (ie, Symbicort® [AstraZeneca, LP]) is approved for use in patients with asthma and COPD.

Glycopyrronium is a LAMA that exerts its bronchodilatory effect via muscarinic receptors located on smooth muscle cells within the trachea and bronchi. Glycopyrronium is approved

in many countries in multiple formulations for different indications, including for the treatment of COPD.

Formoterol fumarate is a selective LABA approved worldwide for use in asthma and COPD. In addition, formoterol fumarate is also approved worldwide in combination with budesonide (eg, Symbicort MDI, Symbicort Turbuhaler® [AstraZeneca, LP]) for use in patients with asthma and COPD. When inhaled, formoterol fumarate acts locally in the lung as a bronchodilator. Formoterol fumarate stimulates β_2-adrenoreceptors in the airways, inducing airway smooth muscle relaxation and reducing or preventing bronchoconstriction.

The purpose of this study is to determine the pharmacokinetics (PK) of BGF MDI in subjects with COPD following single and repeat administration. This will allow determination of accumulation of each component of BGF MDI in plasma during steady-state administration. The plasma concentration data will also contribute to population PK modeling.

2 STUDY OBJECTIVES

2.1 Primary Objective

- To assess the PK profile of BGF MDI in subjects with moderate to severe COPD after single dose administration on the first treatment day and after 7 days of repeat dosing

2.2 Safety Objective

- To assess the safety and tolerability of BGF MDI in subjects with moderate to severe COPD after single dose administration on the first treatment day and after 7 days of repeat dosing

3 STUDY ENDPOINTS

3.1 PK Endpoints

Pharmacokinetics of BGF MDI will be assessed using plasma concentrations of budesonide, glycopyrronium, and formoterol pre-dose and at various times post-dose on Day 1 and Day 8.

3.1.1 Primary PK Endpoints

- Maximum plasma concentration (C_{max})
- Area under the plasma concentration-time curve from 0 to 12 hours (AUC_{0-12})
- Area under the plasma concentration-time curve from 0 to the time of the last measureable plasma concentration ($AUC_{0-tlast}$)

3.1.2 Secondary PK Endpoints

- Time to maximum plasma concentration (t_{max})
- Area under the plasma concentration-time curve from 0 extrapolated to infinity ($AUC_{0-\infty}$)

3.1.3 Other PK Endpoints

The following PK parameters will be calculated at Day 1 only:

- Apparent terminal elimination half-life ($t_{1/2}$)
- Apparent total body clearance (CL/F)
- Apparent volume of distribution (Vd/F)
- Terminal elimination rate constant (λ_z)

The following will be derived based on ratios of Day 8 values to Day 1 values:

- Accumulation ratio for C_{max} (RAC [C_{max}])
- Accumulation ratio for AUC_{0-12} (RAC [AUC_{0-12}])
- Linearity ratio (Rlin [$AUC_{0-12}/AUC_{0-\infty}$])

Other PK parameters may be calculated, as appropriate.

3.2 Safety Endpoints

- Adverse events (AEs)
- 12-lead electrocardiograms (ECGs)
- Clinical laboratory testing
- Vital sign measurements

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

This is a Phase I open-label, single center study to assess the PK and safety of BGF MDI 320/14.4/9.6 µg in subjects with moderate to severe COPD. Pharmacokinetics will be assessed following a single dose administration on the first treatment day (Day 1) and will be assessed again after 7 days of repeat dosing. This study includes a Screening Period of up to 28 days and a single Treatment Period of 8 days. A follow-up phone call will be conducted at least 5 days but no longer than 7 days after the last dose of study drug.

Subjects who provide informed consent before the conduct of any screening assessments will undergo screening procedures to determine eligibility to participate in the study.

To be considered eligible for the study, subjects must have a documented history (ie, within the past 12 months) of COPD defined as a post-bronchodilator FEV_1/forced vital capacity (FVC) <0.70 and a post-bronchodilator FEV_1 <80% predicted normal. Subjects without historical documentation must meet these criteria at the Screening Visit. In addition, subjects must have a pre-bronchodilator FEV_1 between ≥50 and <80% predicted normal during Screening after withholding all COPD medications and after withholding the use of albuterol for at least 6 hours prior to the assessment. All eligible subjects will receive Sponsor-provided Ventolin® hydrofluoroalkane (HFA; albuterol sulfate inhalation aerosol) for rescue use throughout the study. During the Screening Period, eligible subjects will continue the use of their regular COPD maintenance therapy. However, any medication containing any one or more of the components of BGF (all formulations of budesonide, glycopyrronium, or formoterol fumarate) are prohibited a minimum of 4 weeks before Screening and during the study.

Subjects will be admitted to the clinic as an inpatient on Day -1, at which time continuing eligibility will be assessed and subjects will be instructed to discontinue all COPD therapy except study-provided rescue Ventolin HFA after their last dose for the day. Study subjects will use a Placebo MDI for training purposes only to demonstrate proper use of the MDI on Day -1, Day 1, Day 7, and Day 8. The Treatment Period of 8 days will start on Day 1. BGF MDI 320/14.4/9.6 µg will be administered as oral inhalation as follows:

- Single dose administration on the morning of Day 1 (Visit 3) followed by serial blood draws for 24 hours
- BID dosing every morning and evening on Days 2 through Day 7 approximately 12 hours apart
- Single dose administration on the morning of Day 8 (Visit 5) followed by serial blood draws for 12 hours

Subjects will be discharged on Day 2 of the Treatment Period after performing the last PK blood draw and will continue to administer BGF MDI BID at home on Days 2 through 7.

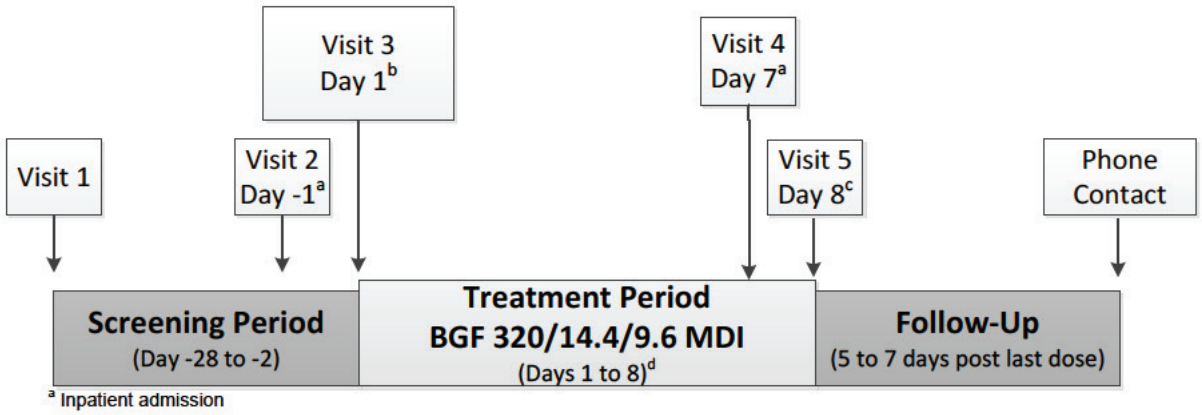
Subjects will return to the clinic for inpatient admission on Day 7 (Visit 4) and administer the evening dose of study drug at the clinic.

Subjects will undergo safety assessments and serial blood draws as defined in Table 8-1, Table 8-2, and Table 8-3. After all protocol-specified assessments are completed and safety data has been reviewed by the PI or designated staff, the subject will be discharged from the clinic on Day 8.

Subjects will return to appropriate COPD maintenance medications after the final assessments on Day 8 are completed.

The overall study design is presented in Figure 4-1.

Figure 4-1. Study Design



[a] Inpatient admission

[b] Day 1, pre-defined serial PK draws for 24 hours following single study drug dose administration

[c] Day 8, pre-defined serial PK draws for 12 hours following single study drug dose administration

[d] Administer study drug once in the morning on Days 1 and 8 and BID each morning and evening approximately 12 hours apart on Days 2 to 7

Note: All study drugs are administered by oral inhalation. Administration of study drug should occur at approximately the same time of day.

4.2 Study Duration

This study will include a Screening Period of up to 28 days and a single Treatment Period of 8 days. A follow up phone call will be conducted at least 5 days but no longer than 7 days after the last dose of study drug on Day 8. For each subject, the total time to complete the study is up to 7 weeks with an expected range of participation between 2.5 to 7 weeks. The study is anticipated to run for approximately 4 to 6 months.

5 STUDY POPULATION SELECTION

Approximately 30 subjects with moderate to severe COPD will be enrolled in this study. Subjects who withdraw from the study after receiving at least 1 dose of study drug will not be replaced. Subjects who are enrolled but do not receive study will be replaced. Subjects who are re-evaluated will maintain 1 screening number throughout the study.

5.1 Inclusion Criteria

Each subject must meet the following criteria to be enrolled in this study.

1. Give their signed written informed consent to participate
2. Are at least 40 and no older than 80 years of age at Visit 1
3. Agree to one of the following to prevent pregnancy:
   - Non-childbearing potential (ie, 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])
     Note: 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 sexually active woman of childbearing potential, agrees to prevent pregnancy by using one of the following methods of birth control from the date the informed consent form (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 or condom plus spermicide)
     - Maintenance of a monogamous relationship with a male partner who has been surgically sterilized by vasectomy
   - If a woman of childbearing potential, have a negative serum pregnancy test at Visit 1
   - Males who are sexually active must agree to use a double-barrier method of contraception (condom with spermicide) from the first dose of study drug until 2 weeks after their last dose, and must not donate sperm during their study participation period
4. COPD Diagnosis: An established clinical history of COPD as defined by the American Thoracic Society (ATS)/European Respiratory Society (ERS) (Celli 2004) characterized by progressive airflow limitation associated with an abnormal inflammatory response of the lungs to noxious particles or gases, primarily caused by cigarette smoking. This includes demonstration (at the Screening Visit or within the past 12 months) of a post-bronchodilator FEV_1/FVC ratio of <0.70 and post-bronchodilator FEV_1 of <80% predicted normal value.

5. Tobacco Use: Current or former smokers with a history of at least 10 pack-years of cigarette smoking. Number of pack-years= (number of cigarettes per day/20) × number of years smoked (eg, 20 cigarettes per day for 10 years, or 10 cigarettes per day for 20 years represent 10 pack-years).
6. COPD Severity: At Visit 1, pre-bronchodilator FEV_1/FVC ratio must be <0.70 and pre-bronchodilator FEV_1 must be ≥50% and <80% predicted normal value calculated using National Health and Nutrition Examination Survey (NHANES) III reference equations.
7. Screening clinical laboratory tests must be acceptable to the Investigator.
8. Screening ECG must be acceptable to the Investigator.
9. Compliance: Must be willing to remain at the study center as required per protocol to complete all visit assessments.
10. Demonstrate correct MDI administration technique. Spacer use is prohibited

5.2 Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from the study:

1. Pregnancy and Lactation: Women who are pregnant or lactating, or are planning to become pregnant during the course of the study, or women of childbearing potential who are not using an acceptable method of contraception.
2. Asthma: Subjects who have a diagnosis of asthma. (**Note:** Subjects with a primary diagnosis of COPD but a prior history of asthma that is remote (ie, more than 10 years since it has been an active diagnosis) are eligible.
3. Alpha-1 Antitrypsin Deficiency: Alpha-1 antitrypsin deficiency as the cause of COPD.
4. Other Respiratory Disorders: Includes other active pulmonary disease such as active tuberculosis, lung cancer, bronchiectasis, sarcoidosis, lung fibrosis, primary pulmonary hypertension, interstitial lung disease and uncontrolled sleep apnea (ie, in the opinion of the Investigator, severity of the disorder would impact the conduct of the study).
5. Lung Resection: Subjects who have undergone lung volume reduction surgery at any time in the past.
6. Exacerbation: Subjects who have had a moderate or severe COPD exacerbation (ie, an exacerbation for which the subject was hospitalized or required systemic corticosteroids or antibiotics) within 3 months of Screening (Visit 1).
7. Lower respiratory tract infections: Subjects who have had lower respiratory tract infections that required antibiotics within 3 months prior to Screening (Visit 1).
8. Spirometry Performance: Subjects who cannot perform acceptable spirometry as per ATS/ERS criteria (Miller 2005).
9. Other Diseases: Subjects who have clinically significant medical conditions, including but not limited to cardiovascular, neurological, psychiatric, hepatic, gastrointestinal, renal (creatinine clearance ≤30 mL/minute), immunological, glaucoma, symptomatic prostatic hypertrophy (if treated and asymptomatic, the subject is eligible for enrollment),

endocrine (including uncontrolled diabetes or thyroid disease), or hematological medical problems.

