Clinical Trial Protocol: PT003013-01

Study Title:	A Randomized, Phase III, Two-period, Open-label, Chronic-dosing (7 Days), Multicenter, Crossover Study to Assess the Efficacy, Safety and Pharmacokinetics of PT003 in Subjects with Moderate to Very Severe COPD with and without a Valved Holding Chamber
Study Number:	PT003013-01
Study Phase:	III
Product Name:	Glycopyrronium and Formoterol Fumarate Inhalation Aerosol; PT003
IND Number:	107739
Indication:	COPD
Investigators:	Multicenter
Sponsor:	Pearl Therapeutics, Inc. [redacted]
Sponsor Contact:	[redacted]

	Version Number	Date
Original Protocol	**Version 1.0**	[redacted]
Amended Protocol	**Version 2.0**	[redacted]

Confidentiality Statement

SUMMARY OF CHANGES TO PROTOCOL PT003013-00 (VERSION 1.0) DATED [redacted]

The amended study protocol, PT003013-01 (Version 2.0), includes the following edits: Newly added text is shown in **bold font** and deleted text is shown as ~~strikethrough~~ font.

No.	Description of Change	Rationale
1	Synopsis: Study Design This study will be conducted at approximately 6 sites in the United States. Across these sites, it is planned that approximately 60 subjects with moderate to very severe COPD will be randomized to the study to provide approximately 50 subjects who will complete the study. **This study will also recruit approximately 12 subjects with impaired renal function (i.e., creatinine clearance of ≥30 - <50 ml/min). The study will remain open until the planned number of approximately 60 subjects have been randomized and the target numbers of subjects with renal impairment have been recruited.** **In the event that the target number of approximately 12 subjects with renal impairment is not reached, the study will remain open to all eligible subjects until approximately 70 subjects are randomized, at that point only subjects with renal impairment will be allowed to proceed and subjects with a creatinine clearance of ≥ 50 ml/min will be screen failed.**	To allow for the study to remain open to recruit a target of approximately 12 subjects with renal impairment
2	Section 4.1: Overall Study Design and Plan This study will be conducted at approximately 6 sites in the United States. Across these sites, it is planned that approximately 60 subjects with moderate to very severe COPD will be randomized to the study to provide	To allow for the study to remain open to recruit a target of approximately 12 subjects with renal impairment

	approximately 50 subjects who will complete the study. **This study will also recruit approximately 12 subjects with impaired renal function (i.e., creatinine clearance of ≥30 - <50 ml/min). The study will remain open until the planned number of approximately 60 subjects have been randomized and the target numbers of subjects with renal impairment have been recruited.** **In the event that the target number of approximately 12 subjects with renal impairment is not reached, the study will remain open to all eligible subjects until approximately 70 subjects are randomized, at that point only subjects with renal impairment will be allowed to proceed and subjects with a creatinine clearance of ≥ 50 ml/min will be screen failed.**	
3	Section 5.2 Exclusion Criteria: Criterion 6(c) **Note: This study will also recruit approximately 12 subjects with impaired renal function (i.e., creatinine clearance of ≥30 - <50 ml/min). The study will remain open until the planned number of approximately 60 subjects have been randomized and the target numbers of subjects with renal impairment have been recruited.** **In the event that the target number of approximately 12 subjects with renal impairment is not reached, the study will remain open to all eligible subjects until approximately 70 subjects are randomized, at that point only subjects with renal impairment will be allowed to proceed and subjects with a creatinine clearance of ≥ 50 ml/min will be screen failed.**	To allow for the study to remain open to recruit a target of approximately 12 subjects with renal impairment

SYNOPSIS

Sponsor:
Pearl Therapeutics, Inc. ("Pearl")
[redacted]

Names of Finished Products:
Glycopyrronium and Formoterol Fumarate Inhalation Aerosol (PT003)
Glycopyrronium and Formoterol Fumarate Metered Dose Inhaler (GFF MDI)

Name of Active Ingredients:
Glycopyrronium and Formoterol Fumarate

Study Title:
A Randomized, Phase III, Two-period, Open-label, Chronic-dosing (7 Days), Multicenter, Crossover Study to Assess the Efficacy, Safety and Pharmacokinetics of PT003 in Subjects with Moderate to Very Severe COPD with and without a Valved Holding Chamber

Study Number: PT003013

Study Phase: III

Primary Objective:

- To compare the efficacy of GFF MDI 14.4/9.6 µg with Aerochamber® Plus Flow-VU valved holding chamber (VHC) relative to GFF MDI 14.4/9.6 µg without Aerochamber Plus VHC based on FEV_1 AUC_{0-12} after 7 days of treatment

Secondary Objective:

- To assess the glycopyrronium and formoterol plasma exposure after 7 days of chronic administration of GFF MDI with, and without use of the Aerochamber Plus VHC

Safety Objective:

- To assess the safety of GFF MDI with and without use of the Aerochamber Plus VHC

Study Design:

This is a randomized, phase III, two-period, open-label, chronic-dosing (7 days), multicenter, crossover study to assess the efficacy, safety and pharmacokinetics of GFF MDI in subjects with moderate to very severe chronic obstructive pulmonary disease (COPD) with and without a VHC.

Subjects will undergo a Screening Period of 7 to 28 days in duration. During the Screening Period, subjects that are receiving an inhaled corticosteroid (ICS)/ long-acting β_2-agonist (LABA) will discontinue the ICS/LABA, but will continue the ICS component for the duration of the study. Similarly, subjects treated with an ICS as part of their inhaled maintenance therapy will also be permitted to continue their ICS for the duration of the study.

All subjects will discontinue their previously prescribed inhaled bronchodilators and switch to Sponsor-provided Atrovent® HFA Inhalation Aerosol (Atrovent) administered four times daily (QID) as COPD maintenance therapy during the Screening Period and during the Washout Period of the study. All subjects will be provided with sponsor-provided Ventolin® HFA Inhalation Aerosol (Ventolin) administered QID as needed for control of symptoms throughout the study. At randomization, subjects will discontinue Atrovent but will be permitted to use their ICS and sponsor-provided rescue albuterol throughout the study.

Subjects will be issued and trained on the use of the electronic diary (eDiary) at Visit 1 (Screening) and will be instructed to collect practice data during the Screening Period (between Visit 1 and Visit 2). Subject eDiary compliance will be reviewed at Visit 2, and the subject will be retrained if necessary.

Subjects that meet all other entry criteria but are using certain prohibited COPD medications must discontinue the use of prohibited medications at Visit 1a (Screening). Prohibited COPD medications include, but are not limited to oral β_2-agonists, LABAs, long-acting muscarinic antagonists (LAMAs), LABA/LAMA, ICS/LABA combination products, cromoglycate or nedocromil inhalers, leukotriene antagonists [e.g., zafirlukast, montelukast, zileuton], or tiotropium [Spiriva], glycopyrronium bromide [e.g., Seebri®], aclidinium [e.g., Tudorza™, Elkira®], and umeclidinium [Incruse® Ellipta®]. The use of these medications is prohibited throughout the screening period and the duration of the study.

Randomized subjects will receive 7 days of study treatment with or without the Aerochamber Plus VHC for a total of two separate Treatment Periods. A study drug Washout Period of at least 7 days (up to 14 days) will occur between each Treatment Period. During the Washout Period between Visits 3 and 4, when subjects are not taking study drug, subjects will use the Sponsor-provided short-acting bronchodilator, Atrovent HFA, administered QID and Ventolin HFA as needed for control of symptoms. During the two Treatment Periods, GFF MDI will be administered twice daily (BID) with or without an Aerochamber Plus VHC in a randomized manner. On Day 8 of each Treatment Period, a 12-hour pulmonary function test (PFT) will be performed, and pharmacokinetic (PK) samples will be collected.

This study will be conducted at approximately 6 sites in the United States. Across these sites, it is planned that approximately 60 subjects with moderate to very severe COPD will be randomized to the study to provide approximately 50 subjects who will complete the study. This study will also recruit approximately 12 subjects with impaired renal function (i.e., creatinine clearance of $\geq$30 - <50 ml/min). The study will remain open until the planned number of approximately 60 subjects have been randomized and the target numbers of subjects with renal impairment have been recruited.

In the event that the target number of approximately 12 subjects with renal impairment is not reached, the study will remain open to all eligible subjects until approximately 70 subjects are randomized, at that point only subjects with renal impairment will be allowed to proceed

and subjects with a creatinine clearance of ≥ 50 ml/min will be screen failed.

It is anticipated that the entire study period will take approximately 7 to 10 weeks for each individual subject from the time of Screening. It is anticipated that the entire study will take approximately 3 months and not exceed 5 months for each individual subject.

Study Population:

It is planned that approximately 60 subjects with moderate to very severe COPD will be randomized to provide an estimated 50 subjects to complete the study.

Product, Dose, and Mode of Administration:

Investigational materials will be provided by Pearl Therapeutics (Pearl), as shown below:

Product Name & Dose	Product Strength	Dose Form/ Fill Count	Administration
Study Medications			
GFF MDI (PT003) 14.4/9.6 µg ex-actuator	7.2/4.8 µg per actuation	MDI/ 120 inhalations	Taken as 2 inhalations (BID)
Open-Label Products			
Albuterol sulfate inhalation aerosol 90 µg[a] ex-actuator	Ventolin® HFA Albuterol sulfate inhalation aerosol. Each inhalation contains 108 µg corresponding to 90 µg albuterol base from the mouthpiece.	MDI/ 60 or 200 actuations	Taken as needed Supplies are open-label
Ipratropium bromide HFA inhalation aerosol 34 µg[b] ex-actuator	Atrovent® HFA. Ipratropium bromide inhalation aerosol. Each inhalation contains 17 µg per actuation.	MDI/ 200 actuations	Taken as 2 inhalations QID Supplies are open-label

BID=twice daily; GFF MDI= Glycopyrronium and Formoterol Fumarate Inhalation Aerosol; HFA=hydrofluoroalkane; MDI=Metered Dose Inhaler; QID=four times daily; US=United States

[a] Reversibility testing at Visit 1 and rescue medication during the study and during washout periods

[b] Chronic obstructive pulmonary disease maintenance therapy during the Screening and Washout Periods

Duration of Treatment:

It is planned that each subject will receive 7 days of study treatment for 2 separate Treatment Periods. A washout period of 7 Days (not to exceed 14 days) will occur between each Treatment Period. It is anticipated that the entire study period will take approximately 7 weeks for each individual subject from the time of Screening.

The first day of treatment in each Treatment Period is Day 1. Each Treatment Period is planned to contain 7 days between the first and last dose corresponding to a span of 8 calendar days. Therefore, assessments collected on Day 8 will occur following 7 days of treatment.

Primary Efficacy Endpoint:

- Forced expiratory volume in 1 second (FEV_1) area under the curve from 0 to 12 hours (AUC_{0-12}) on Day 8

Pharmacokinetic Endpoints:

- Maximum (or peak) plasma concentration (C_{max}) measured on Day 8
- AUC_{0-12} measured on Day 8
- Time to peak concentration (T_{max}) measured on Day 8

Other Efficacy Endpoints:

- FVC AUC_{0-12} and PEFR AUC_{0-12} on Day 8
- Peak change from baseline in FEV_1, FVC, and PEFR on Day 1 and Day 8
- Change from baseline in the morning pre-dose trough FEV_1, FVC, and PEFR on Day 8
- Change from baseline in FEV_1, FVC, and PEFR at each time point assessed on Day 1 and Day 8

Safety Endpoints:

- Adverse Events (AEs)
- 12-lead electrocardiogram (ECG)
- Clinical laboratory testing
- Vital sign measurements

Statistical Methods:

Primary Efficacy Analyses:

FEV_1 AUC_{0-12} is the area under the curve calculated using the trapezoidal rule and will be normalized by dividing the AUC by the length of follow up post-morning-dosing (typically 12 hours).

FEV_1 AUC_{0-12} on Day 8 will be analyzed using a mixed model. The model will include baseline FEV_1 and reversibility to Ventolin® HFA as continuous covariates and period, treatment, smoking status, and ICS use at baseline as unordered categorical covariates. The model will also include subject as a random effect to model correlation within subject across the study. The model will not include treatment sequence unless that term is determined to be important ($p<0.10$). Baseline FEV_1 is defined as the mean of available pre-dose values on the first day of each Treatment Period, i.e., the mean of pre-dose values at Visits 2 and 4, where the mean of the -60 and -30 minute value for each visit day is obtained and then the average of all visit means is obtained.

The comparison of FEV_1 AUC_{0-12} on Day 8 of GFF MDI with Aerochamber Plus VHC relative to GFF MDI without Aerochamber Plus VHC will be based on the above model. The ratio (GFF MDI with Aerochamber Plus VHC / GFF MDI without Aerochamber Plus VHC) and corresponding 90% confidence interval will be calculated using Fieller's Thereom. The primary analysis will use the modified Intent-to-Treat (mITT) Population.

Secondary Analyses:

Log-transformed AUC_{0-12} and C_{max} of glycopyrronium and formoterol will be compared between the two treatments using analysis of variance (ANOVA). A separate model containing effects for treatment, period, sequence and subject within sequence will be fit for each parameter and analyte. Estimated geometric mean ratios (GMRs; GFF MDI with Aerochamber VHC / GFF MDI without Aerochamber Plus VHC) with 90% confidence intervals (CIs) will be produced.

Safety Analyses:

Safety analyses will be based on descriptive statistics by treatment for ECG, vital signs, laboratory measurements, and the frequencies of AEs.

Sample Size Determination:

The sample size was determined based on precision in estimating the secondary endpoints, AUC_{0-12} and C_{max} of glycopyrronium and formoterol. Glycopyrronium and formoterol are both highly variable with intra-subject coefficients of variation of approximately 55% and 40%, respectively. Assuming a 15% dropout rate, randomization of 60 subjects provides this study with ~19% precision in estimating the glycopyrronium GMR (GFF MDI with Aerochamber Plus VHC / GFF MDI without Aerochamber Plus VHC). That is, assuming an observed GMR of 1.05, the upper bound of the 90% CI would be 1.25.

Statistical power was also calculated for the primary endpoint, FEV_1 $AUC_{0-12,}$ on Day 8 of treatment. The estimate of the within-subject standard deviation (SD) of FEV_1 AUC_{0-12} is based on trough FEV_1 data from previous Pearl studies. A within-subject SD of 0.130 L and a mean response of 1.490 L in FEV_1 AUC_{0-12} for GFF MDI BID without Aerochamber Plus VHC are assumed. If approximately 15% of subjects will drop out, and a two-sided alpha level of 0.05 will be used, 60 randomized subjects will provide >99% probability to demonstrate an equivalence of GFF MDI with Aerochamber compared to GFF MDI without Aerochamber.
Date of Approved Protocol: [redacted]
Date of Protocol Amendment 01 (Version 2.0): [redacted]

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	Adverse Event
ALT	Alanine Aminotransferases
ANOVA	Analysis of Variance
AST	Aspartate Aminotransferases
AUC_{x-y}	Area Under the Curve from Time x to Time y
ATS	American Thoracic Society
AV	Atrioventricular
BID	*Bis In Die*, Twice Daily
BMP	Basic Metabolic Panel
bpm	Beats Per Minute
BiPAP	Bilevel Positive Airway Pressure
BTPS	Body Temperature and Pressure Saturated
CBC	Complete Blood Count
CFR	Code of Federal Regulations
CI	Confidence Interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration Equation (according to National Kidney Disease Education Program)
cmH_2O	Centimeter of Water
CMP	Comprehensive Metabolic Panel
CONSORT	CONsolidated Standards of Reporting Trials
COPD	Chronic Obstructive Pulmonary Disease
CPAP	Continuous Positive Airway Pressure
CT	Computerized Tomography
DBP	Diastolic Blood Pressure
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eDiary	Electronic Diary
EDTA	Ethylenediaminetetraacetic Acid

eg.	*Exempli Gratia*, For Example
ERS	European Respiratory Society
etc.	*Et Cetera*, And So Forth
EU	European Union
EV	Back Extrapolation Volume
ex-actuator	Dose Delivered from the Actuator (i.e., Mouthpiece) of the Metered Dose Inhaler
FDA	Food and Drug Administration
FEV_1	Forced Expiratory Volume in 1 Second
FF	Formoterol Fumarate
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GFF	Glycopyrronium and Formoterol Fumarate
GMR	Geometric Mean Ratio
GOLD	Global Initiative for Chronic Obstructive Lung Disease
GP	Glycopyrronium
hCG	Human Chorionic Gonadotropin
HFA	Hydrofluoroalkane
HR	Heart Rate
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ICS	Inhaled Corticosteroid
ID	Identification
ie.	*Id Est*, That Is
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITT	Intent-to-Treat
IUD	Intrauterine Device

IWRS	Interactive Web-based Response System
kPa	Kilopascal
L	Liter
LABA	Long-Acting β_2-Agonist
LAMA	Long-Acting Muscarinic Antagonist
LTOT	Long-term Oxygen Therapy
MDI	Metered Dose Inhaler
MedDRA	Medical Dictionary for Regulatory Activities
µg	Microgram
mITT	Modified Intent-to-Treat
mL	Milliliter
mm	Millimeter
mmHg	Millimeter of Mercury
msec (ms)	Millisecond
NHANES III	Third National Health and Nutrition Examination Survey
NIPPV	Non-Invasive Positive Pressure Ventilation
OTC	Over-the-Counter
PEF	Peak Expiratory Flow
PEFR	Peak Expiratory Flow Rate
PFT	Pulmonary Function Test
PIN	Personal Identification Number
PK	Pharmacokinetics
PV	Pharmacovigilance
QD	*Omne In Die*, Once Daily
QID	*Quarter In Die*, Four Times Daily
QTcF	QT Corrected Using Fridericia's Formula (QT/[RR $^{1/3}$])
s	Second(s)
SABA	Short-Acting β_2-Agonist

SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SD	Standard Deviation
SNRI	Serotonin-Norepinephrine Reuptake Inhibitor
SSRI	Selective Serotonin Reuptake Inhibitor
SUSAR	Suspected Unexpected Serious Adverse Reaction
TNF	Tumour Necrosis Factor
ULN	Upper Limit of Normal
US	United States
VC	Vital Capacity
VHC	Valved Holding Chamber

TRADEMARK INFORMATION

Trademarks Not Owned By Pearl Therapeutics, Inc.

Atrovent	[redacted]
Eklira	Seebri
Ellipta	Tudorza
Foradil	Ventolin
Incruse	Aerochamber

1 INTRODUCTION AND STUDY RATIONALE

Chronic obstructive pulmonary disease (COPD) is a common preventable and treatable disease characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases. 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 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, 2014)].

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, quality of life, and reducing exacerbations in subjects with moderate to very severe COPD [GOLD, 2014].

Pearl Therapeutics, Inc. (hereafter referred to as Pearl) is developing a combination product, Glycopyrronium and Formoterol Fumarate Inhalation Aerosol (PT003, Glycopyrronium and Formoterol Fumarate Metered Dose Inhaler [MDI]; hereafter referred to as GFF MDI), as a maintenance bronchodilator treatment in subjects with COPD. Phase IIb studies were conducted which supported the dose selection of GFF MDI 14.4/9.6 µg BID for Phase III clinical studies, including this study.

In this study, references to strengths/doses of GFF MDI are based on the mass of glycopyrronium instead of the salt form, glycopyrronium bromide. GFF MDI 14.4/9.6 µg contains 14.4 µg of glycopyrronium and 9.6 µg of formoterol fumarate. GFF MDI is administered twice daily (BID). The dose of glycopyrronium (14.4 µg) in GFF MDI is equivalent to 18 µg of glycopyrrolate (glycopyrronium bromide).

Glycopyrronium is a LAMA, which 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. In addition, tiotropium bromide (Spiriva®) is approved worldwide and has been shown to reduce the rate of COPD exacerbations and to improve the effectiveness of pulmonary rehabilitation [Niewoehner, 2005; Casaburi, 2005].

Formoterol fumarate is a potent and selective LABA approved in many countries worldwide for use in 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. Although formoterol fumarate is classified as a LABA, it has a rapid onset of action similar to SABAs. Formoterol fumarate is highly potent, displays high intrinsic activity, and can result in greater than 80% relaxation even under induced tone [Anderson, 1993]. Studies in patients with COPD have demonstrated that the onset of action with formoterol fumarate is faster than with anticholinergic agents or salmeterol and similar to that of SABAs, such as albuterol, and that the duration of action is ≥12 hours [Berger, 2008]. Five large, placebo-controlled clinical studies of up to 12 months in duration in nearly 2500 patients demonstrated that formoterol fumarate is effective and well tolerated in patients with COPD [Dahl, 2001; Rossi, 2002; Aalbers, 2002; Campbell, 2005; Campbell, 2007].

1.1 Study Rationale

The purpose of this study is to support the use of a spacer in those patients who find it difficult to synchronize aerosol actuation with inspiration of breath. The Aerochamber Plus Valved Holding Chamber (VHC) being used in this study is a commonly used spacer worldwide.

2 STUDY OBJECTIVES

2.1 Primary Objective

- To compare the effects of GFF MDI with Aerochamber Plus VHC relative to GFF MDI without Aerochamber Plus VHC based on FEV_1 AUC_{0-12} after 7 days of treatment

2.2 Secondary Objective

- To assess the glycopyrronium and formoterol plasma exposure after chronic administration of GFF MDI with and without use of the Aerochamber Plus VHC

2.3 Safety Objectives

- To assess the safety of GFF MDI with and without use of the Aerochamber Plus VHC

3 STUDY ENDPOINTS

The first day of treatment in each Treatment Period is Day 1. Each Treatment Period is planned to be 7 days between the first and last dose corresponding to a span of 8 calendar days. Therefore, all efficacy assessments collected on Day 8 will occur following 7 days of treatment.

3.1 Primary Efficacy Endpoint

- Forced expiratory volume in 1 second (FEV_1) area under the curve from 0 to 12 hours (AUC_{0-12}) on Day 8

3.2 Pharmacokinetic Endpoints

- Maximum (or peak) plasma concentration (C_{max}) on Day 8
- AUC_{0-12} on Day 8
- Time to peak concentration (T_{max}) on Day 8

3.3 Other Efficacy Endpoints

- FVC AUC_{0-12} and PEFR AUC_{0-12} on Day 8
- Peak change from baseline in FEV_1, FVC, and PEFR on Day 1 and Day 8
- Change from baseline in morning pre-dose trough FEV_1, FVC, and PEFR on Day 8
- Change from baseline in FEV_1, FVC, and PEFR at each time point assessed on Day 1 and Day 8

3.4 Safety Endpoints

- Adverse Events (AEs)
- 12-lead electrocardiogram (ECG)
- Clinical laboratory testing
- Vital sign measurements

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

This is a Phase III, randomized, two-period, open-label, chronic-dosing (7 Days), multi-center, crossover study to assess the efficacy, safety and pharmacokinetics of GFF MDI with and without an Aerochamber Plus VHC in subjects with moderate to very severe COPD.

This multi-center study will be conducted in approximately 6 sites in the United States. Across these sites, approximately 60 subjects with moderate to very severe COPD will be randomized to provide an estimated 50 subjects to complete this study. This study will also recruit approximately 12 subjects with impaired renal function (i.e., creatinine clearance of ≥30 - <50 ml/min). The study will remain open until the planned number of approximately 60 subjects have been randomized and the target numbers of subjects with renal impairment have been recruited.

In the event that the target number of approximately 12 subjects with renal impairment is not reached, the study will remain open to all eligible subjects until approximately 70 subjects are randomized, at that point only subjects with renal impairment will be allowed to proceed and subjects with a creatinine clearance of ≥ 50 ml/min will be screen failed.

Screening Period:

Subjects must sign an informed consent form prior to the conduct of any screening assessments (Visit 1a). At screening, the investigator will determine the subject's eligibility for participation in this study by assessing the inclusion and exclusion criteria, obtaining a medical history, performing a physical examination, and completing all required documentation. Reversibility of FEV_1 30 minutes following 4 puffs of Ventolin HFA will be assessed at Screening to characterize the patient population but will not be used to determine eligibility to participate in the study. Patients who are not using a prohibited medication and meet all other entry criteria will return to the clinic at least 7 days (≥2 weeks if taking tiotropium) after screening for Visit 2 (Randomization).

At the Investigator's discretion, subjects who do not meet spirometry entry criteria at Screening (Visit 1a) may return to repeat spirometry at a second Screening Visit (Visit 1b). Note: Visit 1b is to be used only for repeat spirometry entry criteria; all other repeat assessments, if needed, will be captured as an unscheduled visit. For more details on Visit 1a and 1b procedures, refer to Section 8.1.

Subjects will undergo a Screening Period of 7 to 28 days in duration. During the Screening Period, subjects that are receiving an ICS/LABA will discontinue the ICS/LABA, but will continue the ICS component for the duration of the study.

Similarly, subjects treated with an ICS as part of their inhaled maintenance therapy will also be permitted to continue their ICS for the duration of the study. All subjects will discontinue

their previously prescribed inhaled bronchodilators and switch to Sponsor-provided Atrovent HFA MDI administered four times daily (QID) as COPD maintenance therapy during the Screening Period and during the Washout Period of the study. All subjects will be provided with sponsor-provided Ventolin HFA Inhalation Aerosol (Ventolin) administered QID, or as needed for control of symptoms throughout the study. At randomization, subjects will discontinue Atrovent but will be permitted to use their ICS and sponsor- provided rescue albuterol throughout the study.

Subjects will be issued and trained on the use of the electronic diary (eDiary) at Visit 1 (Screening) and will be instructed to collect practice data during the Screening Period (between Visit 1 and Visit 2). Subject eDiary compliance will be reviewed at Visit 2, and the subject will be retrained if necessary.

Prior to returning to the clinic for Visit 2 (Randomization), all subjects will undergo a Washout Period to allow for an adequate washout of previous maintenance medications. The Washout Period will last for a minimum of 7 days (at least 14 days if taking tiotropium) and no more than 28 days prior to Visit 2 (see Table 5-1 for washout period guidelines).

Treatment Period

Subjects will receive 1 week of study treatment with and without the Aerochamber Plus VHC for each of two separate Treatment Periods. All treatments will include GFF MDI BID. GFF MDI will be administered twice daily as two inhalations. During the two Treatment Periods, GFF MDI will be administered with or without an Aerochamber Plus VHC and the treatment assignment will be randomized.

All COPD medications, including ICS, must be withheld for at least 6 hours prior to each visit, or the visit will need to be rescheduled as soon as it is practical. Rescheduled visits must still take place within the specified visit windows.

At Visit 2 (Randomization Visit; Treatment Period 1, Day 1), subjects will return to the clinic before 10:00 am. Subjects who are unable to meet the reproducibility criteria will be considered a screen failure (refer to Section 7.1.2). Subject eDiary compliance will be reviewed, and subjects who are unable to meet the compliance requirement (>70% subject completion of diary assessments) in the last 7 days preceding the Randomization Visit will also be considered a screen failure (refer to Section 7.1.2). Subjects who continue to meet all eligibility criteria for participation in the study will be randomized to a treatment sequence. Randomization will be centralized through the use of an Interactive Web-based Response System (IWRS).

Before sites may dispense the first dose of study drug and prior to any study procedures being performed, site staff must confirm that the subject meets all protocol-specific requirements and ensure an adequate washout (6 hours or longer) of all COPD medications (including ICS, and rescue medication). Eligible subjects will be dispensed Treatment Period 1 study drug with or without an Aerochamber Plus VHC according to their assigned

treatment sequence. The first dose of study drug will then be administered in the clinic under site personnel supervision.

Subjects will be required to remain at the clinic until completion of all Day 1 protocol-defined assessments up to and including the 2-hour post-dose time point (see Table 8.2). Following completion of all assessments, subjects will be discharged from the clinic and will continue to administer Treatment Period 1 study drug for 1 week at home until Visit 3. During the treatment periods (between Visits 2 and 3, and Visits 4 and 5), subjects will be permitted to use sponsor-provided Ventolin HFA Inhalation Aerosol (Ventolin) on an as needed basis for relief of COPD symptoms.

At Visit 3 (Day 8 of Treatment Period 1), subjects will return to the clinic before 10:00 am. The administration of the final dose of study drug for Treatment Period 1 will take place in-clinic, under site personnel supervision before 10:00 am. Subjects will be required to remain at the clinic until completion of all protocol-defined assessments up to and including the 12-hour post-dose time point (see Table 8-3). This includes the performance of a 12-hour pulmonary function test (PFT) and the collection of PK samples. Subject eDiary compliance will also be reviewed and the subject will be retrained if necessary. Study drug will be collected and the subjects will be discharged from the clinic.

A Washout Period of 7-14 days will occur between each Treatment Period. During the Washout Period between Visits 3 and 4, when subjects are not taking study drug, subjects will use the Sponsor-provided short-acting bronchodilator, Atrovent HFA, administered QID and Ventolin HFA as needed. For more details on Visit 3 procedures, refer to Section 8.4.

At Visit 4 (Day 1 of Treatment Period 2), subjects will return to the clinic before 10:00 am. The study drug for Treatment Period 2 will be dispensed to the subject with or without Aerochamber Plus VHC as per the subject's assigned treatment group. The first dose of study drug for Treatment Period 2 will be administered in the clinic under site personnel supervision before 10:00 am. Subject eDiary compliance will be reviewed and the subject will be retrained, if necessary. Subjects will undergo all protocol-defined assessments (see Table 8-2) prior to being discharged from the clinic. Subjects will then continue with study drug administration for 7 days until Visit 5. For more details on Visit 4 procedures, refer to Section 8.5.

Visit 5 (Day 8 of Treatment Period 2) will serve as the final visit. At Visit 5, subjects will administer the final morning dose of study drug at the clinic under site supervision before 10:00 am. Subjects will complete all post-study assessments, including a final physical examination, 12-hour PFT, PK samples collection, and the documentation of all AEs.The eDiary will be obtained and the subject will then be discharged from the study. Refer to Table 8-3 and Section 8.6 for the study procedures and assessments to be performed at Visit 5.