10. Clinically significant abnormal ECG: Subjects who in the opinion of the Investigator have a clinically significant abnormal 12-lead ECG. A clinically significant abnormal ECG is defined as (but not limited to) any of the following:
    - Clinically significant conduction abnormalities (eg, complete left bundle branch block, Wolff-Parkinson-White syndrome)
    - Clinically significant arrhythmias (eg, atrial fibrillation, ventricular tachycardia)
    - Fridericia-corrected QT interval (QTcF) ≥500 msec in subjects with QRS <120 msec and QTcF ≥530 msec in subjects with QRS ≥120 msec
    - Ventricular rate <45 bpm
    - Evidence of second-degree (Mobitz Type II) or third-degree atrioventricular block
    - Pathological Q waves of 1 year or less
    - ST-T wave abnormalities deemed to be clinically significant by the Investigator. Note: Subjects with non-specific ST-T wave abnormalities that are not deemed clinically significant (per Investigator) are allowed.
11. Uncontrolled Hypertension: Subjects who have clinically significant uncontrolled hypertension.
12. Liver Function: Abnormal liver function tests defined as aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, or total bilirubin ≥1.5 times upper limit of normal on repeat testing
13. Cancer: Cancer that has not been in complete remission for at least 5 years
    Note: Subjects with squamous cell carcinoma and/or basal cell carcinoma of the skin or localized prostate cancer that in the opinion of the Investigator has been adequately worked up, is clinically controlled, and where the subject's participation in the study would not represent a safety concern, are eligible.
14. Drug Allergy: Subjects who have a history of hypersensitivity to any corticosteroid, β2-agonist, muscarinic anticholinergic, or any component of the MDI.
15. Anemia: Subjects with anemia that is considered clinically significant by the Investigator
16. History of blood donation within 90 days before Screening
17. Surgery: Subjects with major surgical interventions within 4 weeks before Screening or minor surgical interventions within 2 weeks before Screening
18. Substance Abuse: Subjects with a known or suspected history of alcohol or drug abuse within 1 year prior to Screening
19. An abnormal clinically significant chest X-ray during Screening or within 6 months prior to Screening. If the subject is able to provide a report of a chest X-ray or computed tomography within 6 months prior to Screening to assess this criterion, a chest X-ray at Screening will not be required.
20. Medication Prior to Spirometry: Subjects who are medically unable to withhold their short-acting bronchodilators for the 6-hour period required prior to spirometry

21. Prohibited COPD Medications: Unable to abstain from protocol-defined prohibited medications during Screening and Treatment Periods (Section 5.4)
22. Oxygen: Requirement for oxygen therapy for >12 hours/day
23. Non-compliance: Unable to comply with study procedures
24. Affiliations with Investigator Site: Study Investigators, Sub-Investigators, study coordinators, employees of a participating Investigator, or immediate family members of the aforementioned are excluded from participation in this study.
25. Questionable Validity of Consent: Subjects with a history of psychiatric disease, intellectual deficiency, poor motivation, substance abuse (including drug and alcohol), or other conditions that might limit the validity of informed consent to participate in the study.
26. Investigational Drugs or Devices: Treatment with an investigational study drug or participation in another clinical trial or study within the last 30 days or 5 half-lives prior to Screening, whichever is longer.
27. Previous treatment in a Pearl BGF MDI or BFF MDI study

5.3 Subject Identification

All subjects who undergo screening procedures will be assigned a unique subject identification number at Screening. Only subjects continuing to meet entry inclusion/exclusion criteria on Day 1 will be assigned a unique subject enrollment number.

5.4 Prior, Concomitant, and Prohibited Medications

All prescription and over-the-counter medications taken by the subject within 30 days prior to Visit 1 will be recorded on the Prior/Concomitant Medications electronic case report form (eCRF).

All concomitant medications taken during the study will be recorded on the Concomitant Medications eCRF page with indication, total daily dose, and dates of drug administration.

Any additions, deletions, or changes in the dose of these medications while in the study should be recorded on the eCRF. Any current ongoing medications, including over-the-counter drugs and herbal supplements, will be allowed provided they are not prohibited by the protocol (see Section 5.4) and are approved by the Investigator.

5.4.1 Prior, Concomitant, and Prohibited COPD Medications

All formulations of budesonide, glycopyrronium, or formoterol fumarate used as monotherapy or in combination to treat COPD or any other condition (eg, allergic rhinitis) are prohibited for a minimum of 4 weeks before Visit 1 and during the study. Examples of these medications are summarized in Table 5-1.

Table 5-1 Prohibited Budesonide, Glycopyrronium, and Formoterol Fumarate COPD Medications

Product	Example Trade Names
Budesonide-containing products	Symbicort, Rhinocort®, Pulmicort®
Glycopyrronium-containing products	Seebri®, Robinul®, Bevespi
Formoterol fumarate-containing products	Symbicort, Foradil®, Perforomist®, Bevespi

All subjects entering the study on allowed inhaled COPD maintenance therapies for the management of their COPD should have been maintained on a stable dose of this treatment for at least 4 weeks prior to Visit 1. These COPD maintenance medications will be withheld after their last dose for the day on Day -1 (Visit 2) and throughout the study.

Additionally, short acting bronchodilators (eg, short-acting β_2-agonists [SABAs] or short-acting muscarinic antagonists [SAMAs] or their combinations) will be withheld 6 hours prior to spirometry assessment at the Screening Visit and throughout the study except study-provided Ventolin HFA for use as needed for symptom relief. Additional prohibited COPD medications and associated cessation periods prior to Visit 1 are summarized in Table 5-2.

Table 5-2 Other Prohibited COPD Medications

Prohibited COPD Medications	Minimum Cessation Period Prior to Visit 1
Parenteral, depot, and oral steroids	3 months
Nebulized albuterol and/or ipratropium COPD medications	6 hours
Oral β-agonists	2 days
Theophylline (total daily dose >400 mg/day)[a]	7 days
SAMA	6 hours
SABA[b]	6 hours
Fixed-dose combinations of SAMA/SABA	6 hours

Note: Subjects requiring chronic maintenance therapy with oral corticosteroids are excluded from participation in this study.

Note: Subjects requiring maintenance therapy with roflumilast (or any phosphodiesterase 4 inhibitor) are excluded from participation in this study.

[a] Theophylline ≤400 mg/day is permitted provided the subject has been on a stable dose of therapy for at least 4 weeks prior to Visit 1.

[b] Discontinue and use Sponsor-provided Ventolin HFA

5.4.2 Other Prohibited Medications

Subjects requiring medications presented in Table 5-3 are prohibited from participating in this study. Subjects who recently discontinued use of these medications may be considered for study enrollment provided they have not received these medications for a minimum of 4 weeks before Visit 1. These medications are prohibited throughout the course of the study.

Table 5-3 Other Prohibited Medications

Any drug with potential to significantly prolong the QT interval (eg, quinidine, bepridil, sotalol, amiodarone, chlorpromazine, erythromycin, etc)[a]
Non-selective beta-adrenergic antagonists
Cardiac antiarrhythmics Class Ia, III
Any drug that causes significant tachycardia (pseudoephedrine, appetite suppressants, etc)
Other investigational drugs[b]
CYP3A4 inhibitors, including amiodarone, diltiazem, cimetidine, erythromycin, itraconazole, norfloxacin, ciprofloxacin, fluconazole, ketoconazole, clarithromycin, fluvoxamine, mifepristone, nefazodone, and troleandomycin
CYP3A4 inducers including barbiturates (eg, phenobarbital), carbamazepine, phenytoin, and rifampin
Anticonvulsants (barbiturates, hydantoins, and carbamazepine) for the treatment of seizure disorder[c]
Tricyclic antidepressants[d]
Antipsychotic drugs (phenothiazines)[d]
Monoamine oxidase inhibitors
Anti-tumor necrosis factor α antibodies (eg, infliximab and any other members of this class of drugs)
Monoclonal antibodies[e]
Systemic calcineurin inhibitors
Protease inhibitors
Systemic anticholinergics[f]
Chinese complementary and alternative bronchodilatory medicines, ie, herbal therapies (eg, *Astragalus membranaceus* [huáng qí], *Panax ginseng* [ginseng products], *Cordyceps sinensis*, and *A. membranaceus* [ghost moth caterpillar fungus])

Table 5-3 Other Prohibited Medications

Abbreviation: CYP3A4=cytochrome P450 3A4.

Note: Benzodiazepines are not exclusionary.

[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 prior to Screening, 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 study.

[b] Investigational therapies are not permitted within 30 days or 5 half-lives (whichever is longer) prior to Screening.

[c] Anticonvulsants for conditions other than seizures may be started and stopped at any time prior to the study and throughout the Treatment Period.

[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 subject safety, and if the subject has been on a stable dose for at least 6 weeks.

[e] Investigators should consult the Medical Monitor to determine the appropriateness and safety of continuing study drug on a case by case basis (eg, XOLAIR® [omalizumab] will not be allowed, whereas a monoclonal for another indication such as osteoporosis may be allowed after consultation).

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

Any other medication that is considered necessary for the subject's safety and well-being may be given at the Investigator's discretion.

5.5 Other Study Restrictions

5.5.1 Dietary Restrictions

Fasting (at least 6 hours) is required for clinical laboratory testing at Visit 1, Visit 2 (Day -1), and Visit 5 (Day 8).

Fasting (at least 6 hours) is required prior to administration of BGF MDI on serial PK sample collection days (Days 1 and 8). Food may be consumed 4 hours after dosing.

Standardized meals will be administered on Days 1, 2, and Day 8 at specified times after observation of fasting time for blood draws. There are no restrictions regarding clear fluid intake.

Subjects are not allowed to consume grapefruits or grapefruit juice throughout the study. Subjects must not ingest xanthine (caffeine)-containing foods, beverages, or medications for at least 6 hours prior to study drug administration and for 4 hours post dose on the days of serial PK assessments (Day1 and Day 8). Examples of such products include coffee, tea, chocolate, and cola. Decaffeinated beverages are acceptable.

5.5.2 Illicit Drugs and/or Drugs of Abuse Restriction

Illicit drugs and/or drugs of abuse will not be allowed from within 1 year of Screening to whenever the subject withdraws from or completes 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.

5.6 Study Withdrawal

The Investigator or medically qualified designee may withdraw a subject at the occurrence of any or all of the following:

- Protocol deviation
- AE
- COPD exacerbation
- Subject becomes pregnant
- Clinically significant change in a laboratory parameter(s)
- Termination of the study by the Sponsor or Investigator
- Request by the subject to be discontinued from the study
- Investigator's discretion

6 LABELING, PACKAGING, STORAGE, DISPENSING, AND RETURN OF CLINICAL SUPPLIES

Study drug will be packaged to support enrollment of the study in an open-label fashion for the 8-day Treatment Period. Clinical supplies will be packaged according to a component schedule generated by the Sponsor or their designee.

6.1 Description of Study Drug

In this protocol, "study drug" refers to an active ingredient or placebo being tested or used as a reference in the study (International Conference on Harmonisation [ICH] E6 R1). The study drug used in this study is described in Table 6-1. Instructions for use/priming are provided in Appendix 2. Subjects meeting all study eligibility criteria (Section 5) will be assigned to open-label study drug at Visit 3 to be administered as directed in Section 6.5.

The BGF MDI active drug substances are budesonide, glycopyrronium, and formoterol fumarate. Study drug will be provided by Pearl.

Table 6-1 Study Drug Description

Product Name & Dose	Product Strength	Dosage Form/Fill Count	Administration
BGF MDI 320/14.4/9.6 µg ex-actuator	160/7.2/4.8 µg/actuation	MDI/120 inhalations	2 inhalations BID

Note: Study drug will be administered by oral inhalation. A single dose of study drug will be administered on Day 1, and BID doses will be administered Day 2 through Day 7, with a final single administration of study drug occurring on the morning of Day 8. Administration of study drug should occur at approximately the same time of day approximately 12 hours apart.

6.2 Other Sponsor-Provided Medications Used in the Study

Other Sponsor-provided medications used during the study are described in Table 6-2. The manufacturer's instructions for administration, cleaning, and storage are provided in Appendix 2 and Appendix 3.