A follow-up telephone call will be performed within 7 to 14 days following Visit 5.

General Guidance for Treatment Visits 2 to 5 (in-clinic):

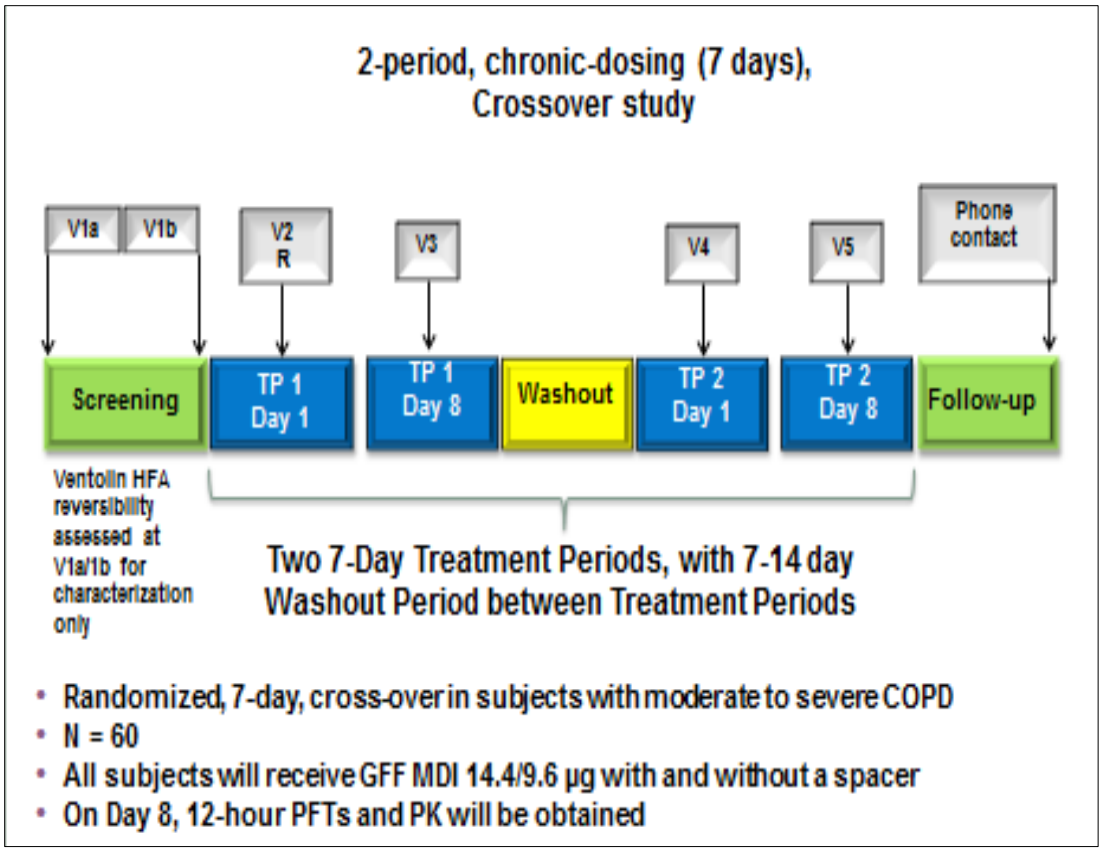
- At the start of each treatment visit, prior to the administration of study drug and performance of any study procedures, site personnel must confirm that the subject withheld all COPD medications (including randomized study medication, ICS and rescue medication, e.g., Ventolin HFA) for at least 6 hours by confirming the last time of dosing for all COPD medication(s).
  - **Note**: For subjects who inadvertently took COPD medication within 6 hours of the start of study procedures, the visit date must be rescheduled within the specified visit window as soon as it is practical.
  - **Note:** Before the in-clinic dose is administered, the site must confirm that the subject meets all protocol-specified requirements (e.g., FEV_1 baseline criteria; see Section 7.1.1.3).
- Subjects must not ingest xanthine-containing foods and beverages for at least 6 hours prior to each study visit and for the duration of each study visit (see Section 5.5).
- Subjects are encouraged to refrain from consuming grapefruits or grapefruit juice throughout the study.
- Subjects will be required to refrain from smoking (nicotine gums and patches are allowed) for at least 4 hours prior to each study visit and throughout the duration of each study visit.
- To ensure standardization of dosing times, it is recommended that sites encourage subjects to maintain a dosing schedule at home that is consistent with their in-clinic dosing time.
- Subjects will be required to take their study drug BID. Each dose will consist of 2 puffs, once in the morning, between 06:00 am and 10:00 am (breakfast time), and once in the evening, between 06:00 pm and 10:00 pm (dinner time).
- In order to minimize diurnal variance, sites should make every effort to assess subjects at the same time throughout the study and to discuss the importance of dosing in a timely manner every 12 hours.
- Subjects will be required to return to the clinic at approximately the same time for all treatment visits (±2 hours) but not past 10:00 am. Subjects will be required to remain at the clinic until completion of all protocol-defined assessments.
- Sites should make every effort to ensure that the in-clinic dosing time is before 10:00 am and within 12±2 hours of the prior at-home evening dosing time.
- Sites are encouraged to call the subject on the day before a scheduled visit to remind the subject of the following:
  - To take their last evening dose 12±2 hours prior to the scheduled visit time.
  - To bring their study drugs with them to the clinic and to withhold all COPD medications (including randomized study medication, ICS, and rescue medication) for at least 6 hours prior to PFTs.

  - To refrain from ingesting xanthine-containing foods and beverages for at least 6 hours prior to each study visit and for the duration of each study visit.
  - To refrain from smoking for at least 4 hours prior to the study visit and throughout the duration of each study visit.

- The in-clinic dosing time will be recorded as the time of administration for the second puff of study drug.
- Site personnel will instruct subjects not to take any COPD medications without site personnel permission during a visit until all study procedures have been completed and the subject has been discharged from the clinic. Site personnel should take every precaution to prevent the use of non-study COPD medications during a test day. Site personnel may request the subject to surrender all non-study COPD medications prior to the start of the visit before performing any study procedures. The medications should be returned to the subject at the end of the visit when all study procedures have been completed.
- If, at any time during a test day, a subject experiences severe COPD symptoms and requires Ventolin HFA for symptom relief, site personnel must note the time and justification for use in the subject's chart, and all subsequent spirometry assessments should be stopped. Safety assessments should be continued at the discretion of the Investigator.
- Every effort must be made to ensure that subjects return to the clinic on Day 8, 1 week following the initiation of each treatment period. Visit dates have a window of 7±2 days to accommodate potential scheduling conflicts.
- During each Treatment Period (between Visits 2 and 3, and Visits 4 and 5), subjects will be permitted to use Sponsor-provided Ventolin HFA on an as-needed basis for relief of COPD symptoms.
- During the Washout Period between Visits 3 and 4, when subjects are not taking study drug, subjects will use the Sponsor-provided short-acting bronchodilator, Atrovent HFA, administered QID and Ventolin HFA as needed.
- Protocol-adjusted ICS therapy defined at Screening, if any, should be continued and remain stable for the duration of the study (see Section 5.4 for further guidance related to phosphodiesterase inhibitors).

A flow diagram of the study design is displayed in Figure 1 below.

Figure 1. Study Design


2-period, chronic-dosing (7 days),
Crossover study
V1a
V1b
V2
R
V3
V4
V5
Phone contact
Screening
TP 1 Day 1
TP 1 Day 8
Washout
TP 2 Day 1
TP 2 Day 8
Follow-up
Ventolin HFA reversibility assessed at V1a/1b for characterization only
Two 7-Day Treatment Periods, with 7-14 day Washout Period between Treatment Periods
• Randomized, 7-day, cross-over in subjects with moderate to severe COPD
• N = 60
• All subjects will receive GFF MDI 14.4/9.6 µg with and without a spacer
• On Day 8, 12-hour PFTs and PK will be obtained

5 STUDY POPULATION SELECTION, PRIOR AND CONCOMITANT MEDICATIONS AND WITHDRAWAL CRITERIA

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 years of age and no older than 80 at Visit 1
3. A female is eligible to enter and participate in the study if she is of:
   - Non-child bearing potential (i.e., physiologically incapable of becoming pregnant, including any female who is 2 years post-menopausal); or
   - Child bearing potential, has a negative serum pregnancy test at Visit 1, and agrees to one of the following acceptable contraceptive methods used consistently and correctly as outlined below (i.e., in accordance with the approved product label and the instructions of the physician for the duration of the study – from Visit 1 (Screening) until 14 days after Visit 5:
   - Complete abstinence from intercourse or
   - Implants of levonorgestrel inserted for at least 1 month prior to the study drug administration but not beyond the third successive year following insertion; or
   - Injectable progestogen administered for at least 1 month prior to study drug administration; or
   - Oral contraceptive (combined or progestogen only) administered for at least one monthly cycle prior to study drug administration; or
   - Double barrier method: condom or occlusive cap (diaphragm or cervical/vault caps) plus spermicidal agent (foam/gel/film/cream/suppository); or
   - An intrauterine device (IUD), inserted by a qualified physician, with published data showing that the highest expected failure rate is less than 1% per year; or
   - Estrogenic vaginal ring; or
   - Percutaneous contraceptive patches.
4. COPD Diagnosis: Subjects with an established clinical history of COPD as defined by the American Thoracic Society (ATS)/European Respiratory Society (ERS) (Celli, 2004) characterized by:
   - Airflow limitation that is not fully reversible. Progressive airflow limitation associated with an abnormal inflammatory response of the lungs to noxious particles or gases, primarily caused by cigarette smoking.
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) x number of years smoked (e.g., 20 cigarettes per day for 10 years, or 10 cigarettes per day for 20 years represent 10 pack-years)].
6. COPD Severity: Subjects with an established clinical history of COPD and severity defined as:

- At Visit 1a (and 1b, if necessary), post-bronchodilator FEV_1/FVC ratio of <0.70
- At Visit 1a (and 1b, if necessary), post-bronchodilator FEV_1 must be <80% predicted normal value, calculated using NHANES III reference equations, and the measured FEV_1 must be ≥750 mL if FEV_1 <30% of predicted normal value.
- At Visit 2, the average of the -60 minute and -30 minute pre-dose FEV_1 assessments must be <80% predicted normal value calculated using 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. Chest X-ray or computed tomography (CT) scan of the chest/lungs within 6 months prior to Visit 1 must be acceptable to the Investigator. Subjects who have a chest X-ray (or CT scan) that reveals clinically significant abnormalities not believed to be due to the presence of COPD should not be included. A chest X-ray must be conducted prior to Visit 2 if the most recent chest X-ray or CT scan is more than 6 months old at the time of Visit 1.
10. Compliance: Subjects must be willing to remain at the study center as required per protocol to complete all visit assessments.

5.2 Exclusion Criteria

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

1. Significant diseases or conditions other than COPD, which, in the opinion of the Investigator, may put the patient at risk because of participation in the study or may influence the results of the study or the subject's ability to participate in the study.
2. 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.
3. Respiratory
   a) Asthma: Subjects, who in the opinion of the Investigator, have a current diagnosis of asthma. (Note: Subjects with a prior history of asthma are eligible if COPD is currently their primary diagnosis).
   b) Alpha-1 Antitrypsin Deficiency: Subjects who have alpha-1 antitrypsin deficiency as the cause of COPD.
   c) Other Respiratory Disorders: Subjects who have other active pulmonary disease such as active tuberculosis, lung cancer, bronchiectasis, sarcoidosis, lung fibrosis, primary pulmonary hypertension, interstitial lung disease, and uncontrolled sleep apnea (i.e., in the opinion of the Investigator severity of the disorder would impact the conduct of the study). Note: Allergic rhinitis is not exclusionary.
   d) Lung Volume Reduction: Subjects who have undergone lung volume reduction surgery, lobectomy or bronchoscopic lung volume reduction (endobronchial blockers, airway bypass, endobronchial valves, thermal vapor ablation, biological sealants, and airway implants) within 1 year of Visit 1.

e) Hospitalization: Subjects who have been hospitalized due to poorly controlled COPD within 3 months prior to Visit 1 (Screening) or during the Screening Period (Visit 1 to Visit 2).

f) Poorly Controlled COPD: Subjects who have poorly controlled COPD, defined as acute worsening of COPD that requires treatment with oral corticosteroids or antibiotics within 6 weeks prior to Visit 1 (Screening) or during the Screening Period (Visit 1 to Visit 2).

Note: Subjects who are steroid dependent and maintained on an equivalent of 5 mg prednisone per day or 10 mg every other day for at least 3 months prior to Visit 1a are eligible for enrollment providing the dose of oral steroids remains stable during the Screening Period (Visit 1 through Visit 2).

g) Lower Respiratory Tract Infection: Subjects who had lower respiratory tract infections that required antibiotics within 6 weeks prior to Visit 1 (Screening) or during the Screening Period (Visit 1to Visit 2).

h) Other Respiratory tract infections that have not resolved at least 7 days prior to Screening

i) Spirometry Performance:

- Acceptability: Subjects who cannot perform acceptable spirometry (i.e., meet ATS/ERS acceptability criteria)
- Repeatability: Subjects who cannot perform technically acceptable spirometry with at least three acceptable flow-volume curves meeting ATS repeatability criteria for FEV_1 during the pre-bronchodilator assessment at Visit 1a/1b **or** at the post-bronchodilator assessment at Visit 1a/1b

j) Oxygen: Subjects receiving long-term-oxygen therapy (LTOT) or nocturnal oxygen therapy required for greater than 12 hours a day. Note: As needed oxygen, use is not exclusionary.

k) Subject use of any non-invasive positive pressure ventilation device (NIPPV).

Note: Subjects using continuous positive airway pressure (CPAP) or bi-level positive airway pressure (BiPAP) for Sleep Apnea Syndrome are allowed in the study.

l) Change in smoking status (i.e., start or stop smoking,) or initiation of a smoking cessation program within 6 weeks of Visit 1 and throughout the Screening Period (Visit 1 to Visit 2).

m) Pulmonary Rehabilitation: Subjects who have participated in the acute phase of a pulmonary rehabilitation program within 4 weeks prior to Visit 1 (Screening) or who will enter the acute phase of a pulmonary rehabilitation program during the study. Subjects who are in the maintenance phase of a pulmonary rehabilitation program are not to be excluded.

n) Subjects who have initiated or altered the dose regimen of intranasal corticosteroids, intranasal antihistamines, or a combination thereof within 7 days prior to Visit 1 or during the Screening Period (Visit 1 to Visit 2)

4. Cardiac disease

a) Subjects who have unstable ischemic heart disease, left ventricular failure, or documented myocardial infarction within 12 months of Screening (Visit 1). Subjects

with a recent history of acute coronary syndrome, or who have undergone percutaneous coronary intervention or coronary artery bypass graft within the past 3 months are to be excluded.

b) Subjects with congestive heart failure: Classes of Heart Failure New York Heart Association Class III/IV(CHF NYHA III-IV).

c) Clinically significant abnormal ECG: A clinically significant abnormal ECG is defined as (but not limited to) any of the following:

- Clinically significant conduction abnormalities [e.g., left bundle branch block, Wolff-Parkinson-White syndrome or evidence of second degree (Mobitz Type II) or third degree atrioventricular (AV) block]
- Clinically significant arrhythmias (e.g., atrial fibrillation with irregular ventricular response, atrial flutter, ventricular tachycardia). Note: atrial fibrillation that has been clinically stable for at least 6 months is appropriately treated with anticoagulation and controlled with a rate control strategy (i.e., selective β-blocker, calcium channel blocker, digoxin or ablation therapy) for at least 6 months is allowed for inclusion. In such subjects, atrial fibrillation must be present at pre-randomization visits, with a resting ventricular rate <100 beats per minute (bpm). At Screening (screening, the atrial fibrillation must be confirmed by central reading.
- A mean corrected QT interval using Fridericia's correction factor (QTcF) value at screening >450 ms for males and >470 ms for females or an ECG that is not suitable for QT measurements (e.g., poorly defined termination of the T wave) at Visit 1 that remains elevated on repeat testing prior to Visit 2.
- Ventricular rate <45 bpm
- Pathological Q waves of ≤1 year
- 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.
- Any other ECG abnormalities not listed above that in the opinion of the Investigator are clinically significant.

d) Clinically Uncontrolled Hypertension: Subjects who have clinically significant uncontrolled hypertension.