Table 6-2 Other Medications Provided by Sponsor

Product Name & Dose	Product Strength	Dosage Form/Fill Count	Administration
Albuterol sulfate inhalation aerosol 90 µg ex-actuator	Ventolin HFA Each inhalation contains 108 µg albuterol sulfate corresponding to 90 µg albuterol base from the mouthpiece	MDI/60 or 200 actuations	Taken as 2 inhalations up to 4 times daily as needed for symptom relief during the study and as 4 puffs for post-bronchodilator testing at Visit 1
Placebo MDI[a]	Formulation does not contain active ingredient	MDI 120 inhalations	Subjects will use the Placebo MDI for training purpose only to demonstrate proper use of the MDI on Day -1, Day 1, Day 7, and Day 8

[a] All Placebos MDIs are identical in appearance to study drug; they have no active moieties and have a different labels because they are only used for training.

6.3 Packaging and Labeling

All clinical trial supplies will be packaged by the Sponsor.

Study drug (BGF MDI) will be packaged in a box and labeled with a single label. Inside the box will be a labeled foil pouch containing a labeled MDI canister and actuator.

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

Lot # (Packaging Lot Trace ID)	Storage Conditions
Space for entry of screening #	Protocol #
Component ID #	Country regulatory requirements
Space for entry of randomization #	Sponsor address
Fill Count & Dosage Form	Translation Key
Visit # (Space for Entry of Interval ID)	

Abbreviations: #=number; ID=identification.

Ventolin HFA will be provided as individually labeled MDIs with a single label on the actuator and canister.

Labels will be printed with black ink and may include the following text:

Lot # (Packaging Lot Trace ID)	Storage Conditions
Space for entry of screening #	Protocol #
Component ID #	Country regulatory requirements
Space for entry of randomization #	Sponsor address
Fill Count & Dosage Form	Translation Key
Visit # (Space for Entry of Interval ID)	

Placebo MDI will be packaged in individual boxes and labeled for training purpose only. Inside the box will be a labeled foil pouch containing a labeled MDI canister and actuator

6.4 Storage Requirements

All study supplies should be kept in a locked cabinet or room with limited access. The temperature of the site's storage area for study supplies must be monitored by site staff for temperature ranges consistent with those specified in the protocol. Documentation of temperature monitoring should be maintained at the site and available for review. All study supplies contain contents under pressure. Do not use or store near heat or open flame. Exposure to temperatures above 49°C (120°F) may cause bursting. Never throw canisters into a fire or incinerator. Avoid spraying in eyes.

BGF MDI and Placebo MDI should be stored below 25°C (77°F) in a dry place. Excursions permitted up to 30°C (86°F).

Ventolin HFA should be stored between 15°C and 25°C (59°F and 77°F). Store the inhaler with the mouthpiece down. For best results, the inhaler should be at room temperature before use.

6.5 Instructions for Preparation of Study Drug for Administration

Individual BGF MDI devices 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. The visit treatment box is labeled with a 2-part label. Write the subject number and treatment visit number on each of the 2-part labels.

All subjects will receive BGF MDI (320/14.4/9.6 µg). Site staff will instruct study subjects on the proper use of an MDI using a bulk-supplied MDI (placebo). Subjects must demonstrate correct use of the MDI at Screening, Day -1, and before study drug dosing on Day 1, Day 7, and Day 8.

All MDIs must be primed 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 the inhaler is ready to use. Priming must occur in a separate room away from the subject treatment area.

Designated study site staff will be responsible for priming the study drug. On Day 1 of the Treatment Period, prior to the first study drug administration, the MDI device will be primed by the site staff in a separate room, or under an externally vented hood away from the treatment area. Priming in the same room as subjects being dosed is strictly prohibited as this could lead to cross contamination of different subjects.

Just prior to dosing, subjects will be trained again on the proper use of the MDI device so that they are able to use it correctly.

Once primed and the subject demonstrates the proper use of the MDI, the first dose (2 puffs) of study drug should be taken by the subject in the clinic under site personnel supervision.

The date and time of the second puff should be recorded as the time of dose administration in the source and eCRF.

Refer to Appendix 2 for additional instructions on the administration and cleaning of the BGF MDI and Placebo MDI.

On serial PK days (Day 1 and Day 8), administration of BGF MDI will take place in a room separate from the room where blood samples will be drawn. Subjects and clinic personnel will wear protective clothing and vinyl gloves which will be discarded immediately after administration in the room used for inhalation, to avoid subsequent contamination of blood samples, according to the routines at the clinic. The subjects will also wash their hands and faces with water and rinse and clean their mouths twice with 25 mL water (rinse and spit out) after the administration of BGF MDI. Each dose will consist of 2 puffs from the MDI.

Study site personnel should clean and dry the inhaler for 12 hours overnight following the evening dose on Day 7.

6.6 Study Drug Dosing

Designated study staff will schedule the first dose of study drug administration in the clinic to occur in the morning, before approximately 10 am.

On Day 2, before discharge, BGF MDI will be dispensed and the subject should be instructed that subsequent morning study drug dosing should occur BID (2 puffs in the morning and 2 puffs in the evening) at approximately the same time every day, and that evening dosing should occur as close as possible to 12 hours from the time of morning dosing. Study drug dosing should continue until the subject returns to the clinic on Day 7. Site staff will contact the subject by telephone each morning and evening during the Treatment Period to ensure study drug dosing compliance.

For each subject, treatment will comprise of single dose administration (Day 1), BID dosing (Day 2 through Day 7), and a single morning dose on Day 8.

6.7 Emergency Unblinding of Treatment Assignment

Not applicable - this is an open-label study.

6.8 Study Drug Accountability/Return of Clinical Supplies

Under no circumstances will the Investigator 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 secure location to which only the Investigator and designated study personnel 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 or designee is responsible for keeping accurate records of the clinical supplies received from the Sponsor, the amount dispensed to and returned by the subject, and the amount remaining at the conclusion of the study. Study drug should be handled in accordance with instructions provided in this section. 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 Pearl representative for appropriate documentation that needs to be completed for drug accountability.

The Investigator or designee should not open the individual clinical supply containers until all pre-dose assessments have been completed and the subject is eligible to be enrolled in the study. Any deviation from this must be discussed with the with the Sponsor's Medical Monitor or designee.

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.

All product complaints (including device malfunctions) must be reported to the Sponsor or the Sponsor's representative using the Product Complaints Form provided in each site's regulatory binder. The Sponsor or the Sponsor's representative will contact the site to evaluate the nature of the complaint, related testing and determine if further action is needed.

7 STUDY PROCEDURES

7.1 Informed Consent

The ICF must be executed *prior* to performing any and all study-related activities. The ICF must be approved by the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) that is reviewing the study documents. The ICF will be obtained for all subjects participating in the study. Subjects may withdraw consent at any time. Participation in the study may be terminated at any time without the subject's consent as determined by the Investigator.

7.2 Subject Eligibility

Eligibility screening of COPD subjects will be completed within 28 days prior to administration of the first dose of study drug and will be documented on the eCRF. Eligibility will be confirmed at each clinic visit. Subjects will be admitted to the clinic on Day -1 and discharged on Day 2 and return for clinic admission on the evening of Day 7, with discharge on Day 8 after all assessments are complete. Screen failure and the reason for screen failure will be documented in the study site source documents and captured in the eCRF.

7.3 Subject Diary Data Collection

Subjects will be provided with a diary to be completed BID to record their at-home study drug dosing (refer to dose indicator instructions in Appendix 1).

The subject is to return the completed diary at Day 7 (Visit 4). The study coordinator will be responsible for reviewing the diary for completeness and accuracy with the subject before dosing study drug in the clinic. All fields should be completed by the subject. The subject will sign (initial) and date each page of the diary on the day it was completed, and the study coordinator will initial and date each diary page at the site visit when the diary is returned to validate the authenticity of the entries. If discrepancies or omissions of data are observed at this review, the subject, not the study coordinator, should make the corrections. The subject should draw a single line through the error and initial and date all corrections. The subject should make all entries in the diary in blue or black ink.

7.4 Pulmonary Function Tests

Forced expiratory maneuvers for derivation of FEV_1 and FVC will be assessed using the site's spirometry equipment, which must comply with the ATS/ERS Task Forces recommendation for standardization of lung function testing (Miller 2005). All spirometry tests, including FEV_1 and FVC maneuvers, will be performed according to the ATS/ERS criteria (Miller 2005) (Appendix 4).

The volume accuracy of the spirometer is to be checked daily 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/ERS specifications and must 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 5).

Spirometry assessments will be conducted at Screening Visit 1.

7.4.1 Lung Function Assessment

A subject may be eligible to participate in this study if they have a confirmed diagnosis of COPD (defined as a post-bronchodilator FEV_1 <80% of predicted normal [calculated using NHANES III reference equations] and a post-bronchodilator FEV_1/FVC ratio of <0.70). Documentation of the COPD diagnosis (defined as FEV_1 <80% predicted and FEV_1/FVC <0.70) within the past 12 months is acceptable. If this is not available, the subject must undergo a post-bronchodilator assessment at Visit 1to confirm the COPD diagnosis as previously defined. All subjects must also have a pre-bronchodilator FEV_1 at Visit 1 that is ≥50% and <80% of predicted normal and a pre-bronchodilator FEV_1/FVC ratio of <0.70.

7.4.2 Pre- and Post-Bronchodilator Assessments

Post-bronchodilator testing to Ventolin HFA will only be conducted at Visit 1 for subjects who do not have documentation of a post-bronchodilator FEV_1 <80% predicted and an FEV_1/FVC <0.70 in the past 12 months:

- Perform pre-bronchodilator pulmonary function tests (PFTs) (within 60 minutes) prior to administration of Ventolin HFA (all subjects)
- Administer 4 puffs of Ventolin HFA (only subjects without documentation in the past 12 months)
- Perform post-bronchodilator PFTs 30 minutes after the administration of Ventolin HFA (only subjects without documentation in the past 12 months)

To determine study eligibility criteria for a study subject, the Investigator and/or designee will review the following:

- Pre- and post-bronchodilator PFTs to ensure the maneuvers meet repeatability and acceptability criteria per ATS/ERS guidelines
- Diagnosis of COPD is confirmed using historical or Visit 1 post-bronchodilator assessments
- Pre-bronchodilator FEV_1 is ≥50% and <80% predicted and pre-bronchodilator FEV_1/FVC ratio is <0.70

7.5 PK Assessments

Pharmacokinetic sampling will occur during the Treatment Period. Sample collections will be scheduled for the nominal time point, and actual collection times will be recorded in the source documents.

7.5.1 Blood Sample Collection Schedule

Approximately 10 mL of whole blood will be collected at each time point indicated below and within 60 minutes prior to the morning administration of study drug as referenced in Table 8-2 and Table 8-3. Subjects must fast for at least 6 hours prior to dosing on serial PK days (Day 1 and Day 8). Meals on Days 1 and 8 will be standard but will not begin until the 4 hours post-dose blood samples are obtained.

- Pre-dose sample collection - Days 1 (morning dose), 7 (evening dose), and 8 (morning dose) (Table 8-2 and Table 8-3)
- Post-dose sample collection
  - Day 1 ONLY (Table 8-2)
  - Day 8 ONLY (Table 8-3)
- The recommended time windows for post-dose PK assessments are as follows:

Time points	Time windows
2 and 6 min	±1 min
20 and 40 min and 1 h	±2 min
2 and 4 h	±5 min
8, 10, 12, 18, and 24 h	±10 min

Collection and storage of PK samples will be detailed in the laboratory manual.

7.5.2 Procedures for Shipping Samples

Samples are to be shipped frozen by overnight courier to the bioanalytical laboratory for analysis. Instructions for sample handling, storage, and shipping will be provided in the laboratory manual.

7.5.3 Storage and Destruction of PK Samples

Samples for determination of study drug concentration in plasma will be analyzed by [redacted] on behalf of Pearl using an appropriate bioanalytical method. Full details of the analytical method used will be described in a separate bioanalytical report.

Pharmacokinetic samples will be disposed of after the bioanalytical report finalization or 6 months after issuance of the draft bioanalytical report (whichever is earlier), unless requested for future analyses.

Pharmacokinetic samples may be disposed of or destroyed and anonymized by pooling. Additional analyses may be conducted on the anonymized, pooled PK samples to further evaluate and validate the analytical method. Any results from such analyses may be reported separately from the clinical study report.

Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples. The results from the evaluation will not be reported in the clinical study report but separately in a bioanalytical report.