5. Neurological

a. Subjects with seizures requiring anticonvulsants within 12 months prior to Visit 1a (Screening). Note: Subjects treated with anticonvulsant medication for 12 months or more with no seizure events are eligible.

b. Subjects taking selective serotonin reuptake inhibitors (SSRIs) or serotonin-norepinephrine reuptake inhibitors (SNRIs) whose dose has not been stable for at least four weeks prior to Visit 1a or is altered at any point during the Screening Period (Visit 1a to Visit 2), or exceeds the maximum recommended dose

c. Subjects who have experienced a cerebrovascular accident within the 6 months prior to Visit 1a

6. Renal
   a) Subjects with symptomatic prostatic hypertrophy that is clinically significant in the opinion of the Investigator. Subjects with a trans-urethral resection of prostate (TURP) or full resection of the prostate within 6 months prior to Visit 1a are excluded from the study.
   b) Subjects with bladder neck obstruction or urinary retention that is clinically significant in the opinion of the Investigator.
   c) Subjects with a calculated creatinine clearance <30 mL/minute using Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula (Levey, 2009) at Visit 1a and on repeat testing prior to Visit 2.

      Note: This study will also recruit approximately 12 with impaired renal function (i.e., creatinine clearance of ≥30 - <50 ml/min). The study will remain open until the planned number of approximately 60 subjects have been randomized and the target numbers of subjects with renal impairment have been recruited. In the event that the target number of approximately 12 subjects with renal impairment is not reached, the study will remain open to all eligible subjects until approximately 70 subjects are randomized, at that point only subjects with renal impairment will be allowed to proceed and subjects with a creatinine clearance of ≥ 50 ml/min will be screen failed.

      Note: Subjects with overactive bladder syndrome, treated with oral anticholinergics, who have been on treatment for at least one month, are allowed in the trial.
7. Endocrine
   a) Subjects, who, in the opinion of the Investigator, have uncontrolled hypo-or hyperthyroidism, hypokalemia or hyperadrenergic state
   b) Subjects, who, in the opinion of the Investigator, have uncontrolled Type I or II diabetes
8. Liver: Subjects with abnormal liver function tests defined as aspartate aminotransferase (AST), alanine aminotransferase (ALT), or total bilirubin ≥1.5 times upper limit of normal (ULN) at Visit 1a and on repeat testing prior to Visit 2. Note: Chronic stable hepatitis B and C is acceptable if the subject otherwise meets study entry criteria.
9. Cancer: Subjects who have cancer that has not been in complete remission for at least five years. Note: Subjects with squamous cell carcinoma of the skin, basal cell carcinoma of the skin, or localized prostate cancer are eligible, if in the opinion of the Investigator, the condition has been adequately worked up, is clinically controlled and the subject's participation in the study would not represent a safety concern.
10. Glaucoma: Subjects with a diagnosis of narrow-angle glaucoma that, in the opinion of the Investigator, has not been adequately treated. All medications approved for control of intraocular pressures are allowed including topical ophthalmic non-selective beta-blockers such as betaxolol, carteolol, levobunolol, metipranolol, timolol, and prostaglandin analogues.
11. Drug Allergy: Subjects who have a history of hypersensitivity to β_2-agonists, glycopyrronium or other muscarinic anticholinergics, or any component of the MDI.

12. Substance Abuse: Subjects, who in the opinion of the Investigator, significantly abuse alcohol or drugs (refer to Exclusion Criterion 1).
13. Medication prior to spirometry: Subjects who are medically unable to withhold their short-acting bronchodilators for the 6-hour period required prior to spirometry testing at each study visit will be excluded.
14. Prohibited Medications: Subjects who, in the opinion of the Investigator, would be unable to abstain from protocol-defined prohibited medications during the Screening Period and treatment phases of this study (refer to Section 5.4).
15. Vaccinations: Subjects who received a live attenuated vaccination within 30 days prior to Visit 1 (Screening) or during the Screening Period (between Visits 1a to Visit 2). Note: Inactivated influenza vaccination, pneumococcal vaccination or any other inactivated vaccine is acceptable provided it is not administered within 48 hours prior to Visit 1a (Screening) or Visit 2 (Randomization).
16. Non-compliance: Subjects unable to comply with study procedures including eDiary completion (i.e., <70% subject completion of diary assessments in the last 7 days preceding Visit 2).
17. 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.
18. 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 will limit the validity of informed consent to participate in the study.
19. Investigational Drugs or Devices: Treatment with investigational study drug or device in another clinical trial within the last 30 days or five half-lives prior to Visit 1a (Screening), whichever is longer. Note: Subject participation in observational studies (i.e., studies that do not require change to medication or an additional intervention) is not exclusionary.
20. Previous Participation: Subjects who were previously randomized in any trial conducted or sponsored by Pearl Therapeutics that included PT001, PT003, or PT005 are not allowed to participate in this study. Note: Subjects who were screen failures and never randomized in any Pearl Therapeutics trials that included PT001, PT003, or PT005) may be enrolled.
21. Hand-to-Breath Coordination: Subjects who requires the use of a spacer device to compensate for poor hand-to-breath coordination with a MDI. Note: Use of a nebulizer to deliver COPD medications is prohibited throughout the trial.

5.3 Subject Identification

All subjects who undergo screening will be assigned a unique screening identification number at the Screening Visit (Visit 1a). Only subjects continuing to meet entry inclusion/exclusion criteria at Visit 2 will be assigned a unique subject randomization number. Randomization will be centralized through the use of an IWRS.

5.4 Prior, Concomitant, and Prohibited Medications

All prescription and over-the-counter (OTC) medications taken by the subject during 30 days before Screening (Visit 1a) will be recorded on the Concomitant Medications electronic Case Report Form (eCRF) page. Any additions, deletions, or changes in the dose of these medications while in the study should be entered on the eCRF. Any current ongoing medications, including OTC drugs and herbal supplements, will be allowed provided they are not prohibited by the protocol (see Section 5.4.1) and are approved by the Investigator. Subjects should also be instructed to contact the Investigator if they develop any illnesses.

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.

5.4.1 Prohibited COPD Medications

Subjects requiring the prohibited COPD medications listed in Table 5-1 are not permitted to enroll in this study. These medications must be discontinued at Visit 1a (Screening) and are not permitted during the Screening Period. The minimum washout period between Visit 1a and Visit 2 is shown in Table 5-1.

Table 5-1. Prohibited COPD Medications and Required Washout Periods, Prior to Visit 2

Class of medications	Minimum Washout Period prior to Visit 2
LAMAs	Tiotropium: 14 days Aclidinium: 7 days Glycopyrronium: 7 days Umeclidinium: 7 days
Short-acting muscarinic antagonists (SAMA) [a]	6 hours
LABAs (inhaled)	7 days (indacaterol and olodaterol: 15 days)
Fixed-combinations of LABA/LAMA	7 days or the duration of the individual agents if longer
Fixed-combinations of LABA/ICS	7 days
Fixed-combinations of SABAs and SAMAs	6 hours
SABAs [b]	6 hours
ICS	7 days

Table 5-1. Prohibited COPD Medications and Required Washout Periods, Prior to Visit 2

Class of medications	Minimum Washout Period prior to Visit 2

Abbreviations: COPD=chronic obstructive pulmonary disease; HFA=hydrofluoroalkane; ICS=inhaled corticosteroid; LABA=long-acting β_2-agonist; LAMA=long-acting muscarinic antagonist; SABA=short-acting β_2-agonist; SAMA=short-acting muscarinic antagonist

Note: Subjects taking roflumilast are allowed provided they have been on stable dose of therapy for at least 2 months prior to Randomization.

Note: Theophylline ($\leq$400 mg/day) is permitted provided the subject has been on a stable dose of therapy for at least 4 weeks prior to Randomization.

a. Discontinue and use only sponsor provided Atrovent HFA during screening

b. Discontinue and use only sponsor provided rescue Ventolin HFA throughout the study

Subjects taking the above listed COPD medications at Visit 1a (Screening) will discontinue these medications for the duration of the trial and be switched to sponsor-provided Atrovent HFA MDI administered QID and sponsor-provided Ventolin HFA to be administered up to four times per day as needed for control of symptoms during the Screening Period.

Subjects receiving a maintenance dose of an ICS as part of a fixed dose combination therapy containing fluticasone furoate and vilanterol, fluticasone propionate and salmeterol, mometasone and formoterol, budesonide and formoterol or fluticasone propionate and formoterol must have been maintained on a stable dose of the ICS component for at least 4 weeks prior to Visit 1a (Screening). These subjects will be switched to the corresponding dose of fluticasone propionate, fluticasone furoate, mometasone or budesonide to be administered throughout the duration of the study.

All subjects treated with either a LABA (salmeterol, formoterol, indacaterol or olodaterol) or currently marketed long- acting anti-muscarinic agent (LAMA) (tiotropium, aclidinium, glycopyrronium bromide, [e.g., Seebri], umeclidinium) administered alone or as a loose combination will have these medications discontinued and replaced with sponsor-provided Atrovent HFA MDI administered QID, and sponsor-provided Ventolin HFA to be administered up to four times per day as needed for control of symptoms during the Screening Period.

Note: During the Screening Period (between Visits 1a and 2) and Washout Periods (between Visits 3 and 4), Sponsor-provided Atrovent HFA MDI is to be used as maintenance medication administered QID, and Sponsor-provided Ventolin HFA is to be used as rescue medication administered as needed; however, both medications must be withheld for at least 6 hours before each study visit.

Note: During study treatment (i.e., between Visits 2 and 3, and Visits 4 and 5), subjects will be provided with and allowed to use Sponsor-provided Ventolin HFA as needed for relief of COPD symptoms.

- The following respiratory medications are not permitted during this study (Table 5-2 Other Respiratory/Nasal Medications: Required Washout Period Prior to Visit 2

Table 5-2 Other Respiratory/Nasal Medications: Required Washout Period Prior to Visit 2

Class of Medication	Minimum Washout Period Prior to Visit 2
Leukotriene antagonists (eg., zafirlukast, montelukast, and zilueton)	7 days
Cromoglycate	7 days
Nedocromil	7 days
Ketotifen [a]	7 days

[a] Ketotifen eye drops are allowed.

5.4.2 Other Prohibited Medications

The following medications should be used under the stated conditions during this study (Table 5-3. Non-COPD Medications Allowed Under Certain Conditions

). Each concomitant drug must be individually assessed against all exclusion criteria. If in doubt, the Investigator should contact the Pearl Medical Monitor before randomizing a subject or allowing a new medication to be started.

Table 5-3. Non-COPD Medications Allowed Under Certain Conditions

Medications Allowed Under Certain Conditions	Condition
SSRIs or SNRIs	Treatment regimen has been stable for at least 4 weeks prior to Visit 1 and not altered during the Screening Period, and does not exceed the maximum recommended dose
Intranasal corticosteroids, intranasal antihistamines or combination thereof	Administered at constant dose and dosing regimen for at least 7 days prior to Visit 1a (Screening) and prior to Visit 2

Abbreviations: COPD=chronic obstructive pulmonary disease; SNRI=serotonin–norepinephrine reuptake inhibitors; SSRI=selective serotonin reuptake inhibitors

Subjects requiring the following medications are prohibited from this study (

Table 5-4. Prohibited Medications

5-4). Subjects who recently discontinued use of these medications may be considered for study enrollment providing they have met the minimum washout period prior to Screening (Visit 1a). These medications are prohibited throughout the course of the study, and should a subject require use of any of the listed medications, the subject should be discontinued.

Table 5-4. Prohibited Medications

Prohibited Medications	Minimum cessation period prior to Visit 1 (Screening)
Any drug with potential to significantly prolong the QT interval	14 days or 5 half-lives, whichever is longer
Other investigational drugs	30 days or 5 half-lives, whichever is longer
Non-selective beta-blocking agents	7 days
Cardiac antiarrhythmics Class Ia, III	7 days; amiodarone, 3 months
Anticonvulsants for seizure disorder	Allowed if stable dose for 12 months and free of seizures for 1 year
Anticonvulsants for other indications	Allowed if stable dose for at least 3 months and the Investigator confirms there have been no seizures within the past 12 months.
Tricyclic antidepressants	14 days
Monoamine oxidase inhibitors	14 days
Anti-tumor necrosis factor α (TNF α) antibodies (e.g., infliximab and any other members of this class of drugs)	30 days or 5 half-lives, whichever is longer
Monoclonal antibodies	30 days or 5 half-lives, whichever is longer
Antipsychotic drugs [a]	30 days
Systemic calcineurin inhibitors, systemic antifungal agents, protease inhibitors and cimetidine	30 days
Systemic anticholinergics [b]	7 days

[a] Antipsychotic agents used for other indications may be allowed after consultation with the Medical Monitor of the trial.

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

Note: Benzodiazepines are not exclusionary.

5.5 Other Restrictions, Illicit Drugs or Drugs of Abuse

5.5.1 Illicit Drugs and/or Drugs of Abuse

Illicit drugs or drugs of abuse will not be allowed from the start of Screening (Visit 1a) to the end of Visit 7 or to whenever the subject discontinues 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. Medical marijuana is not an exclusionary drug if used for medical purposes, and there is no change in the dose or frequency of consumption. Inhaled medical marijuana must be withheld for at least 4 hours prior to each study visit and throughout the duration of each study visit.

5.5.2 Dietary Restrictions

Subjects are encouraged to refrain from consuming grapefruits or grapefruit juice throughout the study. After the screening visit (Visit 1a), subjects must not ingest xanthine-containing foods and beverages for at least 6 hours prior to each study visit and for the duration of each study visit. Examples of such products include coffee, tea, chocolate, and cola. Decaffeinated beverages are acceptable.