7.6 Safety Assessments

7.6.1 Medical History

Relevant medical history, based on the opinion of the Investigator, will be obtained from the subject at Screening and recorded on the source document. Medical history will include the subject's family health history, history of hospitalization, and history of surgeries.

7.6.2 Physical Examination

A complete physical examination including evaluation of the following will be performed at Screening and on Day -1 and Day 8:

- General appearance, skin, head, eyes, ears, nose, throat, neck (including thyroid), lymph nodes, respiratory, cardiovascular, musculoskeletal, abdominal, extremities, neurological and dermatological.
- Weight and height, assessed in ordinary indoor clothing with shoes removed, will also be recorded during Screening only

7.6.3 Vital Signs

Vital signs including blood pressure (BP) and heart rate will be assessed after the subject has been supine for 5 minutes at the Screening Visit, Day -1, Day 7, and Day 8 (Table 8-1 and Table 8-3).

7.6.4 12-Lead ECG

Twelve-lead ECGs will be recorded at Screening, Day -1, and Day 8 (Table 8-1 and Table 8-3).

Subjects should be supine and resting for at least 5 minutes before and during the ECG recording procedure. Subjects with any ECG abnormality should be evaluated by the Investigator to determine if the abnormality is clinically significant. All clinically significant

abnormalities after the first dose of study drug throughout the Treatment Period until the follow-up telephone will be reported as treatment-emergent adverse events (TEAEs) and followed closely by the Investigator in order to assure the safety of the study subject.

7.6.5 Clinical Laboratory Tests

Subjects must fast for at least 6 hours prior to any scheduled complete clinical laboratory assessment blood draw (chemistry and hematology).

Laboratory testing (hematology with differential, chemistry, and urinalysis) will be performed using standard methods. Blood and urine samples for the clinical laboratory tests listed in Table 7-1 will be collected at Screening, Day -1, and Day 8.

Standardized meals will be administered on Days 1, 2, and 8 at specified times after observing fasting times for blood draws. There are no restrictions regarding clear fluid intake.

Table 7-1 Laboratory Tests

Hematology	Chemistry	
Hematocrit[a]	Creatinine[b]	Bilirubin (direct)
Hemoglobin	Potassium	ALT
Serum iron	Sodium	AST
Ferritin	Chloride	Gamma-glutamyltransferase
Platelet count	Magnesium	Alkaline phosphatase
Red blood cell count	Calcium	Total protein
White blood cell count	Inorganic phosphate	Albumin
White blood cell differential	Glucose	
Mean corpuscular volume	Urea	
Mean cell hemoglobin	Bilirubin (total)	
Mean corpuscular hemoglobin concentration	Blood urea nitrogen	
Urinalysis: Macroscopic examination routinely including specific gravity, pH, protein, glucose, ketones, blood, and urobilinogen. A microscopic examination will be performed based on macroscopic results.		
Urine drug screen: A urine sample will be collected and analyzed (positive or negative) at Screening and on inpatient admission days for drugs of abuse including amphetamine, opiate, cocaine, barbiturates, benzodiazepines, and marijuana (tetrahydrocannabinol).		
Alcohol breathalyzer test: A breathalyzer test will be performed at Screening and on inpatient admission days for the presence of alcohol (positive or negative).		
For all females: A serum hCG test at Screening and urine hCG test on inpatient admission days.		

Table 7-1 Laboratory Tests

Hematology	Chemistry

Abbreviations: hCG=human chorionic gonadotropin.

[a] Packed cell volume

[b] Estimated glomerular filtration rate will be calculated by the Chronic Kidney Disease Epidemiology Collaboration Equation

7.6.5.1 Laboratory Sample Collection, Storage and Shipping

Detailed instructions for laboratory sample collection, processing, and shipping instructions will be provided in the laboratory manual.

Approximately 320 mL of blood will be collected per subject during the study. The exact blood volume collected may vary depending on laboratory procedures or changes in PK sampling. However, it will not exceed 400 mL per subject during the study.

Biological material will be stored and secured in a way that assures that unauthorized access is prohibited and the samples are not lost, deteriorated, or accidentally or illegally destroyed. Details for storage and shipping will be provided in the laboratory manual.

7.7 AEs

7.7.1 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 7.7.10) are classified as 'serious' and must be reported no later than 24 hours after the Investigator recognizes/classifies the event as a serious adverse event (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 study drug.

7.7.2 AE Definitions

The following definitions of terms are guided by the ICH, the US Code of Federal Regulations (21 Code of Federal Regulations 312.32) and European Union Directive 2001/83/EC 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 the following:

- Medical or surgical procedures (eg, surgery, endoscopy, tooth extraction, blood transfusion); the condition that leads 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
- Abnormal laboratory values that are not clinically significant; if accompanied by signs/symptoms, the signs or symptoms are considered an AE

For subjects discontinuing study drug and withdrawing from the study, all AEs/SAEs will be collected through the 5- to 7-day follow up telephone call.

7.7.3 Pre-Treatment AEs

Adverse events that occur between the time subject signs the ICF for the study and the time when that subject receives first dose of study drug will be summarized as medical history and not as an AE unless the event meets the definition of an SAE as defined in Section 7.7.10.

7.7.4 TEAEs

All AEs that occur at the time of and following the first administration of study drug through the final telephone follow-up will be considered as being TEAEs.

7.7.5 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.

7.7.6 Relationship

The investigator will assess causal relationship between investigational product and each AE, and answer yes/no to the question. 'Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?'

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'.

7.7.7 COPD Exacerbations

Subjects experiencing a COPD exacerbation will be discontinued from the study and treated with appropriate therapy. Chronic obstructive pulmonary disease exacerbations will be considered expected events, as a general part of the disease, and will not be reported as AEs unless considered an SAE.

7.7.8 AEs of Special Interest

Certain AEs have been identified as adverse events of special interest (AESIs) due to the class of drugs being studied. These AEs will be captured through spontaneous reports and the reporting of these AESIs will be described in the statistical analysis plan (SAP). Some events are described below but this is not a comprehensive list of all AESIs.

7.7.8.1 LABA and LAMA Effects

Known effects of LAMAs and LABAs include cardiovascular effects, ocular disorders, urinary retention, gastrointestinal disorders, and anticholinergic effects for LAMAs and cardiovascular, potassium, glucose and tremor effects for LABAs.

7.7.8.2 Local Steroid Effects

Local steroid effects include oral candidiasis, hoarseness, dysphonia, and throat irritation.

7.7.9 Clinical Laboratory AEs

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). In such cases, the laboratory abnormality itself (eg, elevated creatinine in a setting of renal failure) does not need to be recorded as an AE. However, isolated laboratory abnormalities should be reported as AEs if they are considered to be clinically significant by the Investigator.

Criteria for a "clinically significant" laboratory abnormality are the following:

- A laboratory abnormality that leads to a dose-limiting toxicity (eg, an abnormality that results in study drug dose reduction, suspension, or discontinuation)
- A laboratory abnormality that results in any therapeutic intervention (eg, concomitant medication or therapy)
- 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 normal range (eg, < or > normal reference range), the Investigator should indicate whether the value is clinically significant or not clinically significant for the subject.

7.7.10 SAEs

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
- In patient 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 serious when, based upon appropriate judgment, they may jeopardize the subject or subject and may require medical or surgical intervention to prevent one of the outcomes listed in the 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 subject hospitalization, or the development of drug dependency or drug abuse.

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

An AE or suspected adverse reaction is considered "life threatening' if, in the view of the Investigator or Sponsor, its occurrence places the 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.

An AE or suspected adverse reaction is considered unexpected if it is not listed in the current investigator brochure or is not listed at the specificity or severity that has been observed.

7.7.10.1 Reporting 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 Pearl Pharmacovigilance or designee. All SAEs must be reported to Pearl Pharmacovigilance 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 Pearl Pharmacovigilance 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 and withdrawing from the study, all AEs/SAEs will be collected through the 5- to 7-day follow up telephone call.

Post-study SAEs following the last dose of study drug must be reported to Pearl Pharmacovigilance as described in Section 7.7.10.4.

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

7.7.10.2 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.

7.7.10.3 Post-Study Follow-up of AEs

Any AEs that are unresolved at the subject's last AE assessment in the study are followed up by the Investigator for as long as medically indicated, but without further recording in the

eCRF. Pearl 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.

7.7.10.4 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 the 5 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.

7.7.10.5 IRB/IEC Notification of SAEs

The Investigator is responsible for promptly notifying her/his IRB/IEC 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/IEC submission must be retained for each safety report. The Investigator is also responsible for notifying the Sponsor if their IRB/IEC requires revisions to the ICF or other measures based on its review of an SAE Report.

7.7.10.6 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 Pearl sponsored clinical studies. Safety reports must also be submitted to the appropriate IRBs/IECs as soon as possible. Documentation of submission to the IRB/IEC must be retained for each safety report.

7.7.11 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 Medical Monitor should 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 brochure for BGF MDI and approved product labeling for open-label products.

7.7.12 Pregnancy

To ensure subject safety, each pregnancy from Visit 1 until study completion must be reported to the Sponsor within 24 hours of learning of its occurrence. The pregnancy should

be followed in its entirety to ascertain outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. Pregnancy should be recorded on a Paper Pregnancy Report Form and reported by the Investigator to Pearl Pharmacovigilance or designee. Pregnancy follow-up should be recorded on the same pregnancy paper 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.

7.7.13 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 study drug 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.

7.8 Termination of the Study

An Investigator may choose to discontinue study participation at any time with sufficient notice by the Investigator for any reason as per the terms of the contract with the Sponsor.

The Sponsor reserves the right to discontinue 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.

8 STUDY ACTIVITIES

A schedule of events is provided in Table 8-1. Detailed schedules of inpatient assessments on Visit 3 (Day 1) and Visit 5 (Day 8) are provided in Table 8-2 and Table 8-3, respectively.

Table 8-1 Schedule of Events for Screening, Treatment, and Follow-up

	Screening		Treatment Period[a]			Follow up
	Visit 1	Visit 2 Clinic Admission	Visit 3	Visit 4 Clinic Admission	Visit 5	Telephone Follow up
Procedure/Assessment	**Days -28 to -2**	**Day -1**	**Day 1**	**Day 7**	**Day 8**	**5 to7 days post last dose**
Informed consent	X					
Inpatient admission		X		X		
Medical history	X					
Demographics	X					
Physical examination	X	X			X	
Spirometry testing	X[b]					
Smoking status	X	X		X		
Vital signs (BP, heart rate)	X	X		X	X	
Chest x-ray[c]	X					
Eligibility review[d]	X	X	X	X	X	
Subject enrollment number			X			
Placebo MDI usage demonstration/practice[e]	X[f]	X[f]	X[f]	X[f]	X[f]	
12-lead ECG	X	X			X	
Clinical laboratory testing[g]	X	X			X	
AEs	X[h]	X[h]	X	X	X	X
Concomitant medications	X	X	X	X	X	X
Urine drug screen	X	X		X		
Alcohol breathalyzer test	X	X		X		

Table 8-1 Schedule of Events for Screening, Treatment, and Follow-up

	Screening		Treatment Period[a]			Follow up
	Visit 1	Visit 2 Clinic Admission	Visit 3	Visit 4 Clinic Admission	Visit 5	Telephone Follow up
Procedure/Assessment	**Days -28 to -2**	**Day -1**	**Day 1**	**Day 7**	**Day 8**	**5 to7 days post last dose**
Pregnancy test (females only)[i]	X	X		X		
PK assessment[j]			X	X	X	
Dispense/collect Ventolin HFA[k]	X	X	X		X	
Dispense/collect study drug MDI			X		X	
Study drug administration[l]			X[m]	X	X[m]	
Dispense/collect/review diary[n]			X	X		
Clean study drug MDI device[o]				X		
Inpatient discharge			X[p]		X[q]	

Abbreviations: AE=adverse event; BID=twice daily; BP=blood pressure; COPD=chronic obstructive pulmonary disorder; ECG=electrocardiogram; FEV_1=forced expiratory volume in 1 second; FVC=forced vital capacity; hCG=human chorionic gonadotropin; HFA=hydrofluoroalkane; MDI=metered dose inhaler; PK=pharmacokinetic; SAE=serious adverse event.

[a] Sites must call subjects for morning and evening study drug administration confirmation on Days 2 to 7.