5.6 Smoking Status

Changes in a subject's smoking status (e.g., stopping or restarting smoking) may have an impact on the efficacy outcome measures. At all visits the subject will be asked about any recent change in their smoking status (i.e., whether a subject's status has changed from smoker to non-smoker or vice versa). Any change in smoking status during the Screening Period (Visit 1a to Visit 2) will result in a screen failure. Smoking status changes during Treatment Periods 1 to 2 will be captured in the eCRF, but the subject will be permitted to continue in the study. Subjects will be required to refrain from smoking (including medical marijuana and electronic cigarettes) for at least 4 hours prior to each study visit and throughout the duration of each study visit. Study participants may utilize various nicotine replacement treatments such as chewing gum and patches as needed, in accordance with recommendations from the Investigator during the entire study visit.

Note: For this study, the use of electronic cigarettes will be treated in the same manner as smoking.

5.7 Reasons and Procedures for Early Termination from the Study

5.7.1 Reasons for Discontinuation

Subjects may be withdrawn from the study at any time at their own request, upon request of the Investigator, or by Pearl at any time or for any reason. If a subject is lost to follow up (i.e., fails to return for study visits), reasonable efforts must be made to contact the subject and complete study termination procedures. All subjects who discontinue the study because of AEs will be followed up at suitable intervals in order to evaluate the course of the AE and to ensure the reversibility or stabilization of the abnormality. All subjects who prematurely

discontinue the study after Randomization, regardless of the cause, should undergo only the assessments outlined in Section 8.7 on the date of discontinuation.

If a subject experiences any of the changes of concern listed below, a repeat assessment should be obtained, and, if confirmed, the Investigator or designee needs to make a determination as to the suitability of continuing the subject in the study. The changes of concern include:

- Following dosing, a heart rate increase of greater than 40 bpm from the pre-dose value obtained on that specific test day and the measured value is also >120 bpm.
- Following dosing, a systolic BP (SBP) increase of more than 40 mmHg from the pre-dose value obtained on that specific test day and the measured value is also >160 mmHg.
- Decrease in creatinine clearance to a value below 30 mL/minute using CKD-EPI formula clinically relevant change from baseline as determined by the Investigator.
- Calculated QTcF intervals >500 msec, and have increased by 60 msec or more over baseline value obtained at Randomization (Visit 2).

Subjects who suffer a moderate or severe COPD exacerbation will be discontinued from the study.

A COPD exacerbation will be defined as a change in the subject's baseline dyspnea, cough, and/or sputum (increase in volume or change in color towards purulence) that lasts ≥2 days, is beyond normal day-to-day variations, is acute in onset, and may warrant a change in regular medication. The severity of COPD exacerbations will be classified as follows:

- Mild: Exacerbations that do not require systemic steroids or antibiotics and do not result in hospitalization or death
- Moderate: Exacerbations that require treatment with systemic steroids and/or antibiotics, and do not result in hospitalization or death

  Severe: Exacerbations that result in hospitalization or death

Subjects who failed to meet FEV_1 baseline stability criteria (see section 7.1.1.1)
An Investigator may choose to discontinue a subject from study participation at any time or for any reason, with sufficient notice by the Investigator, as per the terms of the contract with Pearl. The reason for discontinuation will be documented in the source documents.

Pearl 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 Pearl, in a timeframe that is compatible with the subjects' well-being.

If a subject requires the following prohibited medications, they should be discontinued from the study:

- Initiation of maintenance therapy with any prohibited medications (see Section 5.4).

- Initiation of maintenance therapy with a marketed LABA (e.g., salmeterol, formoterol, indacaterol, vilanterol, olodaterol) administered alone or in combination with an ICS or a marketed LAMA (e.g., tiotropium, aclidinium, umeclidinium, or glycopyrronium bromide [Seebri]).

If a female subject becomes pregnant during the course of the study, the subject will be discontinued and the pregnancy will be followed full-term through delivery or final outcome. (Refer to Section 7.5.11).

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

6.1 Subject Information

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

6.2 Product Description

Investigational materials will be provided by Pearl as summarized in Table 6-1. Treatments will be open-label. Atrovent HFA and Ventolin HFA will be supplied as open-label MDIs.

Table 6-1. Product Descriptions

Product Name & Dose	Product Strength	Dose Form/Fill Count	Administration
Study Medications			
GFF MDI (PT003) 14.4/9.6 µg ex-actuator	7.2/4.8 µg per actuation	MDI/ 120 inhalations	Taken as 2 inhalations BID
Open-Label Products			
Albuterol sulfate inhalation aerosol 90 µg[a] ex-actuator	Ventolin® HFA Albuterol sulfate inhalation aerosol. Each inhalation contains 108 µg corresponding to 90 µg albuterol base from the mouthpiece	MDI/ 60 or 200 actuations	Taken as needed Supplies are open-label
Iipratropium bromide) HFA inhalation aerosol 34 µg[b]	Atrovent® HFA. Ipratropium bromide HFA. Each inhalation contains 17 µg per actuation	MDI/ 200 actuations	Taken as 2 inhalations QID Supplies are open-label

Abbreviations: BID=twice daily; GFF MDI= Glycopyrronium and Formoterol Fumarate Inhalation Aerosol; HFA=hydrofluoroalkane; MDI=Metered Dose Inhaler; QID=four times daily; US=United States

Note: All study drugs will be administered by oral inhalation.

[a] Reversibility testing at Visit 1 and rescue medication during the study and during washout periods

[b] Chronic obstructive pulmonary disease maintenance therapy during the Screening and Washout Periods

Open-label Atrovent HFA MDIs will be provided from commercial supplies. Manufacturer's instructions for study drug administration are provided in Appendix 5.

Open-label Ventolin HFA with dose counters will be provided from commercial supplies. Manufacturer's instructions for study drug administration are provided in Appendix 6.

6.3 Primary Packaging and Labeling Information

Investigational materials will be packaged by the Sponsor. Atrovent HFA and Ventolin HFA will be supplied as open-label MDIs.

GFF MDI Supplies: Each MDI will be labeled with a single label. The foil pouch will be labeled with an one-part label.

Open-label Supplies: Open-label Atrovent HFA and Ventolin HFA will be provided as individually labeled MDIs. Each MDI will contain a single label.

Single and two-part 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 Translation Key
Fill Count & Dosage Form	
Visit # (Space for Entry of Interval ID)	

ID = identification; # = number

6.4 Secondary Packaging and Labeling Information

Open-label investigational supplies (GFF MDI) and open label supplies (Atrovent HFA, and Ventolin HFA) will be packaged in individual boxes as outlined in Table 6-2. Box configuration is subject to change as a result of packaging constraints.

Table 6-2. Description of Boxes

Drug Supplies	Box Contents
GFF MDI	1 MDI
Atrovent HFA	1 MDI
Ventolin HFA	1 MDI

Abbreviations: HFA=hydrofluoroalkane; MDI=metered dose inhaler

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

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

ID = identification; # = number

6.5 Storage Requirements

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

Ventolin® HFA supplies: Store 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. Do not use or store near heat or open flame. Exposure to temperatures above 120°F (49°C) may cause bursting. Never throw into a fire or incinerator.

Atrovent® HFA supplies: Store at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [Refer to Unites States Pharmacopoeia Controlled Room Temperature]. For optimal results, the canister should be at room temperature before use. Do not puncture. Do not use or store near heat or open flame. Exposure to temperatures above 120°F (49°C) may cause bursting. Never throw the inhaler into a fire or incinerator.

The clinical supplies storage area at the site must be monitored by the site staff for temperature consistency with the acceptable storage temperature range specified in accordance with the product label. Documentation of temperature monitoring should be maintained.

6.6 Instructions for Preparation of Treatments for Administration and Dispensing

6.6.1 GFF MDI

Individual GFF MDIs will be packaged in a foil pouch and contained in an individual visit treatment box. Both the visit treatment box and the foil overwrap will have a label with a component ID number. Confirm that the identifier given by IWRS and the component ID number written on the label are the same. 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. The "tear-off" part of the label is to be placed on the IWRS confirmation report.

GFF MDI must be primed before the first use. Priming involves releasing a certain number of sprays (four) into the air before the first use of the inhaler. Shaking and priming the inhaler fills a chamber inside the canister with the correct dose and mix of medication so that it is ready to use.

GFF MDI must be primed in a separate room from the subject treatment area, which may result in a delay between priming and dosing. To ensure consistency in the administration for all subjects, the MDIs are to be gently shaken (5 to 10 seconds) immediately before each actuation (puff). To prepare the inhaler for first use please refer to the instruction in Appendix 3. Each dose will consist of two puffs from the MDI. Subjects will be dispensed the MDI and instructed to continue taking study drug BID, two puffs in the morning and two puffs in the evening approximately 12 hours apart, until subject returns to the clinic. The MDI should be stored at room temperature by the subject, avoiding temperature extremes and storage in direct sunlight. See Appendix 3 for instructions on the administration of GFF MDIs.

6.6.2 Atrovent® HFA (Ipratropium Bromide)

Refer to Appendix 5 for instructions on the administration of Atrovent® HFA.

6.6.3 Ventolin HFA® (Albuterol Sulfate)

Refer to Appendix 6 for the manufacturer's instructions on the administration of Ventolin HFA.

6.7 Aerochamber Plus Flow-Vu Instructions for Administration and Dispensing of Treatments

The Aerochamber Plus Flow-Vu VHC can be used directly out of package. Before use remove the VHC cap and examine the chamber for any obvious defects.

At the time of first use, ensure that the GFF MDI is primed outside of the VHC according to the instructions in Section 6.6. Once the MDI is primed, shake the inhaler immediately before use per the instructions in Section 6.6. Insert the inhaler into the Back piece of the chamber, which is the opposite end as the mouthpiece (refer to Appendix 4 for a diagram of the VHC).

The inhalation instruction with the mouthpiece should be followed for taking each dose. Put the mouthpiece into mouth and close lips around the mouthpiece to ensure an effective seal. The ***Flow-Vu*** indicator only moves if there is a good seal. ***Breath out gently and press the inhaler at the beginning of a slow inhalation***. Use the ***Flow-Vu*** indicator to assist in the coordination of this step. Breath in slowly and deeply through the mouth until a full breath has been taken. Hold breath for 5-10 seconds. Slow down inhalation if you hear the ***Flow Signal*** whistle sound. This means you are inhaling too quickly. Administer one (1) puff at a time. Shake the GFF MDI prior to each dose administration and repeat VHC instructions for use.

The VHC should not be cleaned throughout the study duration.

Store the VHC at room temperature and keep dry between use.

Refer to Appendix 4 for instructions for use of the Aerochamber Plus Flow-Vu VHC

6.8 Drug Accountability/Return of Clinical Supplies

Under no circumstances will the Investigator(s) allow the study drug to be used other than as directed by this protocol.

Investigational clinical supplies must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the Investigator and designated assistants have access. Storage conditions for the clinical supplies should be observed, monitored, and documented. Clinical supplies are to be dispensed only in accordance with the protocol. The Investigator is responsible for keeping accurate records of the clinical supplies received from Pearl, the amount dispensed to and returned by the subjects/patients, and the amount remaining at the conclusion of the study. Study drug should be handled in accordance with Good Pharmacy Practices. The Clinical Monitor should be contacted with any questions concerning investigational products where special or protective handling is indicated. At the end of the study, all clinical supplies including partial and empty containers must be returned as directed by Pearl.

Sites should check with the Pearl representative for appropriate documentation that needs to be completed for drug accountability.

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

For each subject, all used study drug materials will be collected and consolidated. Used subject supplies will be kept at room temperature in a secure and locked cabinet until returned to Pearl or designee.

Note: Used study drug will be stored separately from unused study drug.

All product complaints (including device malfunctions) must be reported to Pearl using the Product Complaints Form provided in each site's regulatory binder. Pearl will contact the site to evaluate the nature of the complaint and determine what further action is needed.

7 STUDY PROCEDURES

A time and events schedule is provided in Table 8-1. Detailed schedules for pre- and post-dose procedures to be performed on Day 1 (Visits 2 and 4) and on Day 8 (Visits 3 and 5) of each Treatment Period are provided in Table 8-2 and Table 8-3.

It is recommended that all assessments for Visits 2 through 5 be conducted in the following order: vital signs, ECGs, clinical laboratory assessments, and spirometry.

7.1 Efficacy Assessments

7.1.1 Pulmonary Function Tests (Spirometry)

Forced expiratory spirometry for derivation of FEV_1, FVC and PEFR will be assessed using a spirometer that meets or exceeds minimum performance recommendations of the ATS (Refer to Appendix 1).

The volume accuracy of the spirometer is to be checked daily using a 3 L syringe across 3 flow ranges e.g., at <2 L/sec, 4-6 L/sec and >8 L/sec with temperature and barometric pressure correction. The calibration syringe must meet ATS specifications and must not be used beyond the expiry date. Required accuracy is ± 3%, i.e., 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 (Refer to Appendix 2, Spirometry Assessment Criteria).

All PFTs including FEV_1, FVC, and PEFR as defined in ATS/ERS guidelines will be performed in accordance with ATS criteria [Miller, 2005].

To standardize spirometry, all sites will be provided with identical spirometry systems [redacted] with customized, study-specific software. All study staff responsible for performing pulmonary function testing will receive standardized training at the Investigator meetings. All technicians are required to demonstrate proficiency in the use of the equipment and the ability to perform technically acceptable PFTs [ATS criteria, Miller, 2005] prior to performing testing on study subjects. After each test is performed, the spirometry software will provide immediate feedback to the technician indicating whether the effort meets ATS acceptability and repeatability standards. All efforts will be stored electronically. After completion of testing, the study staff will electronically transmit the spirometric measurements for centralized quality assurance review [redacted]. Feedback on the quality of the measurements will be provided to the investigational site and to Pearl or designee for central data management.

On Day 1 of each treatment period (Visits 2 and 4), spirometry will be conducted 60 minutes and 30 minutes prior to study drug administration. The average of these two assessments will be used to establish test-day baseline FEV_1, FVC and PEFR. Following study drug administration, spirometry will be obtained at 15 minutes, 30 minutes, 1 hour, and 2 hours post-dosing of study drug.

On Day 8 of each treatment period (Visits 3 and 5), spirometry will be conducted 60 minutes and 30 minutes prior to study drug administration. The average of these two assessments will be used to establish Day 8 pre-dose FEV_1, FVC, and PEFR. Following study drug administration, spirometry will be obtained at 15 minutes, 30 minutes, and 1 hour, 2 hours, 4 hours, 8 hours, 10 hours, 11.5 hours, and 12 hours post-dosing of study drug.

7.1.1.1 FEV_1 Baseline Stability Criteria

It is important to ensure that the baseline FEV_1 is stable and reflective of the subject's COPD severity prior to continuation in the second treatment period. As such, the baseline FEV_1 at Visit 4 must be within ±20% or 200 mL of the pre-dose FEV_1 obtained at the Randomization Visit (Visit 2).

At Visit 4, if the pre-dose FEV_1 average is outside of the ±20% or 200 mL range, but the 30-minute pre-dose assessment is within ±22% or 220 mL, then another assessment may be conducted 30 minutes later. If the last two assessments meet the reproducibility requirements (i.e., within ±20% or 200 mL), the initial 60-minute pre-dose assessment will not be used and the last two assessments will be used to establish the eligibility criteria.

If the baseline FEV_1 is not within ±20% or 200 mL, the visit may be rescheduled (for a maximum of three attempts) at the Investigator's discretion (e.g., within 1 week), or the subject may be discontinued.

7.1.1.2 Characterization of Reversibility

Reversibility is defined as ≥12% and ≥200 mL improvement in baseline FEV_1 following administration of four puffs of Ventolin HFA. Reversibility to Ventolin HFA will be evaluated at Screening (Visit 1a/1b) to characterize the subject population.

The procedure is as follows:

- Reversibility testing to Ventolin HFA (Visit 1a/1b Only):
    - Perform pre-bronchodilator pulmonary function tests within 60 minutes prior to administration of Ventolin HFA (albuterol)
    - Administer 4 puffs of Ventolin HFA
    - Perform post-bronchodilator PFT within 30-60 minutes after the administration of Ventolin HFA

7.1.2 Subject Electronic Diary Data Collection

Subjects will be provided with an eDiary to be completed twice daily. Before issuing the eDiary to the subject, site personnel will be responsible for programming the eDiary and training the subject on the eDiary use.

The eDiary data report will be available to site personnel through the vendor's server. The eDiary data report should be reviewed by the study personnel at each visit. The review should verify that morning and evening diary entries have been recorded by the subject for compliance requirements. The subject should be reinstructed at each Visit, as appropriate, on the importance of recording twice daily entries if missing entries are observed.

At Visit 1a (Screening), subjects will be issued an eDiary and trained on how to use it. Subjects will be instructed to collect practice data during the Screening Period (from Visit 1a to Visit 2). eDiary compliance will be assessed at Visit 2. Subjects who are unable to meet the compliance requirement (>70% subject completion of eDiary assessments) in the last 7 days preceding the Randomization Visit (Visit 2) will be considered screen failures.

For the duration of the study, subjects will be expected to complete the eDiary twice daily by recording time of study medication administration, morning and evening symptoms, and the use of rescue medication, albuterol (Ventolin HFA). The dose indicator reading will also be recorded twice daily from Visit 2 to Visit 5 and once daily thereafter. In-clinic dosing times and dose indicator readings will be documented in the eCRF by the site staff and will not be entered by the subject in their eDiary.

As defined for this study, eDiary compliance requires >70% subject completion of eDiary assessments. Subject participation may be terminated at any time during the study for chronic failure, in the judgment of the Investigator, to comply with eDiary compliance, despite documentation at the site of repeated efforts to train the subject and reinforce compliance. The Sponsor may also instruct a site to discontinue a subject based on consistent noncompliance.

7.1.3 Rescue Ventolin HFA Use

The subject will record the total number of “puffs” of rescue Ventolin HFA used on a daily basis in the eDiary. The number of “puffs” of rescue Ventolin HFA to be recorded is the number of actuations of the canister. For example, when rescue Ventolin HFA is required and two actuations are inhaled, this should be recorded as two “puffs.” In the event the subject requires 4 actuations, this should be recorded as 4 “puffs.” Subjects requiring more than 8 puffs per day on 3 or more consecutive days with worsening symptoms should contact the site.

7.1.4 Medication Compliance

Time of dosing with study drug will be recorded in the subject's eDiary for each day of treatment (except the in-clinic dosing time). Study drug compliance will be checked at all visits, and any issues identified will be noted in the appropriate study files.

7.2 Safety Assessments

The safety assessments include AEs, SAEs, vital sign measurements, ECGs, and clinical laboratory testing.

7.2.1 Medical/Surgical History and Physical Examination

Medical history will be taken at Screening (Visits 1a) and updated at the Randomization Visit (Visit 2). History of COPD exacerbation within 12 months of Screening will also be collected. A complete physical examination will be performed at the Screening (Visit 1a) and the Final Visit (Visit 5, Day 8 of Treatment Period 2). A complete physical examination will include the following: general appearance, skin, head, eyes, ears, nose, throat, neck (including thyroid), lymph nodes, chest, heart, abdomen, extremities, and nervous system. Weight, assessed in ordinary indoor clothing with shoes removed will be recorded at the Screening (Visit 1a) and at the Final Visit (Visit 5). Height will be recorded at the Screening (Visit 1a) only.

7.2.2 Vital Sign Measurements

Vital signs (HR, SBP, and diastolic blood pressure [DBP]) will be assessed at each visit prior to and after dosing. Assessments conducted at -30 minutes prior to study drug administration, and at 30 minutes post-dose will be obtained after the subject has been in the supine position for 5 minutes. Thereafter, measurements may be obtained with the subject in the supine or seated position. If, in the opinion of the Investigator, a clinically significant vital sign change occurs, then the measurement will be repeated at medically appropriate intervals until the value returns to within an acceptable range. Temperature will be collected at Screening (Visit 1a) and at pre-dose at all visits and will not be repeated post-dose at subsequent time points unless clinically indicated.

Refer to Section 5.7 for specific criteria for HR and SBP/DBP readings that will issue cause for the investigator to discontinue the subject from the study.

Obtain heart rate and SBP/DBP, as directed above:

- **At Screening (Visits 1a):**
- Baseline measures will be obtained
- **At Day 1 of each Treatment Period (Visits 2, and 4):**
- 30 minutes *prior* to study drug administration and 30 minutes, and 2 hours *after* study drug administration

- **At Day 8 of each Treatment Period (Visits 3 and 5):**
- 30 minutes *prior* to study drug administration; 30 minutes, and 2, 4, 8, 10, 11.5, and 12 hours *after* study drug administration

7.2.3 12-Lead Electrocardiogram

- **At Visit 1a (Screening) or Discontinuation Visit**: A single ECG will be obtained
- **At Visit 2 (Randomization):** Each subject will undergo a 12-lead ECG obtained at -30 minutes *prior* to study drug administration; 30 minutes and 2 hours *after* study drug administration. Note: Two pre-dose ECG will be obtained at least 5 minutes apart at Randomization (Visit 2) only.
- **At Visits 3 and 5 (Day 8 of each Treatment Period):** Each subject will undergo a 12-lead ECG at -30 minutes *prior* to study drug administration; 30 minutes and 2 hours *after* study drug administration.

Note: ECG will not be performed at Visit 4 (Day 1 Treatment Period 2)

Note: Baseline ECG values are defined as the last value obtained *prior* to dosing at Randomization (Visit 2).

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

The ECG parameter that will be assessed include heart rate, PR interval, QRS axis, QRS interval, QT/QTcF interval.

QT intervals and calculated QTcF intervals will be reviewed and checked for gross inaccuracies by the Investigator or designated ECG reviewer. If the calculated QTcF intervals are >500 msec, and have increased by ≥60 msec over the baseline value obtained just prior to Randomization (Visit 2), the Investigator will determine the suitability of continuing the subject in the study. Refer to Section 5.7 for specific QTcF criteria that warrant discontinuation from the study. If QTcF interval prolongation exceeding these limits is verified during treatment, the subject's medical background should be examined closely for risk factors that may have contributed to the event, including genotyping for hereditary long QT syndromes, if appropriate.

Any sign of arrhythmia should be noted. During treatment, any indication of Torsade de Pointes, a polymorphic ventricular tachyarrhythmia that appears on the ECG as continuous

twisting of the vector of the QRS complex around the isoelectric baseline, must be recorded as an AE and reported to the Pearl Medical Monitor.

All such subjects, including subjects with cardiac arrhythmias, should be monitored closely. If appropriate, ECG monitoring should be performed until the QT and QTcF interval and waveform morphology have returned to normal. If the prolongation or abnormal rhythm persists, the Pearl Medical Monitor must be contacted immediately.

7.2.4 Clinical Laboratory Tests

Clinical safety laboratory tests will be analyzed by designated central laboratories according to standardized, validated assays. The laboratory will supply detailed instructions and all containers for blood and urine investigations.

7.2.4.1 Hematology

Hemoglobin, hematocrit, red blood cell count, white blood cell count with differential, and platelet count will be measured at Visit 1a (Screening) Visit 2 (Treatment Period 1, Day 1)and Visit 5 (Treatment Period 2, Day 8) within 60 minutes prior to dosing.

7.2.4.2 Clinical Chemistry

Comprehensive Metabolic Panel will be obtained at Visit 1a (Screening) and prior to dosing at Visit 4 (Day 1) and Visit 5 (Day 8) of each Treatment Period and the Treatment Discontinuation/Withdrawal Visit.

A Basic Metabolic Panel (BMP) will be obtained within 60 minutes prior to dosing at Visit 3 and Visit 2. A BMP will be obtained at 30 minutes and 2 hours post dose at Visits 2-5.

Refer to Table 7-1 below for a list of study-associated laboratory tests. The central laboratory will supply procedures for the preparation and collection of these samples.

Table 7-1. Clinical Laboratory Tests

Hematology	
Hemoglobin	Mean corpuscular hemoglobin
Hematocrit	Mean corpuscular hemoglobin concentration
White blood cell count with differential	Mean corpuscular volume
Red blood cell count	Eosinophils
Platelet count	
Clinical Blood Chemistry	
Liver Enzyme and Other Liver Function Tests	**Other Clinical Blood Chemistry**
Alanine aminotransferase	Albumin
	Blood urea nitrogen[a]
Aspartate aminotransferase	Calcium[a]
Alkaline phosphatase	Chloride[a]
Bilirubin, total	Cholesterol
Gamma-glutamyl transferase	Bicarbonate
	Creatinine[a]
	Glucose[a]
	Magnesium
	Potassium[a]
	Phosphate
	Protein, total
	Sodium[a]
	Triglycerides

Other Tests

Pregnancy test (women of childbearing potential only): Serum hCG at Screening and the Final/Premature Discontinuation.

Creatinine clearance will be estimated by the CKD-EPI published formula.

Abbreviations: CKD-EPI=Chronic Kidney Disease Epidemiology Collaboration Equation (according to National Kidney Disease Education Program); hCG=human chorionic gonadotropin

[a] Parameters included in the Basic Metabolic Panel.

[b] Parameters included in the Comprehensive Metabolic Panel.

7.2.4.3 Pregnancy Test

In women of childbearing potential, serum pregnancy testing will be performed at Screening (Visit 1a) and at the Final Visit (Visit 5, Day 8 of Treatment Period 2).

7.3 Pharmacokinetic Assessments

Pharmacokinetic sampling will occur on Day 8 of each Treatment Period (Visits 3 and 5). Approximately 5 mL of whole blood will be collected at 30 minutes prior to dosing and then at 2, 6, 20, and 40 minutes post-dose and 1, 2, 4, 8, 10, and 12 hours post-dose. Sample collection instructions will be provided in the laboratory manual.

7.4 Procedure for Shipping Blood Samples

Samples are to be shipped frozen by overnight courier to the bioanalytical laboratory [redacted] for analysis. Plasma levels of glycopyrronium and formoterol will be determined using validated High Performance Liquid Chromatography tandem Mass Spectrometry methodology. Instructions for sample handling, storage, and shipping will be provided in the [redacted] laboratory manual.

7.5 Adverse Event

7.5.1 Performing Adverse Event Assessments

The Investigator is responsible for promptly documenting and reporting all AEs observed during the study in the subject's case report form and on the AE Reporting Form. If the AE is "alarming," the Investigator must report the AE immediately to Pearl. In addition, certain AEs (as described in Section 7.5.9**)** are classified as "serious" and must be reported no later than 24 hours after the Investigator recognizes/classifies the event as an SAE to Pearl or its designee.

In the case of SAEs, after discussing the details of the AE, the Investigator and the Medical Monitor may discontinue the subject prematurely.

7.5.2 Adverse Event Definitions

The following definitions of terms are guided by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), the US Code of Federal Regulations (21 CFR 312.32) and EU 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 (e.g., 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 (e.g., off-label use, use in combination with another drug) and from any route of administration, formulation, or dose, including an overdose.

Adverse events include, but are not limited to:

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

An AE does **not** include:

- Medical or surgical procedures (e.g., surgery, endoscopy, tooth extraction, blood transfusion); the condition that leads to the procedure are an AE (e.g., bleeding esophageal varices, dental caries)
- Overdose of either study drug or concurrent medication without any clinical signs or symptoms
- Non-clinically significant abnormal laboratory values. (If accompanied by signs/symptoms, the signs or symptoms are considered an AE.)

7.5.3 Pre-Randomization Adverse Events

Adverse events that occur between the time subject signs the ICF for the study and the time when that subject is randomized will be summarized as medical history and not as a treatment-emergent adverse event unless the event meets the definition of an SAE as defined in Section 7.5.9.

7.5.4 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 life threatening; resulting in significant disability or incapacity; and requiring therapeutic intervention.

7.5.5 Relationship

The relationship of each AE to the study drug administration will be assessed by the Investigator after careful consideration, and according to the following guidelines:

Definitely: A reaction that follows a reasonable temporal sequence from administration of study drug; that follows a known or expected response pattern to the study drug; it disappears or decreases on cessation or reduction in study drug dose; and/or it reappears or worsens when the study drug is administered.

Probably: A reaction that follows a reasonable temporal sequence from administration of study drug; that follows a known or expected response pattern to the study drug; and/or that could not be reasonably explained by other factors such as underlying disease, complications, concomitant drugs, or concurrent treatments.

Possibly: A reaction that follows a reasonable temporal sequence from administration of study drug; that follows a known or expected response pattern to the study drug, but that could reasonably have been produced by a number of other factors including underlying disease, complications, concomitant drugs, or concurrent treatments.

Not Related: A reaction for which sufficient data exist to indicate that the etiology is unrelated to the study drug.

7.5.6 Chronic Obstructive Pulmonary Disease Exacerbations

All moderate or severe COPD exacerbations must be captured using the COPD Exacerbation eCRF. Mild COPD exacerbations will be captured based on symptoms as recorded by the subject in the eDiary. COPD exacerbations of any severity will be considered expected study endpoints and will not be reported as adverse events (AEs) unless considered a serious AE (SAE).

Exacerbation(s) of COPD is expected to occur as a progression of disease despite standardized drug treatment, or treatment(s) with combination therapies. As a result, the Sponsor has classified this event as a protocol specified criteria expected event. Any individual case safety reports received related to exacerbation of COPD will not be submitted on an expedited basis as a Suspected Unexpected Serious Adverse Reaction (SUSAR) unless otherwise required as per the Sponsor's medical assessment.

7.5.7 Adverse Events of Special Interest

Paradoxical bronchospasm may occur following inhalation from an MDI.

Monitoring for paradoxical bronchospasm will occur at each visit during the Treatment Period (Visits 2 through 5) at 15 and 30 minutes post-dose. In this study, paradoxical bronchospasm is defined as a reduction in FEV_1 of >20% from test day baseline (i.e.., the mean FEV_1 values obtained 60 and 30 minutes prior to study drug administration) with

associated symptoms of wheezing, shortness of breath, or cough. All AEs and SAEs will be recorded, as appropriate.

7.5.8 Clinical Laboratory Adverse Events

Many laboratory abnormalities observed during the course of a study will be included under a reported AE describing a clinical syndrome (e.g., 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). However, when an isolated laboratory abnormality is considered clinically significant by the Investigator, it must be reported as an AE.