[b] Pre-bronchodilator FEV_1 must be ≥50% and <80% predicted and pre-bronchodilator FEV_1/FVC must be <0.70 in all subjects at Visit 1. Post–bronchodilator assessments to confirm the diagnosis of COPD (defined as FEV_1 <80% predicted and FEV_1/FVC<0.70) must be performed to confirm the diagnosis of COPD if not documented and available in the 12 months prior to Visit 1.

[c] Chest x-ray to be completed if chest x-ray or computed tomography not available within the 6 months before Visit 1.

[d] Confirm subjects continued eligibility to continue in the study.

[e] Inhalation training tools may be utilized to ensure appropriate training of subjects for the correct use of an MDI.

[f] Subjects will use the Placebo MDI for training purposes only to demonstrate proper use of the MDI.

[g] Creatinine clearance calculated as described in Section 7.6.5. Subjects must fast for a minimum of 6 hours before clinical laboratory assessment blood draw.

[h] Only SAEs will be recorded prior to first dose as defined in Section 7.7.10. All AEs prior to first dose will be recorded as medical history.

[i] For all women, obtain serum hCG at Screening and urine hCG thereafter.

Table 8-1 Schedule of Events for Screening, Treatment, and Follow-up

	Screening		Treatment Period[a]			Follow up
	Visit 1	Visit 2 Clinic Admission	Visit 3	Visit 4 Clinic Admission	Visit 5	Telephone Follow up
Procedure/Assessment	**Days -28 to -2**	**Day -1**	**Day 1**	**Day 7**	**Day 8**	**5 to7 days post last dose**

[j] PK samples will be collected predose on Days 1 (morning dose), 7 (evening dose), and 8 (morning dose).

[k] Ventolin HFA will dispensed at Visits 1, 2, and 3 as needed and collected at Visit 5.

[l] See Table 8-2 and Table 8-3 for details regarding times and events for the 12-lead ECG, vital signs, drug administration, and PK assessments during the Treatment Period. All study drugs will be administered by oral inhalation. A single dose of study drug will be administered on Day 1 and BID doses will be administered Day 2 through Day 7, with a final single-dose administration of study drug occurring on the morning of Day 8. Administration of study drug should occur at approximately the same time of day.

[m] Refer to instructions in Section 6.5 for procedures to prevent possible cross-contamination.

[n] Dispense diary on Day 2 prior to discharge. Subjects should be instructed to record their at-home BID study drug dosing. Site staff should collect the diary on Day 7 and review study drug dosing before admission to the clinic.

[o] Clean study drug device on Day 7 after dosing in the evening and dry for approximately 12 hours overnight per instructions in Appendix 2.

[p] Subjects will be discharged on Day 2 after all assessments have been completed.

[q] Discharge will occur after completion of all assessments and subjects have been instructed about resuming appropriate COPD therapy. The site should schedule the subject's follow-up phone call at least 5 days but no longer than 7 days after the date of last administration of study drug.

Table 8-2 Timing of Assessments on Day 1 (Visit 3)

	Time Relative to Drug Administration													
Procedure	**-60 min**	**0 hr**	**2 min**	**6 min**	**20 min**	**40 min**	**1 hr**	**2 hrs**	**4 hrs**	**8 hrs**	**10 hrs**	**12 hrs**	**18 hrs**	**24 hrs[a]**
PK blood draw	X[b]		X	X	X	X	X	X	X	X	X	X	X	X
Placebo MDI usage demonstration/practice	X													
Administration of study drug[c]		X												X[d]
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X

[a] The 24-hour post-dose assessment occurs on Day 2.

[b] Within 60 minutes prior to dosing. A pre-dose sample will be collected on Day 7 before the evening dose.

[c] Study drug will be administered by oral inhalation. A single dose of study drug will be administered on Day 1.

[d] Administer morning dose of study drug in the clinic on Day 2 after the 24-hour post-dose PK sample has been collected and before discharge from the clinic.

Table 8-3 Timing of Assessments on Day 8 (Visit 5)

Procedure	Time Relative to Drug Administration											
	-60 min	**0 hr**	**2 min**	**6 min**	**20 min**	**40 min**	**1 hr**	**2 hrs**	**4 hrs**	**8 hrs**	**10 hrs**	**12 hrs**
PK blood draw	X[a]		X	X	X	X	X	X	X	X	X	X
Placebo MDI usage demonstration/practice	X											
Administration of study drug[b]		X										
12-lead safety ECG	X											
Clinical laboratory tests	X[c]											
Vital signs	X											X
Physical examination			X[d]									
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X

[a] Within 60 minutes prior to dosing.

[b] Study drug will be administered by oral inhalation. A final single-dose administration of study drug will occur on the morning of Day 8.

[c] Complete clinical laboratory testing - chemistry and hematology (includes glucose and potassium) fasting required.

[d] Complete any time prior to discharge.

8.1 Screening Visit 1 (Screening, Day -28 to Day -2)

After obtaining written and signed informed consent, the following procedures and assessments will be performed during the Screening period and results will be documented in the eCRF and/or source documents:

- Obtain informed consent (obtain first, before other study procedures)
- Record demographics and relevant medical history
- Perform physical examination
- Record smoking status
- Obtain vital signs
- Practice Placebo MDI usage and demonstrate proper technique
- Conduct spirometry for all subjects and post-bronchodilator spirometry for subjects who do not have confirmation of COPD diagnosis (post-bronchodilator FEV_1 <80% predicted and FEV_1/FVC <0.70) in the past 12 months
- Obtain 12-lead ECG
- Collect blood and urine samples for clinical laboratory evaluations (hematology, chemistry, and urinalysis)
- Document concomitant medications
- Perform urine drug test
- Perform alcohol breathalyzer test
- Perform serum pregnancy test (women only)
- Obtain chest x-ray if needed
- Review eligibility criteria
- Dispense Ventolin HFA
- Document AEs (Note: AEs that occur prior to dosing will be recorded as medical history unless the event meets the definition of an SAE as defined in Section 7.7.10)

8.2 Visit 2 (Admission to Clinic, Day -1)

The following study activities and assessments will be performed on Day -1, and results will be documented in the eCRF and/or source documents:

- Perform physical examination
- Record smoking status
- Obtain vital signs

- Obtain 12-lead ECG
- Collect blood and urine samples for clinical laboratory evaluations (hematology, chemistry, and urinalysis)
- Document AEs (Note: AEs that occur prior to dosing will be recorded as medical history unless the event meets the definition of an SAE as defined in Section 7.7.10)
- Document concomitant medications
- Perform urine drug test
- Perform alcohol breathalyzer test
- Perform urine pregnancy test (women only)
- Review eligibility criteria
- Admit subject to the clinic
- Practice Placebo MDI usage and demonstrate proper technique
- Dispense Ventolin HFA (if needed)

8.3 Visit 3 (Day 1/Day 2 of the Treatment Period)

The following study activities and assessments will be performed on Day 1 and Day 2, and results will be documented in the eCRF and/or source documents:

- Review eligibility criteria
- Obtain subject enrollment number
- Practice Placebo MDI usage and demonstrate proper technique
- Document AEs (Note: AEs that occur prior to dosing will be recorded as medical history unless the event meets the definition of an SAE as defined in Section 7.7.10)
- Document concomitant medications
- Collect pre-dose PK samples per Table 8-2
- Administer study drug; a single dose of study drug will be administered by oral inhalation (refer to Section 6.5 for details regarding study drug dispensing and administration).
- Collect post-dose PK samples per Table 8-2. The 24-hour post-dose sample will be collected on the morning of Day 2.
- Dispense study drug MDI and Ventolin HFA
- Administer morning dose of study drug in the clinic on Day 2 after the 24-hour post-dose PK sample has been collected and before discharge from the clinic
- Schedule telephone calls with subjects for dose administration confirmation

- Schedule Visit 4
- Dispense diary
- Discharge subject on Day 2 after all assessments have been completed

8.4 Telephone Contact (Days 2 to 7 of the Treatment Period)

- Call subjects for morning and evening dose administration confirmation.
  Note: Dosing must be scheduled relative to the subject's first morning dose in clinic on Day 1 (Visit 3). Subjects must be advised that subsequent morning study drug dosing must occur at approximately the same time every day and that evening dosing should occur as close as possible to 12 hours from the time of morning dosing.

8.5 Visit 4 (Day 7)

The following study activities and assessments will be performed on Day 7, and results will be documented in the eCRF and/or source documents:

- Document AEs
- Document concomitant medications
- Collect diary and review with subject
- Record smoking status
- Obtain vital signs
- Confirm subject's eligibility to continue in the study
- Practice Placebo MDI usage and demonstrate proper technique
- Perform urine drug test
- Perform alcohol breathalyzer test
- Perform urine pregnancy test (women only)
- Admit the subject to the clinic
- Collect PK sample within 60 minutes prior to evening dose
- Administer the evening dose of study drug as close as possible to 12 hours from the time of morning dose
- After the evening dose, study site staff should wash the study drug device and dry for approximately 12 hours overnight per instructions in Appendix 2

8.6 Visit 5 (Day 8)

The following study activities and assessments will be performed on Day 8, and results will be documented in the eCRF and/or source documents:

- Perform physical examination
- Obtain vital signs
- Obtain 12-lead ECG
- Collect blood samples and urine for clinical laboratory evaluations (hematology, chemistry, and urinalysis)
- Confirm subject's eligibility to continue in the study
- Document AEs
- Document concomitant medications
- Practice Placebo MDI usage and demonstrate proper technique
- Collect pre-dose PK samples per Table 8-3
- Administer study drug; a single dose of study drug will be administered by oral inhalation (refer to Section 6.5 for details regarding study drug dispensing and administration).
- Collect post-dose PK samples per Table 8-3
- Collect study drug MDI and Ventolin HFA
- Restart subject's COPD medications after all assessments are completed
- Schedule follow-up telephone call

After all scheduled protocol-specified assessments are complete, and safety data, including vital signs, have been reviewed by the Investigator, the subject will be discharged from the clinic.

8.7 Follow-up Telephone Call

Upon completion of the study, a follow-up phone call will be completed at least 5 days but no longer than 7 days from the date of last administration on Visit 5 (Day 8). Subjects will be asked about any new or ongoing AEs, and any new concomitant medication. This will be documented appropriately in the subject source documents and eCRFs.

9 PLANNED STATISTICAL METHODS

9.1 General Considerations

The general approach for the statistical analyses is provided below. A detailed SAP will be finalized prior to database lock.

9.2 Analysis Populations

Two subject populations will be evaluated during this study and are defined as follows:

- **PK Population:** All treated subjects who have sufficient data to reliably calculate at least 1 PK parameter and do not have major protocol deviations. Subjects will be analyzed according to treatment received.
- **Safety Population:** All subjects who receive at least 1 dose of study drug.

Safety and tolerability analyses will be performed on data from all subjects in the Safety Population.

Pharmacokinetic analysis will be performed using the PK population.

9.3 Demographics and Baseline Characteristics

Demographic information will include month/year of birth, gender, ethnicity, and race. Demographics and baseline characteristics will be summarized descriptively for both the Safety and PK Populations. Height and weight, which are considered baseline characteristics and documented as part of the physical examination performed at Screening, will be reported with the demographic information.

9.4 Analysis of PK Variables

Pharmacokinetic and statistical analysis will be performed using the PK population. The initial estimation of PK parameters will be performed using non-compartmental methods.

Pharmacokinetic parameters calculated using pre-defined post dose serial blood draws over 24 hours on the first day (Day 1) and using pre-defined post dose serial blood draws over 12 hours after the last dose (Day 8) will include the following:

- C_{max}
- AUC_{0-12}
- t_{max}

The following PK parameters will be calculated at Day 1 only:

- $AUC_{0\text{-}tlast}$
- $AUC_{0\text{-}\infty}$
- $t_{1/2}$
- CL/F
- Vd/F
- λ_z

The following will be derived based on ratios of Day 8 values to Day 1 values:

- Accumulation ratio for C_{max} (RAC [C_{max}])
- Accumulation ratio for $AUC_{0\text{-}12}$ (RAC [$AUC_{0\text{-}12}$])
- Linearity ratio (Rlin [$AUC_{0\text{-}12}/AUC_{0\text{-}\infty}$])

Other PK parameters may be calculated, as appropriate.

Descriptive statistics for plasma concentrations of budesonide, glycopyrronium, and formoterol by day and nominal time point will be summarized on the raw and log-normal scales using the PK Population. Individual plasma concentration at each nominal and actual time point for each Day will be listed by subject using the Safety Population.

All budesonide, glycopyrronium, and formoterol PK parameters will be presented by visit (Visit 3 [Day 1] or Visit 5 [Day 8]) with number of measurements, number of subjects with non-missing data (n), mean, standard deviation, coefficient of variation (CV%), median, minimum, maximum, geometric mean, and geometric CV%. For t_{max}, the geometric mean and the CV% will be omitted, and only the number of observations (n), median, minimum and maximum will be provided.

To estimate the RAC values and Rlin, natural-log transformed $AUC_{0\text{-}12}$, $AUC_{0\text{-}\infty}$, and C_{max} of budesonide, glycopyrronium, and formoterol between Day 8 and Day 1, a mixed model with day as a fixed effect and subject as a random effect will be employed. A separate mixed model will be fit for each analyte and ratio type. For each analyte, the estimated ratio of geometric least square mean (LSM) for Day 8 to Day 1 and the corresponding 90% confidence interval (CI) will be determined by exponentiating the mean difference between Day 8 and Day 1 and the associated CI (on the logarithm scale). The estimated ratio of geometric LSM and its corresponding 90% CI will be an estimate of RAC or Rlin with the 90% CI. The residual variance component from the model estimating Rlin will provide an estimate of intra-subject variability.

If the effective rate of drug accumulation is estimable, the time to reach steady state will be estimated for each analyte using the methodology of Panebianco and Maes (Panebianco 2009).

9.5 Safety Analyses

Safety data will be summarized and listed. The safety of BGF MDI will be assessed from AE reporting including SAE reporting, vital signs (BP, heart rate), clinical laboratory values (hematology, chemistry, and urinalysis), and findings from 12-lead ECGs. The incidence of AEs and SAEs will be tabulated. Summary statistics of assessed laboratory values and vital signs by visit and change from baseline will be provided. Subjects with out-of-range values of 12-lead ECGs will be listed.

9.6 Randomization

Not applicable.

9.7 Determination of Sample Size

This study is descriptive in nature. The planned sample size of approximately 30 enrolled subjects is selected to provide approximately 24 completers for assessment of the single- and multiple-dose PK of BGF MDI in subjects with COPD.

10 ADMINISTRATIVE CONSIDERATIONS

10.1 Regulatory Authority Approval

The Sponsor will obtain approval to conduct the study from the appropriate regulatory agency in accordance with any applicable country-specific regulatory requirements prior to a site initiating the study in that country.

10.2 Ethical Conduct of the Study and IRB or IEC Approval

The study will be conducted in accordance with Good Clinical Practice (GCP), Declaration of Helsinki, concerning medical research in humans (Ethical Principles for Medical Research Involving Human Subjects), and regulatory requirement if applicable.'

The Investigator (or The Sponsor, where applicable) is responsible for ensuring that this protocol, the site's ICF, and any other information that will be presented to potential subjects (eg, advertisements or information that supports or supplements the ICF) are reviewed and approved by the appropriate IRB/IEC. The Investigator agrees to allow the IRB/IEC direct access to all relevant documents. The IRB/IEC must be constituted in accordance with all applicable regulatory requirements.

The Sponsor will provide the Investigator with relevant document(s)/data that are needed for IRB/IEC review and approval of the study. If the protocol, the ICF, or any other information that the IRB/IEC has approved for presentation to potential subjects is amended during the study, the Investigator is responsible for ensuring the IRB/IEC reviews and approves, where applicable, these amended documents. The Investigator must follow all applicable regulatory requirements pertaining to the use of an amended ICF including obtaining IRB/IEC approval of the amended form before new subjects consent to take part in the study using this version of the form. The IRB/IEC approval of the amended ICF/other information and the approved amended ICF/other information must be forwarded to The Sponsor promptly.

10.3 Subject Information and Consent

The study will be conducted in accordance with applicable subject privacy requirements. The proposed ICF, which must be in compliance with applicable regulations, must be reviewed and approved by the IRB/IEC and the Sponsor prior to initiation of the study.

The Investigator will be responsible for obtaining written informed consent from potential subjects prior to any study-specific screening and entry into the study. The subject will be provided with 2 original ICFs. One original will be retained by the study Investigator and the subject will retain the second original.

10.4 Laboratory Accreditation

Any laboratory facility intended to be used for analysis of clinical laboratory samples required by this protocol must provide evidence of adequate licensure or accreditation according to the prevailing regulations in that state and/or country. Reference values and/or

normal ranges for the test results must be provided to the Sponsor. The Sponsor must be notified promptly in writing of any changes occurring in reference values during the course of the study.

10.5 Confidentiality

10.5.1 Confidentiality of Data

By signing this protocol, the Investigator affirms to the Sponsor that information furnished to the Investigator by the Sponsor will be maintained in confidence and such information will be divulged to the IRB/IEC, or similar or expert committee; affiliated institution; and employees only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees. Data generated by this study will be considered confidential by the Investigator, except to the extent that it is included in a publication.

10.5.2 Confidentiality of Subject/Patient Records

By signing this protocol, the Investigator agrees that the Sponsor (or representative), IRB/IEC, or Regulatory Agency representatives may consult and/or copy study documents in order to verify worksheet/case report form data. By signing the consent form, the subject/patient agrees to this process. If study documents will be photocopied during the process of verifying worksheet/case report form information, the subject/patient will be identified by unique code only; full names/initials will be masked prior to transmission to the Sponsor. In addition, the Investigator agrees to treat all subject data used and disclosed in connection with this study in accordance with all applicable laws, rules and regulations.

10.6 Quality Control and Assurance

The Sponsor or its designee is responsible for implementing and maintaining quality control and quality assurance systems with written standard operating procedures to ensure that trials are conducted and data are generated, documented, and reported in compliance with the protocol, accepted standards of GCP, and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the clinical study.

10.7 Data Management

Data management procedures and information for this protocol will be provided by the Sponsor or their designee.

10.8 Study Monitoring

In accordance with applicable regulations, GCP, and the Sponsor procedures, clinical monitors will contact the site prior to subject enrollment to review the protocol and data collection procedures with site staff. In addition, the monitor will periodically contact the site, including conducting on-site visits. The extent, nature, and frequency of on-site visits

will be based on such considerations as the study objective and/or endpoints, the purpose of the study, study design complexity, and enrollment rate.

During these contacts, the monitor will:

- Check the progress of the study
- Review study data collected
- Conduct source document verification
- Identify any issues and address their resolution

This will be done in order to verify that the:

- Data are authentic, accurate, and complete
- Safety and rights of subjects are being protected
- Study is conducted in accordance with the currently approved protocol (and any amendments), GCP, and all applicable regulatory requirements

The Investigator agrees to allow the monitor direct access to all relevant documents and to allocate his/her time and the time of his/her staff to the monitor to discuss findings and any relevant issues

Upon completion of the study, the monitor will conduct the following activities in conjunction with the Investigator or site staff, as appropriate:

- Return of all study data to the Sponsor
- Data queries
- Accountability, reconciliation, and arrangements for unused investigational product(s)
- Review of site study records for completeness

After the final review of the study files, the files should be secured for the appropriate time period as specified in Section 10.9. The Investigator will also permit inspection of the study files by the Sponsor' Quality Assurance auditors, and authorized representatives of the Food and Drug Administration (FDA) or other applicable regulatory agencies.

10.9 Retention of Data

Documents that individually and collectively permit evaluation of the conduct of the study and the quality of the data produced must be maintained for review by the Sponsor' quality assurance auditors and by all applicable regulatory authorities. The period of time these

documents must be maintained is governed by applicable regulations. The Sponsor or its designee will inform the Investigator when these documents may be destroyed. The Sponsor or it's designee should contact the site *at least 6 months prior to the intended date of disposal* of any study record related to this protocol to allow the Sponsor to make alternate storage arrangements.

10.10 Financial Disclosure

The Investigator or sub-Investigators named on FDA Form 1572 will need to complete a financial disclosure form prior to study initiation, at any time during the study execution if new information needs to be disclosed, and for 1 year after study completion. Investigators should make the IRB/IEC aware of any financial interests that the Investigator has in the investigational product.

10.11 Investigator's Final Report

Shortly after completion of the Investigator's participation in the study, the Investigator will submit an end of study summary report to the Sponsor.

10.12 Publication Policy

The Sponsor intends to publish the results of all of the clinical studies that it sponsors in compliance with the Declaration of Helsinki (http://www.wma.net/en/10home/index.html). Consistent with the recommendations of the editors of several leading medical journals, the International Committee of Medical Journal Editors (ICMJE), authorship of publications resulting from Sponsor-sponsored studies should fairly recognize the activities of those that have made a significant contribution to the study. In addition, the Sponsor recognizes and adheres to the precepts of the International Society for Medical Publication Professionals (ISMPP), which provides guidance to the preparation of publications, disclosure of conflicts of interest, and the protection of intellectual property. Thus, it is anticipated that authorship will reflect the contribution made by the Sponsor personnel, the Investigators, and others involved, such as statisticians.

In recent years, issues about conflicts of interest and accuracy of the study data have been raised in the medical press. Accordingly, the Sponsor has developed publication guidelines as described below:

1. Responsibility: Each Principal Investigator is responsible for the accuracy and completeness of all data from their site. The Sponsor (or its representative) is responsible for the accuracy of the data entered into the study databases and for the accuracy of the analyses conducted.
2. Authorship and Publication Committee: The Sponsor, in collaboration with the Investigators, will establish the appropriate authorship and responsibility for drafting study documents in accordance with the principles of the ICMJE and ISMPP. It is anticipated that a publication committee will be formed to assume oversight of these

activities. All manuscripts will be reviewed and agreed upon before submission for publication by all authors.

3. Sponsor Review of External Manuscripts: Consistent with the first bullet point, drafts of any and all publications or presentations that may arise from this study must be submitted at least 30 days prior to submission for publication or presentation to the Sponsor for review and approval and to ensure consistency with the policy in this protocol. The Sponsor will have the right to request appropriate modification to correct facts and to represent its opinions, or the opinions of the publication committee, if these differ with the proposed publication.
4. Confidentiality: Investigators will conduct all interactions with the Sponsor and with third parties consistent with the executed confidentiality agreements. While publication, by intention, presents the critical scientific data in a public forum, some information (such as future plans, results of nonclinical studies, or chemical formulae) may still need to remain confidential.
5. Medical Journal Review: Consistent with the intention of the Sponsor to publish the study in a fair and accurate manner, the Sponsor supports diligence in the publication review process of medical journals. Accordingly, upon request, all pertinent study data and information will be made available as supplemental information for journal editors and reviewers to evaluate and audit, eg, protocol and amendments, data tabulations. The journal and reviewers will need to make arrangements to maintain the confidentiality of such supplemental information, where relevant, and the Sponsor will make suitable arrangements to ensure that the identity of journal reviewers is kept confidential. Records will be maintained of reviewers and the respective documents and datasets that were reviewed by each of them.
6. Reporting of Clinical Trial Results: To provide transparency in the conduct and reporting of randomized clinical trials, the Sponsor reports clinical findings based on the guidance of The CONsolidated Standards of Reporting Trials Statement (Mohler 2012) and a 25-item checklist, which is intended to improve the reporting of a randomized controlled study; facilitate reader understanding of the study design, conduct, analysis and interpretation; and support their ability to assess the validity of its results.
7. Internet Clinical Trial Listing: In addition, also consistent with the recommendations of the ICMJE, the Sponsor will make available appropriate information regarding the study via the internet. This will include registration and listing of the study on www.clinicaltrials.gov, the US National Institutes of Health listing of clinical trials. Per AstraZeneca policy, The Sponsor posts clinical study protocols for public viewing when a manuscript is published in a medical journal. Prior to being made public, the protocol is reviewed by AstraZeneca Intellectual Property.

11 REFERENCE LIST

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Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global Strategy for Diagnosis, Management, and Prevention of COPD-2017. http://www.goldcopd.org/. Accessed 31 January 2017.

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12 APPENDICES

Appendix 1 Dose Indicator Reading

130 Count (Actuation) Version Shown				
 If your dose indicator display looks like this record **120+**	 If your dose indicator display looks like this record **120**	 If your dose indicator display looks like this record **110**	 If your dose indicator display looks like this record **100**	 If your dose indicator display looks like this record **90**
 If your dose indicator display looks like this record **80**	 If your dose indicator display looks like this record **70**	 If your dose indicator display looks like this record **60**	 If your dose indicator display looks like this record **50**	 If your dose indicator display looks like this record **40**
 If your dose indicator display looks like this record **30**	 If your dose indicator display looks like this record **20**	 If your dose indicator display looks like this record **10**	 If your dose indicator display looks like this record **0**	

Appendix 2 Subject Instructions for Use of BGF MDI and Placebo MDI

How do I store the Inhaler?