Criteria for a "clinically significant" laboratory abnormality are:

- A laboratory abnormality that leads to dose-limiting toxicity (e.g., an abnormality that results in study drug dose reduction, suspension, or discontinuation).
- A laboratory abnormality that results in any therapeutic intervention (i.e., concomitant medication or therapy).
- Any other laboratory abnormality judged by the Investigator to be of any particular clinical concern (e.g., significant fall in hemoglobin not requiring transfusion).

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

7.5.9 Serious Adverse Events

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 an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Hospitalization for a pre-existing condition, including 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 patient or subject at immediate risk of death. It does not include an adverse reaction or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

An AE or suspected adverse reaction is considered unexpected if it is not listed in the current Investigator Brochure (IB) or is not listed at the specificity or severity that has been observed.

7.5.9.1 Reporting of Serious Adverse Events

In agreeing to the provisions of this protocol, the Investigator accepts all legal responsibilities for AE identification, documentation, grading, assignment of causality, and prompt notification of SAEs to the Pearl Pharmacovigilance or designee. All SAEs must be reported to Pearl no later than 24 hours after the Investigator recognizes/classifies the event as an SAE. 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 two working days after he/she receives that information. This follow-up information will be a detailed written report that will include copies of hospital records, case reports, and autopsy reports, and other pertinent documents, if deemed necessary.

Post-study SAEs following the last dose of study drug must be reported to Pearl Pharmacovigilance as described in Section 7.5.9.4.

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

7.5.9.2 Supplemental Investigation of SAEs

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

7.5.9.3 Post-Study Follow Up of Adverse Events

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.

7.5.9.4 Notification of Post-Study Serious Adverse Events

Investigators are not obligated to actively follow subjects after the completion of the study. However, if the Investigator becomes aware of a post-study SAE occurring up to 14 days following the last dose of study drug, it must be reported to Pearl, whether or not the event is attributable to study drug. All SAEs must be reported to Pearl no later than 24 hours after the Investigator recognizes/classifies the event as an SAE.

7.5.9.5 Investigational Research Board/Independent Ethics Committee Notification of Serious Adverse Events

The Investigator is responsible for promptly notifying her/his Institutional Review Board (IRB)/Independent Ethics Committee (IEC) of all SAEs, including any follow-up information, occurring at her/his site and any SAE regulatory report, including any follow-up reports that she/he receives from Pearl. Documentation of the submission to the IRB/IEC must be retained for each safety report. The Investigator is also responsible for notifying Pearl if their IRB/IEC requires revisions to the ICF or other measures based on its review of an SAE report.

7.5.9.6 Health Authority Safety Reports

Pearl or its representatives will submit a safety report to the Food and Drug Administration (FDA) and/or any other appropriate regulatory agencies, for any suspected adverse reaction that is both serious and unexpected within the appropriate time frame.

Pearl or its representatives will send copies of each safety report submitted to the FDA and/or other regulatory agencies to the Investigators who are actively participating in Pearl-sponsored clinical studies. Safety reports must be submitted to the appropriate IRB/IEC as soon as possible. Documentation of the submission to the IRB/IEC must be retained for each safety report.

7.5.10 Overdose

An overdose is defined as a dose greater than the highest dose level evaluated in this study as described in Section 6.2 (Product Descriptions), which results in clinical signs and symptoms. In the event of an overdose of study drug, the Investigator should use clinical judgment in treating the overdose and contact the study Medical Monitor. The Investigator should refer to the relevant document(s) for detailed information regarding warnings, precautions, contraindications, AEs, and other significant data pertaining to the study drugs being used in this study. Such documentation may include, but not be limited to the IBs for GFF MDI and the approved product labeling for Spiriva, Ventolin HFA, and Atrovent HFA.

7.5.11 Pregnancy

To ensure subject safety, each pregnancy in a female subject from Visit 1 (Screening) until study completion must be reported to Pearl within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine 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 Clinical Trial Pregnancy Form and reported by the Investigator to Pearl Pharmacovigilance or designee. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the Pearl study drug of any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

7.6 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 Pearl.

Pearl 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 Pearl, in a timeframe that is compatible with the subjects' wellbeing.

8 STUDY ACTIVITIES

A schedule of events is provided in Table 8-1. Detailed schedules for pre- and post-dose procedures to be performed on Day 1 (Visits 2 and 4) and on Day 8 (Visits 3 and 5) are provided in Table 8-2 and Table 8-3, respectively.

Table 8-1. Schedule of Events

Procedures	Screening Period		Treatment Period				Telephone Follow-up	Premature Discontinuation Visit
			Treatment 1		Treatment 2			
	Visit 1a	Visit 1b	Visit 2	Visit 3	Visit 4	Visit 5		
Study Day[a]	**Up to-28 Days**		**Day 1**	**Day 8 ±2Days[a]**	**Day 1[a]**	**Day 8 ±2Days[a]**	**7-14 Days**	
Obtain Informed Consent	X							
Review Inclusion/Exclusion Criteria	X		X					
Verify Continued Eligibility				X	X	X		
Reversibility	X	X						
Demographics and Medical/Surgical History	X							
Smoking Status	X	X	X	X	X	X		
Prior/Concomitant Medications[b]	X	X	X	X	X	X	X	X
Spirometry[c]	X	X	X		X			
12-hour spirometry[c]				X		X		
Physical Examination[d]	X					X		X
Vital Signs[e]	X		X	X	X	X		X
12-Lead ECG[f]	X		X	X		X		X
Pregnancy Test[g]	X					X		X
Clinical Laboratory Testing[g]	X		X	X	X	X		X
PK Sampling[h]				X		X		
Chest X-ray[i]	X							
Adjust COPD Medications[j]	X					X		
COPD Exacerbations and Adverse Events	X	X	X	X	X	X	X	X
Inhalation Device Training[k]	X							
Study Drug Dispensing/Collection[l]	X[k]		X	X	X	X		X
Study Drug Administration[m]			X	X	X	X		
eDiary Training[n]	X							
Review of Electronic Diary[o]		X	X	X	X	X		
Telephone Reminder[p]		X	X	X	X	X		
Telephone Contact							X	

Abbreviations: COPD=chronic obstructive pulmonary disease; ECG=electrocardiogram; HFA= hydrofluoroalkane; PK=pharmacokinetic

Note: Where data collection time points are concurrent, variables are recommended to be performed in the following order in the following order: vital signs, ECG, clinical laboratory assessments, and spirometry.

a. **Scheduling visits:** The maximum Screening Period is 28 days. The earliest a subject can be randomized from the Visit 1 date (Visits 1a and 1b) is 7 days (7 days for LABA washout) or 14 days if the subject is washing out from tiotropium. The site should make every effort to maintain subjects within the scheduled visit window. Subjects who fall outside the visit window will be placed in the appropriate visit window at the next scheduled visit.

b. At all visits beyond Visit 1 (Screening), note the time of last dose of COPD medications, including rescue medication and ICS (if <6 hours, visit should be rescheduled).

c. Refer to Section 7 for the spirometry assessments and specific time points to be performed at each treatment visit. Twelve-hour spirometry will be performed on Day 8 of each Treatment Period (Visits 3 and 5).

d. Includes evaluation of height and weight at Visit 1a (Screening) only. Weight only will be assessed at Visit 5.

e. Refer to Section 7 for vital sign assessments and specific time points to be performed at each treatment visit.

f. An ECG will be obtained at Visits 1a, 2, 3 and 5. Refer to Section 7 for ECG assessments and specific time points to be performed at each treatment visit

g. Refer to Section 7 for clinical laboratory assessments (hematology refer to Section 7.2.4.1, chemistry refer to Section 7.2.4.2) and specific time points to be performed at each treatment visit. A serum pregnancy test will be obtained at Screening (Visit 1a) and at Day 8 of Treatment Period 2 (Visit 5).

h. Pharmacokinetic sampling will be performed on Day 8 of each Treatment Period. Refer to Section 7 for further information on PK collection time points.

i. Obtain a new chest x-ray if the chest x-ray or CT scan performed within the 6 months prior to Visit 1 (Screening) is not available.

j. At Visit 1 (Screening), stop prohibited COPD medications and change COPD medications as specified in the protocol (.i.e., Sponsor-provided Atrovent HFA with or without ICS). At the end of Visit 5, return subject to pre-study or other appropriate inhaled maintenance COPD medications.

k. Sites may use Sponsor-provided Atrovent HFA or Ventolin HFA to train subjects on the use of MDIs. Subjects will also be trained on the use of the Aerochamber valved holding chamber. Please refer to Section 7 for further information.

l. Sponsor-provided Atrovent HFA or Ventolin HFA is dispensed only after a subject is determined to be eligible to proceed to Visit 2 (Day 1) (i.e., only if a subject meets the definition of COPD following spirometry assessments at Screening).

m. In-clinic dosing time is recorded as time of the second puff/inhalation. The in-clinic dosing time should be timed to be within 12±2 hours of the prior evening dosing time.

n. Refer to Section 7.1.2 for details of electronic diary review. The in-clinic dosing time should be timed to be within 12±2 hours of the prior evening dosing time.

o. Issue and train subjects on eDiary use only after a subject is determined to qualify to proceed to Visit 2

p. It is recommended that sites call the subject on the day before a scheduled visit and remind the subject of the expectations for the upcoming visit (eg., dosing appropriately the day before the visit, withholding COPD medications the morning of the scheduled visit, bringing all study drug to the visit, etc.).

Table 8-2. Visit Procedures on Day 1 of Each Treatment Period (Visits 2 and 4)

	Pre-dosing		Post-dosing			
Clinical Variable[a]	**-60 mins**	**-30 mins**	**15 min**	**30 min**	**1 hr**	**2 hr**
Review of Electronic Diary Data	**X**[b]					
Vital Signs[c]		**X**		**X**		**X**
12- Lead ECG[d]		**X**		**X**		**X**
Clinical Laboratory Testing[e]	**X**			**X**		**X**[e]
Spirometry (FEV_1, FVC, PEFR)[f]	**X**	**X**	**X**	**X**	**X**	**X**
Study Drug Collection[g]	**X**					
Study Drug Dispensing[h]						**X**

Abbreviations: ECG=electrocardiogram; FEV_1=forced expiratory volume in 1 second; FVC=forced vital capacity; PEFR=peak expiratory flow rate

Note: Sites should plan to perform these activities so as not to interfere with collection of timed assessments such as spirometry. Where data collection time-points are concurrent, variables are recommended to be collected in the following order: vital signs, ECG, clinical laboratory assessments, and spirometry.

a. In-clinic dosing time is recorded as time of the second puff. Safety assessments (vital signs and ECG) should be started approximately 5 to 10 minutes ahead of the specified time point to ensure that spirometry for FEV_1, FVC, and PEFR assessments will be conducted as close to the specified time points as possible (i.e., FEV_1, FVC, and PEFR assessments need to be conducted within ±15 minutes of specified time points prior to study drug administration; ±5 minutes of specified time points for the first 60 minutes post study drug administration; ±15 minutes of specified time point for assessments obtained thereafter).

b. This is not a timed assessment. Sites should plan to perform these activities so as not to interfere with collection of timed assessments such as spirometry.

c. Refer to Section 7 for vital signs assessments and specific time points to be performed at each treatment visit.

d. ECG on Day 1 occurs at Randomization Visit only (Not at Visit 4). Refer to Section 7 for ECG assessments and specific time points to be performed at each treatment visit. Two pre-dose ECG will be obtained 5 minutes apart at Randomization (Visit 2) only.

e. Refer to Section 7 for clinical laboratory assessments (hematology refer to Section 7.2.4.1, chemistry refer to Section 7.2.4.2) and specific time points to be performed at each treatment visit.

f. Spirometry will be collected at -60 and -30 minutes prior to dosing. Post-dose spirometry assessments on Day 1 (Visits 2 and 4) will be obtained at 15 and 30 minutes, and at 1 and 2 hours post-dosing.

g. At the start of each treatment visit, subject must withhold all COPD medications, including study drug, rescue medication, and ICS for at least 6 hours prior to start of test day procedures..

h. Dispense study drug to subject following completion of all post-dose assessments. See Appendix 3 for Instructions for Preparation of Treatments for Administration and Dispensing.

Table 8-3. Visit Procedures on Day 8 of Each Treatment Period (Visits 3 and 5)

Clinical Variable[a]	Pre-dosing		Post-dosing													
	-60 min	-30 min	2 min	4 min	6 min	15 min	20 min	30 min	40 min	1 hr	2 hr	4 hr	8 hr	10 hr	11.5 hr	12hr
Review of Electronic Diary Data	X[b]															
Vital Signs[c]		X						X			X	X	X	X	X	X
12- Lead ECG[d]		X						X			X					
Clinical Laboratory Testing[e]	X[e]							X			X					
PK Sampling		X	X		X		X		X	X	X	X	X	X		X
12-hour Spirometry (FEV_1, FVC, PEFR)[f]	X	X				X		X		X	X	X	X	X	X	X
Study Drug Collection[g]	X															
Study Drug Dispensing[h]																X

Abbreviations: ECG=electrocardiogram: FEV_1=forced expiratory volume in 1 second; FVC=forced vital capacity; PEFR=peak expiratory flow rate; PK=Pharmacokinetic

Note: Sites should plan to perform these activities so as not to interfere with collection of timed assessments such as spirometry. Where data collection time-points are concurrent, it is recommended variables are collected in the following order: vital signs, ECG, clinical laboratory assessments, and spirometry.

a. In-clinic dosing time is recorded as time of the second puff. Safety assessments (vital signs and ECG) should be started approximately 5 to 10 minutes ahead of the specified time point to ensure that spirometry for FEV_1, FVC, and PEFR assessments will be conducted as close to the specified time points as possible (i.e., FEV_1, FVC, and PEFR assessments need to be conducted within ±15 minutes of specified time points prior to study drug administration; ±5 minutes of specified time points for the first 60 minutes post study drug administration; ±15 minutes of specified time point for assessments obtained thereafter).

b. This is not a timed assessment. Sites should plan to perform these activities so as not to interfere with collection of timed assessments such as spirometry.

c. Refer to Section 7 for vital signs assessments and specific time points to be performed at each treatment visit.

d. Refer to Section 7 for ECG assessments and specific time points to be performed at each treatment visit.

e. Refer to Section 7 for clinical laboratory assessments (hematology refer to Section 7.2.4.1, chemistry refer to Section 7.2.4.2) and specific time points to be performed at each treatment visit. A serum pregnancy test will be obtained at Screening (Visit 1) and at Day 8 of Treatment Period 2 (Visit 5).

f. Spirometry will be collected at -60 and -30 minutes prior to dosing. Post-dose spirometry assessments will be obtained on Day 8 (Visits 3 and 5) at 15 and 30 minutes, and 1, 2, 4, 8, 10, 11.5, and 12 hours post-dosing.

g. At the start of each treatment visit, subject must withhold all COPD medications, including study drug, rescue medication, and ICS for at least 6 hours prior to start of test day procedures. Study drug will be collected at Day 29 of each Treatment Period (Visits 3, 5, and 7).

h. Dispense study drug to subject following completion of all post-dose assessments.