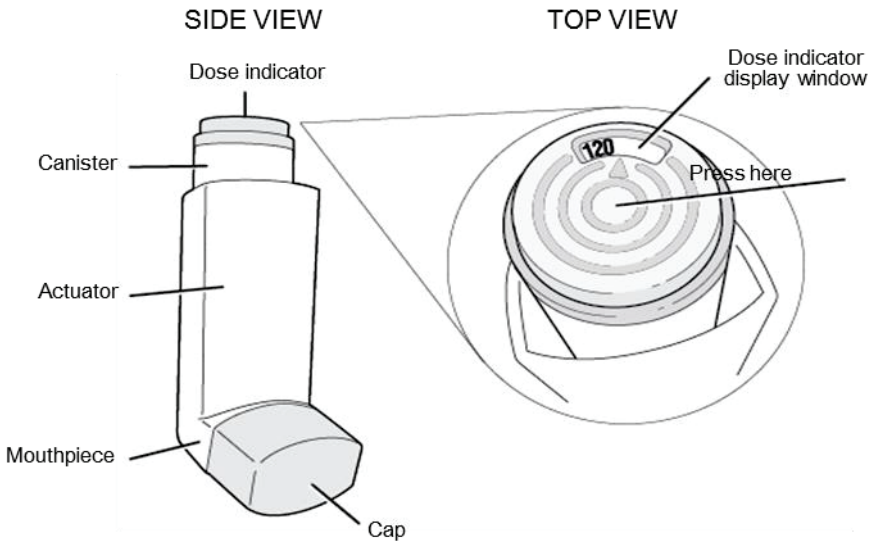
- The inhaler should be stored below 25°C (77°F) in a dry place. Excursions permitted up to 30°C (86°F).
- The contents of the canister are under pressure. Do not puncture or throw the canister into a fire or incinerator. Do not use or store it near heat or open flame. Storage above 120ºF may cause the canister to burst.
- **Keep the product and all medicines out of the reach of children.**

For Oral Inhalation Only

Parts of the Inhaler:

- The parts of your inhaler are seen in **Figure 1**.

Figure 1



- The **Dose indicator** lets you know about how many puffs are left in your inhaler and is the part of the inhaler that is pressed to dispense a puff of medication. **See Figure 1**.
- The **Dose indicator** should be pointing just to the right of 120 when your inhaler is new. **See Figure 1**.

- The **Dose indicator** has numbers for every 20 puffs. The **Dose indicator** display will move after every tenth puff.
- For example, if the **Dose indicator** is pointing to 120 (**see Figure 2a**) and you take 10 puffs it will move between 120 and 100. This means that there are 110 puffs of medicine left (**see Figure 2b**). After 10 more puffs are used, the **Dose indicator** pointer will move to the number 100. This means that there are 100 puffs of medicine left (**see Figure 2c**).
- The **Dose indicator** number will continue to change after every 20 puffs.
- When the number in the **Dose indicator** window changes to 20 and the color behind the number changes to red, this means that there are only 20 puffs left in your inhaler. **See Figure 2d**.

Figure 2

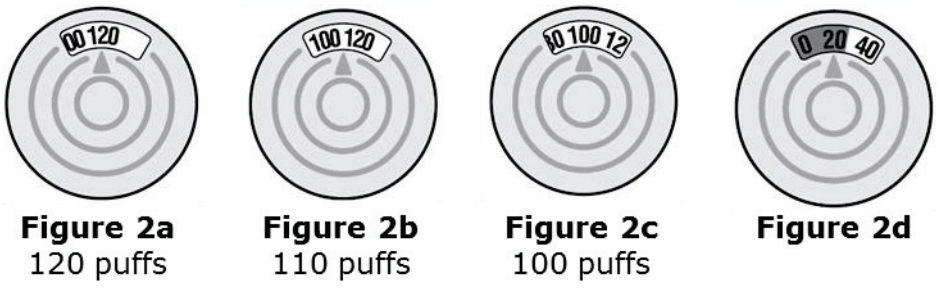


Figure 2a
120 puffs

Figure 2b
110 puffs

Figure 2c
100 puffs

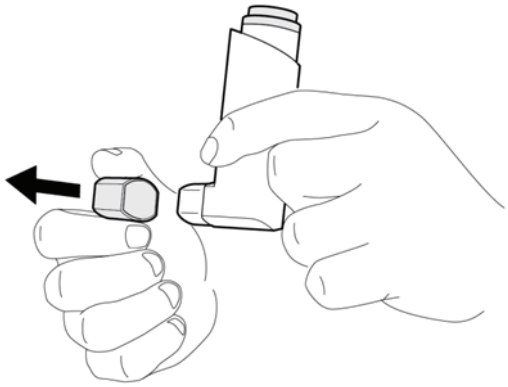
Figure 2d

Preparing the Inhaler for Use:

The inhaler comes in a foil pouch that contains a drying packet (desiccant).

- Take the inhaler out of the foil pouch.
- Throw away the pouch and the drying packet. Do not eat or inhale the contents of the drying packet.
- Remove the Cap from the Mouthpiece as shown in **Figure 3**.

Figure 3



- Prime the inhaler before you use it for the first time.

Priming the Inhaler:

- Check inside the **Mouthpiece** for objects before use.
- Hold the **Actuator** with the **Mouthpiece** pointing away from you and others as shown in **Figure 4a**.
- Shake the inhaler well before each puff.
- Push down fully on the center (not 'off center') of the **Dose indicator** on top of the **Canister (see Figure 1)** until the **Canister** stops moving in the **Actuator** to release a puff from the **Mouthpiece as shown in Figure 4b**. Note: It is normal to hear a soft click from the dose indicator as it counts down during use.
- Repeat this priming step 3 more times for a total of 4 times, shaking the inhaler each time before you press it.
- After completing the 4 priming puffs, your inhaler is now primed ready to use for the first time.

You must re-prime your inhaler again if you have not used it in more than 7 days. Take the cap off the mouthpiece and shake and spray the inhaler 2 times into the air away from your face.

Figure 4

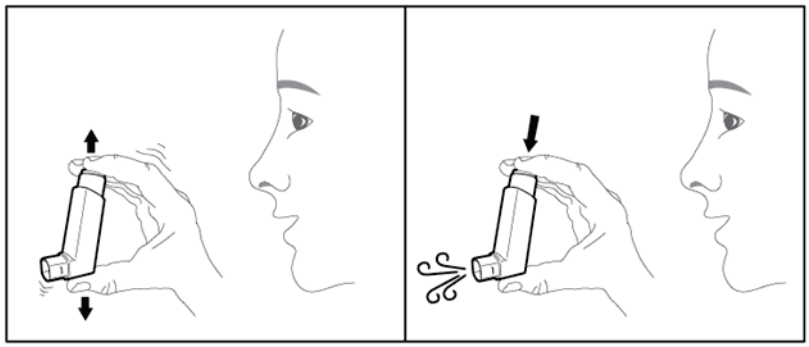


Figure 4a **Figure 4b**

Using the Inhaler:

Your dose of medicine comes from **2 puffs** from the inhaler.

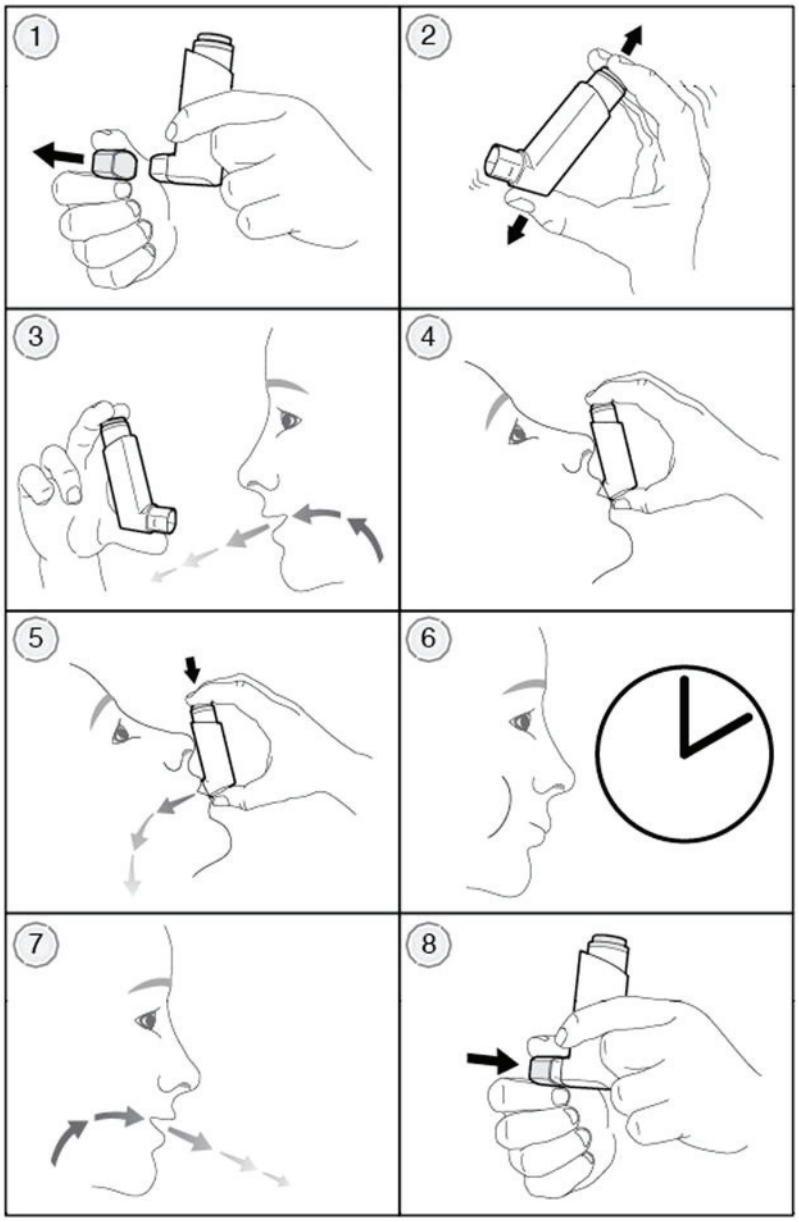
Refer to **Figure 5** for Step 1 through Step 8.

- **Step 1**: Remove the **Cap** from the **Mouthpiece**.
- **Step 2**: Shake the inhaler well before each puff.
- **Step 3**: While holding the inhaler with the **Mouthpiece** pointing towards you breathe out through your mouth to empty as much air from your lungs as possible.
- **Step 4**: Close your lips around the **Mouthpiece** and tilt your head back slightly to make sure your tongue is away from the **Mouthpiece**.
- **Step 5**: Take a deep breath in (inhale) slowly through your mouth while pressing down firmly on the center (not 'off center') of the **Dose indicator** until the **Canister** stops moving in the **Actuator** and a puff has been released. Then, stop pressing the **Dose indicator.**
- **Step 6**: When you have finished breathing in, remove the **Mouthpiece** from your mouth and hold your breath for 10 seconds or as long as comfortable.
- **Step 7**: Then, breathe out normally.

Take your second puff of medicine by repeating Step 2 through Step 7.

- **Step 8**: Replace the **Cap** back on the **Mouthpiece**.

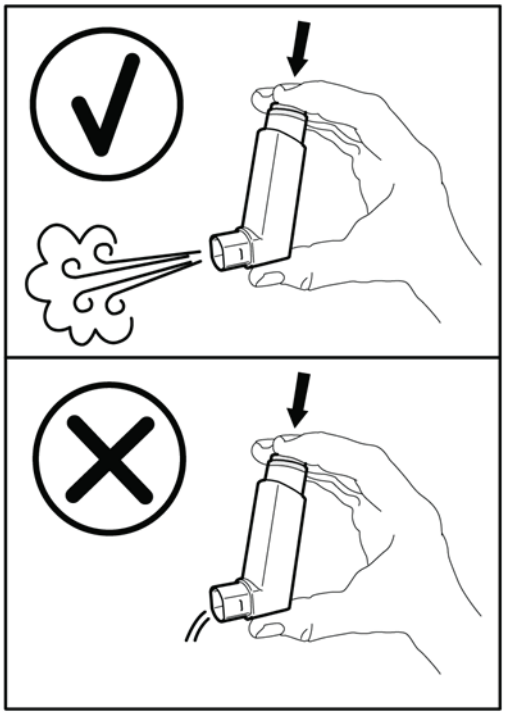
Figure 5



How to clean the Inhaler:

It is very important to keep your inhaler clean so medicine will not build-up and block the spray through the **Mouthpiece**. **See Figure 6.**

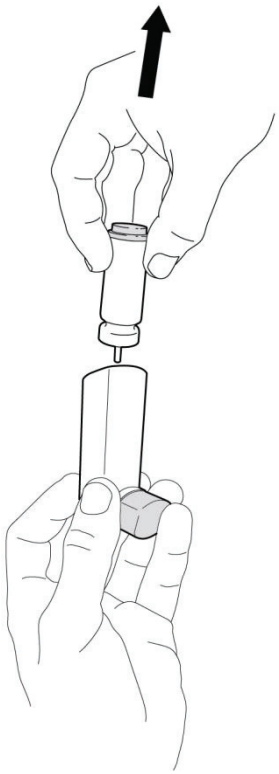
Figure 6



The **Canister** should be gently pulled from the top of the **Actuator** once a week and the **Actuator** cleaned. **Do not clean the Canister or let it get wet.**

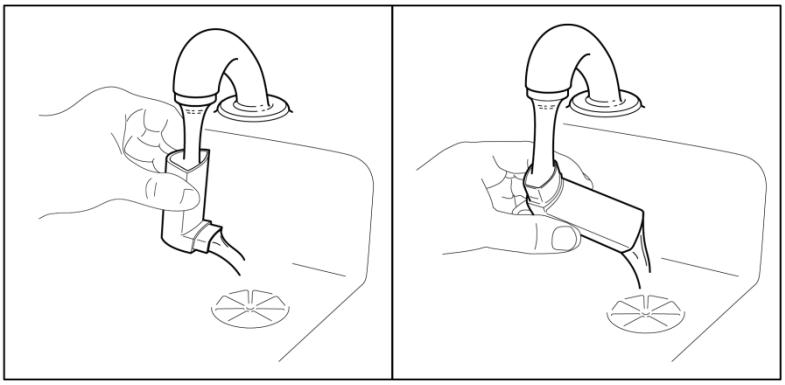
- **Step 1**: Pull the **Canister** out of the **Actuator** as shown in **Figure 7.**

Figure 7



- **Step 2**: Set the **Canister** aside where it will not get wet.
- **Step 3**: Take the **Cap** off the **Mouthpiece**.
- **Step 4**: Rinse the **Actuator** through the top with warm running water for 30 seconds. Then rinse the **Actuator** again through the **Mouthpiece** (**see Figure 8**).

Figure 8



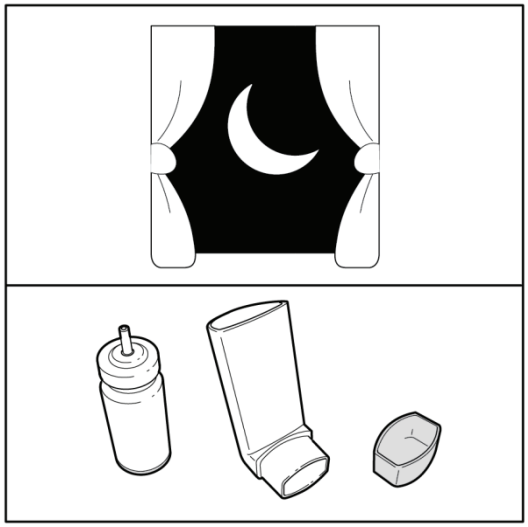
- **Step 5**: Shake all of the water droplets out of the **Actuator**.

- **Step 6**: Look in the **Actuator** and the **Mouthpiece** to make sure it is clean and clear.

Repeat **Step 4** through **Step 6**, until the **Actuator** and the **Mouthpiece** are clean and clear.

- **Step 7**: Let the **Actuator** dry completely, such as overnight as shown in Figure 9. Do not put the **Canister** back into the **Actuator** if it is still wet.

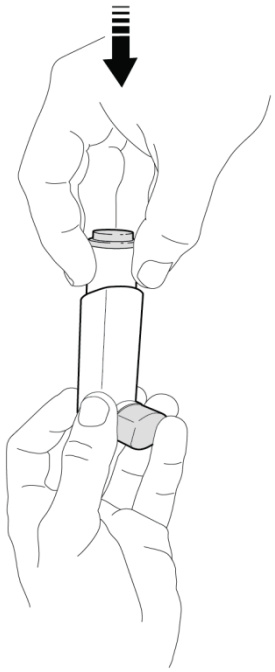
Figure 9



Reassembly of the Inhaler and Instructions for Use after Cleaning:

- After the **Actuator** is completely dry, gently press the **Canister** down in the **Actuator** as shown in **Figure 10**. It is not necessary to press down on the **Canister** hard enough to cause a puff to be released.

Figure 10



- Re-prime your inhaler 2 times after each cleaning.
- Hold the **Actuator** with the **Mouthpiece** pointing away from you and others as shown in **Figure 4**.
- Shake the inhaler well before each puff.
- Push down fully on the center (not 'off center') of the **Dose indicator** on top of the **Canister** until the **Canister** stops moving in the **Actuator** to release a puff from the **Mouthpiece**.
- Repeat this re-priming step 1 more time for a total of 2 times.
- After re-priming your inhaler 2 times, your inhaler is now ready to use.

Appendix 3 Instructions for Use of Ventolin HFA Inhalation Aerosol Device

Instructions for Use
For Oral Inhalation Only
Your VENTOLIN HFA inhaler

The metal canister holds the medicine. **See Figure A.**

Figure A

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**.

Figure B

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 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**.

Figure C

Figure C

- 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**.

Figure D

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.

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**.

Figure E

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**.

Figure F

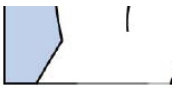


Figure F

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 as 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:

Clean your inhaler at least 1 time each week. You may not see any medicine build-up on the inhaler, but it is important to keep it clean so medicine build-up will not block the spray. **See Figure G**.

Figure G

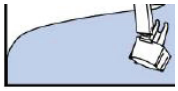


Figure G

Step 8. Take the canister out of the actuator, and take the cap off the mouthpiece. The strap on the cap will stay attached to the actuator.

Step 9. Hold the actuator under the faucet and run warm water through it for about 30 seconds. **See Figure H**.

Figure H

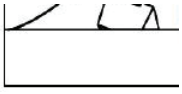


Figure H

Step 10. Turn the actuator upside down and run warm water through the mouthpiece for about 30 seconds. **See Figure I**.

Figure I

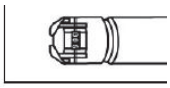


Figure I

Step 11. Shake off as much water from the actuator as you can. Look into the mouthpiece to make sure any medicine build-up has been completely washed away. If there is any build-up, repeat Steps 9 and 10.

Step 12. Let the actuator air-dry overnight. **See Figure J**.

Figure J

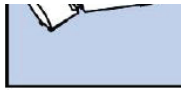


Figure J

Step 13. When the actuator is dry, put the protective cap on the mouthpiece and then put the canister in the actuator and make sure it fits firmly. Shake the inhaler well, remove the cap,

and spray the inhaler once into the air away from your face. (The counter will count down by 1 number.) Put the cap back on the mouthpiece.

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

Appendix 4 Spirometry Assessment Criteria

Acceptable Versus Usable Tests

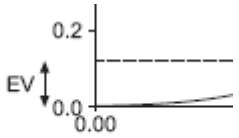
***Acceptable* tests must meet the following 7 criteria:**

1. Acceptable start of exhalation with brisk upstroke, no hesitation or false start, and back extrapolation volume (EV) <5% of FVC or 0.150 L, whichever is the greater. (Refer to example in Figure A1-1)
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 ≥1 second, and the patient has tried to exhale for at least 6 seconds.

An acceptable test meets all 7 criteria listed. This is to be considered the "gold standard".

Useable spirometry tracings are those that only meet criteria 1 and 2 (Figure A1-1). When this occurs, repeat testing up to 8 attempts in an effort to obtain 3 acceptable spirograms. If only usable tests are obtained, report results based on the 3 best usable results with observed limitations.

Figure A1-1 Example of a Usable Spirogram



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 peak expiratory flow (PEF), to determine the new "time zero". Forced vital capacity (FVC)-4.291 L; back extrapolated volume (EV) – 0.123 L (2.9% FVC): back extrapolation line through PEF.

Between-Maneuver Reproducibility Criteria

After 3 acceptable spirograms have been obtained, apply the following tests:

a. The 2 largest values of FVC must be within 0.150 L of each other
b. The 2 largest values of FEV_1 must be within 0.150 L of each other

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

If acceptability criteria are not met, continue testing until they are met or the patient cannot/should not continue (maximum of 8 attempts).

Appendix 5 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), central training provided, qualification will be required, and specific operating instruction will also be provided.

The following instructions are supported by ATS/ERS defined criteria (Miller 2005).

FEV_1 AND FVC 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, body temperature and pressure saturated [BTPS]) with an accuracy of at least ±3% of reading or ±0.050 L, whichever is greater, with flows between 0 and 14 L-s $^{-1}$. The total resistance to airflow at 14.0 L-s $^{-1}$ must be <1.5 cmH_2O L^{-1} $1s^{-1}$ (0.15 kPa L^{-1} $1s^{-1}$). 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 eight 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 vs. 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, 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 two units of flow per one 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 cmH_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 three 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 one 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 cmH_2O (0.3 kPa) with the spirometer outlet occluded (preferably at or including the mouthpiece). Any observed volume loss of 0.30 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 one 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 three times to give a range of flows varying between 0.5 and 12 $L\text{-}s^{-1}$ (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 subject tests should be tested each day.

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

VITAL CAPACITY AND INSPIRATORY CAPACITY MANEUVERS

Equipment

For measurements of vital capacity (VC) and inspiratory capacity, 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 one 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 ($L\text{-}s^{-1}$)	Resistance and Back Pressure	Test Signal
VC	0.5–8 L, ±3% of reading or ±0.050 L, whichever is greater	0-14		3-L Calibration syringe
FVC	0.5–8 L, ±3% of reading or ±0.050 L, whichever is greater	0-14	<1.5 $cmH_2O\ L^{-1}\ s^{-1}$ (0.15 $kPa\ L^{-1}s^{-1}$)	24 ATS waveforms, 3-L Cal Syringe
FEV_1	0.5–8 L, ±3% of reading or ±0.050 L, whichever is greater	0-14	<1.5 $cmH_2O\ L^{-1}\ s^{-1}$ (0.15 $kPa\ L^{-1}s^{-1}$)	24 ATS waveforms
Time Zero	The time point from which all FEVt measurements are taken		Back extrapolation	

FEVt: forced expiratory volume in t seconds

BTPS 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 6 Sponsor Signatory

Study Title: A Study to Assess the Pharmacokinetics and Safety of PT010 in Subjects With Moderate to Severe COPD Following Single and Repeat Dose Administration

Study Number: PT010018

Final Date: [redacted]

This clinical study protocol was subject to critical review and has been approved by the Sponsor.

Signed [redacted] Date: [redacted]

Pearl Therapeutics, Inc.

Appendix 7 Investigator's Signature

Study Title: A Study to Assess the Pharmacokinetics and Safety of PT010 in Subjects With Moderate to Severe COPD Following Single and Repeat Dose Administration

Study Number: PT010018

Final Date: [redacted]

I have read the protocol described above. I agree to comply with all applicable regulations and to conduct the study as described in the protocol. I agree:

- To assume responsibility for the proper conduct of the study at this site.
- 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).
- 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).
- That I am aware of, and will fully comply with GCP and all applicable regulatory requirements.
- That I am thoroughly familiar with the appropriate use of the investigational product(s), and other information provided by Pearl including, but not limited to, the following: the protocol and the current Investigator's Brochure (IB).
- 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.
- 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.
- I agree to report all information or data in accordance with the protocol and any other study conduct procedures provided by Pearl.
- 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.
- To accurately transfer all required data from each subject's source document to the CRFs. The CRFs will be provided to the Sponsor in a timely manner at the completion of the study, or as otherwise specified by the Sponsor.
- 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.

Signed:_____ Date:_____

Name: _____

Site Name: _____