8.1 Screening Visit 1a (Up to Day -28)

- Prior to any study related procedures, obtain informed consent; prior to *or* at Screening.
- Register subject in IWRS to obtain subject screening number.
- Obtain demographic data, including age, race, smoking history, medical/surgical history (including cardiovascular risk factors and history), including glaucoma, and age at onset of COPD.
- Obtain history of COPD exacerbation within 12 months of the Screening Visit.
- Check inclusion/exclusion criteria.
- Obtain medication history, including COPD medications.
- Conduct a serum pregnancy test for all female subjects unless it is documented in the medical history that the subject has been irreversibly surgically sterilized (hysterectomy, oophorectomy, or bilateral tubal ligation) or they are at least 2 years post-menopausal.
- Conduct a complete physical examination (general appearance, skin, head, eyes, ears, nose, throat, neck [including thyroid], lymph nodes, chest, heart, abdomen, extremities, and nervous system).
- Obtain height, weight, and vital signs (HR and SBP/DBP after being supine for 5 minutes, and oral or tympanic temperature).
- Obtain a 12-lead ECG (refer to Section 7.2.3)
- Conduct baseline spirometry assessments (FEV_1, FVC, and PEFR) (Refer to Section 7.1.1).
- Conduct inhalation device training.
- Administer four puffs of Ventolin HFA. **Note:** The administration of Ventolin HFA for reversibility characterization should be within 60 minutes of pre-bronchodilator spirometry:
  - Confirm subject's ability to use MDI correctly (provide coaching as needed).
  - Repeat spirometry assessments within 30-60 minutes following four puffs Ventolin HFA (to characterize the subject population only; not to be used to determine eligibility to participate in the study).
- Obtain laboratory samples (hematology and chemistry).
- Complete chest x-ray or CT scan if not performed within the last 6 months.
- Stop prohibited COPD medications and change concurrent COPD medications as specified in protocol (see Section 5.4).

- Adverse events must be recorded during the Screening Period, i.e., from the time of consent to the start of study treatment. Adverse events that occur between the time the subject signs the ICF for the study and the time when that subject is randomized will be summarized as medical history and not as a study AE unless the event meets the definition of an SAE (see Section 7.5.9).
- Dispense and train subject on eDiary use.
- Arrange date of Visit 1b or Visit 2 as appropriate.

8.2 Screening Visit 1b (Up to Day -21)

- At the Investigator's discretion, subjects who do not meet spirometry entry criteria at Screening (Visit 1a) may return to repeat spirometry at a second Screening Visit (Visit 1b).

  Note: Visit 1b is to be used only for repeat spirometry entry criteria; all other repeat assessments, if needed, will be captured as an unscheduled visit.

8.3 Randomization Visit (Visit 2; Day 1 of Treatment Period 1)

- Review subject eDiary entries and retrain subject if subject has not met eDiary compliance requirement of >70% subject completion of eDiary assessments in the last 7 days preceding Visit 3.
- Review inclusion/exclusion criteria to confirm subject eligibility.
- Review concomitant medications to ensure adherence to COPD regimen.
- Note time of last dose of short-acting bronchodilator and other COPD medications on the eCRF (if <6 hours, Visit 2 must be rescheduled).
- Review of clinical laboratory results from Visit 1. Please note whether the results are clinically significant and include comments where applicable.
- Record COPD exacerbations and AEs, if any.
- Perform all pre-dose assessments (see Table 8-1).
  - Obtain vital signs
  - Obtain two 12-lead ECGs at least 5 minutes apart within 30 minutes prior to dosing.
  - Obtain clinical laboratory samples.
  - Perform spirometry assessments (FEV_1, FVC, and PEFR) (Refer to Section 7.1.1). Spirometry to be conducted 60 and 30 minutes pre-dose.
  - Obtain subject randomization number and treatment assignment (with/without Aerochamber Plus VHC information from IWRS.

- Allow proper time prior to dosing to remove the seal around the study day treatment box is to be opened and the instructions for administration of study drug on the inner flap of the study day treatment box are to be followed.
- Refer to Section 6.6 for detailed instructions for preparation of treatments for administration. These instructions are to be adhered to and are relevant to all study treatment visits.
- The subject is to be considered randomized after receiving a randomization number from the IWRS.

- Subject will administer first dose of newly assigned study drug at the clinic, with or without the Aerochamber Plus VHC as appropriate.
- Perform all post-dose assessments (see Table 8-1).
- Schedule Visit 3 and ensure that the subject has an adequate supply of study drug and rescue Ventolin HFA.

8.4 Visit 3 (Day 8 of Treatment Period 1)

- Confirm subject's eligibility to continue.
- Review subject eDiary entries and retrain subject if subject has not met eDiary compliance requirement of >70% subject completion of eDiary assessments in the last 7 days preceding Visit 4.
- Review smoking status and concomitant medications and ensure adherence to COPD regimen.
- Note time of last dose of short-acting bronchodilator and other COPD medications on the source (if <6 hours, reschedule visit).Collect previously dispensed study medication.
- Record COPD exacerbations and AEs, if any.
- Perform all pre-dose assessments (see Table 8-2).
  - Obtain vital signs and 12-lead ECG at 30 minutes prior to dosing.
  - Obtain pharmacokinetic sampling. Refer to Section 7.2.5.
  - Perform spirometry assessments (FEV_1, FVC, and PEFR) (Refer to Section 7.1.1). Spirometry to be conducted 60 and 30 minutes pre-dose.
  - Record dose indicator reading (refer to Appendix 7).
  - Refer to Section 6.6 for detailed instructions for preparation of treatments for administration.
- Administer in-clinic study drug with or without Aerochamber as assigned at the start of the treatment period by IWRS.

- Perform all post-dose assessments (see Table 8-3).
- Collect study drug.
- At the conclusions of Visit 3, schedule Visit 4 (to follow a Washout Period of at least 7 days but no longer than 14 days duration) and ensure subject has adequate supply of COPD medication, including Atrovent HFA and Ventolin HFA. Additional Atrovent HFA and Ventolin HFA may be requested using the IWRS.

8.5 Visit 4 (Day 1 of Treatment Period 2)

- Confirm subject's eligibility to continue.
- Review subject eDiary entries and retrain subject if subject has not met eDiary compliance requirement of >70% subject completion of eDiary assessments in the last 7 days preceding Visit 5.
- Review of clinical laboratory results from previous visit. Please note whether the results are clinically significant and include comments where applicable.
- Review smoking status and concomitant medications to ensure adherence to COPD regimen.
- Note time of last dose of short-acting bronchodilator and other COPD medications on source (if <6 hours, visit must be rescheduled).
- Record COPD exacerbations and AEs, if any.
- Confirm FEV_1 baseline stability criteria (see Section 7.1.1).
- Perform all pre-dose assessments (see Table 8-2).
    - Obtain vital signs 30 minutes prior to dosing.
    - Perform spirometry assessments (FEV_1, FVC, and PEFR) (Refer to Section 7.1.1.). Spirometry to be conducted 60 and 30 minutes pre-dose.
    - Obtain subject treatment assignment (with/without Aerochamber Plus VHC information from IWRS.
    - At 15 to 30 minutes prior to dosing, the seal around the study day treatment box is to be opened and the instructions for administration of study drug on the inner flap of the study day treatment box are to be followed.
    - Refer to Section 6.6 for detailed instructions for preparation of treatments for administration. These instructions are to be adhered to and are relevant to all study treatment visits.
- Subject will administer first dose of newly assigned study drug at the clinic.
- Record dose indicator reading (refer to Appendix 7).

- Perform all post-dose assessments (see Table 8-2).
- Schedule the next visit and ensure that the subject has an adequate supply of study drug and rescue Ventolin HFA.

8.6 Visit 5 (Day 8 of Treatment Period 2)

- Review subject eDiary entries and retrain eDiary.
- Review dose indicator reading.
- Review smoking status and concomitant medications and ensure adherence to COPD regimen.
- Note time of last dose of short-acting bronchodilator and other COPD medications on the source (if <6 hours, reschedule visit).
- Confirm eligibility to continue.
- Collect previously dispensed study medication.
- Record COPD exacerbations and AEs, if any.
- Perform all pre-dose assessments (see Table 8-2)
    - Obtain vital signs and 12-lead ECG at 30 minutes prior to dosing.
    - Perform spirometry assessments (FEV_1, FVC, and PEFR). (Refer to Section 7.1.1). Spirometry to be conducted 60 and 30 minutes pre-dose.
    - Perform serum pregnancy test.
    - Obtain pharmacokinetic sampling. Refer to Section 7.2.5.
    - Perform clinical laboratory testing (refer to Section 7.2.4). Please note that when lab results are clinically significant; report the value as an AE.
    - Conduct a complete physical examination (general appearance, skin, head, eyes, ears, nose, throat, neck [including thyroid], lymph nodes, chest, heart, abdomen, extremities, and nervous system).
    - Refer to Section 6.6 for detailed instructions for preparation of treatments for administration.
- Record dose indicator reading (refer to Appendix 7).
- Administer in-clinic study drug with or without Aerochamber as assigned at the start of the treatment period by IWRS.
- Perform all post-dose assessments (see Table 8-1).
- Collect study drug.

- Return subject to pre-study or appropriate maintenance COPD medications.
- Schedule telephone Follow-up within 7-14 days.

8.7 Unscheduled Visits/Premature Discontinuation

Visit 1b is to be used only for repeat spirometry entry criteria, all other repeat assessments, if needed, will be captured as an unscheduled visit.

Premature discontinuations visits will be captured as unscheduled visits. The following minimum procedures should be completed at the premature discontinuation visit:

- Record adverse events (if any).
- Review concomitant medications
- Conduct a physical examination, including vital signs.
- Perform ECG and collect blood samples for hematology and chemistry.
- Collect a blood sample for pregnancy test for women of childbearing potential.
- Collect all study drugs.
- Inform subject about reporting all SAEs up to 14 days following the last dose of study drug.
- Return subject to pre-study or appropriate maintenance COPD medications.
- Capture the subject discontinuation reason.
- Schedule a follow-up telephone call 7-14 days post last study drug dosing. If the discontinuation visit is performed > 7 days post last study drug dosing a follow-up telephone call will not be required.

8.8 Follow-Up Telephone Call

Subjects will be followed-up through a telephone call 7-14 days post last study drug dosing. The following information will be requested:

- Review previously on-going adverse events and record new AEs (if any)
- Review concomitant medications

8.9 Completion of the Study

The Investigator will document the completion or the reason for early withdrawal by a subject in the eCRF. The following categories should be used to describe these events in the eCRF:

- Subject discretion (document reason)
- Investigator considers it to be in the best interest of the subject
- AEs
- Administrative reasons (e.g., early termination of the study)
- Subject lost to follow up
- Major protocol deviation
- Lack of efficacy
- Death
- Completion of the study
- Protocol-specified criteria such as QTc prolongation, HR, SBP/DBP, or FEV_1 changes (see Section 5.7)

9 PLANNED STATISTICAL METHODS

9.1 Introduction

This study will be conducted as an open-label, chronic dosing (7 days), two-period, two-treatment, crossover design evaluating the following two treatments in approximately 60 subjects:

- GFF MDI 14.4/9.6 µg BID with Aerochamber Plus VHC
- GFF MDI 14.4/9.6 µg BID without Aerochamber Plus VHC

The primary objective of this study is to compare the effects of GFF MDI 14.4/9.6 µg with Aerochamber Plus VHC relative to GFF MDI 14.4/9.6 µg without Aerochamber Plus VHC based on FEV_1 AUC_{0-12} after 7 days of treatment.

9.2 Protocol Variables

9.2.1 Efficacy Endpoints

The first day of treatment in each Treatment Period is Day 1. Each Treatment Period is planned to contain 7 days between the first and last dose corresponding to a span of 8 calendar days. Therefore, assessments collected on Day 8 (Visits 3 and 5) will occur following 7 days of treatment.

9.2.1.1 Primary Endpoint

- FEV_1 AUC_{0-12} on Day 8

9.2.1.2 Pharmacokinetic Endpoints measured on Day 8

- Maximum (or peak) plasma concentration (C_{max})
- AUC_{0-12}
- Time to peak concentration (T_{max})

9.2.1.3 Other Efficacy Endpoints

- FVC AUC_{0-12} and PEFR AUC_{0-12} on Day 8
- Peak change from baseline in FEV_1, FVC, and PEFR on Day 1 and Day 8
- Change from baseline in morning pre-dose trough FEV_1, FVC, and PEFR on Day 8
- Change from baseline in FEV_1, FVC, and PEFR at each time point assessed on Day 1 and Day 8

9.2.2 Safety Endpoints

- Adverse Events, Treatment-emergent AEs (TEAEs) and serious AEs (SAEs)
- 12-Lead ECG: Change from baseline heart rate, PR interval, QRS axis, QRS interval, QT interval and QTcF interval
- Clinical laboratory testing
- Vital sign measurements

9.3 Analysis

9.3.1 Primary Efficacy Analysis

FEV_1 AUC_{0-12} is the area under the curve calculated
using the trapezoidal rule and will be normalized by dividing the AUC by the length of follow up post-morning-dosing (typically 12 hours).

FEV_1 AUC_{0-12} on Day 8 will be analyzed using a mixed model. The model will include baseline FEV_1 and reversibility to Ventolin HFA as continuous covariates and period, treatment, smoking status, and ICS use at baseline as unordered categorical covariates. The model will also include subject as a random effect to model correlation within subject across the study. The model will not include treatment sequence unless that term is determined to be important ($p<0.10$).

Since pre-dose values are known to be variable and an isolated time point may not accurately reflect the true baseline, the following definition will be implemented for the model's baseline covariate: the mean of available pre-dose values on the first day of each Treatment Period, i.e., the mean of pre-dose values at Visits 2 and 4, where the mean of the -60 and -30 minute values for each visit is obtained and then both visit means are averaged.

The comparison of FEV_1 AUC_{0-12} on Day 8 of GFF MDI 14.4/9.6 µg BID with Aerochamber Plus VHC relative to GFF MDI 14.4/9.6 µg BID without Aerochamber Plus VHC will be based on the above model. The ratio (GFF MDI with Aerochamber Plus VHC / GFF MDI µg without Aerochamber Plus VHC) and corresponding 90% confidence interval will be calculated using Fieller's Thereom. In addition, the least squares means for each treatment, the least squares mean difference between treatments, and a measure of within-subject variability will be reported. The primary analysis will use the modified Intent-to-Treat (mITT) Population. Analyses using the Intent-to-Treat (ITT) Population will be considered supportive.

9.3.2 Secondary Analysis

The primary pharmacokinetic parameters to be estimated after chronic administration of GFF MDI with or without the Aerochamber Plus VHC will be glycopyrronium and formoterol C_{max}, AUC_{0-12}, and t_{max}. Other PK parameters such as $t_{½}$ and λ_z may be

calculated, as appropriate. The calculation of PK parameters will be performed using non-compartmental analysis.

Log-transformed AUC_{0-12} and C_{max} of glycopyrronium and formoterol will be compared between the two treatments using analysis of variance. A separate model containing effects for treatment, period, sequence and subject within sequence will be fit for each parameter and analyte. Only subjects that have data for both treatments for the relevant PK parameter will be included in the model. Estimated geometric mean ratios (GMRs; GFF MDI with Aerochamber Plus VHC / GFF MDI without Aerochamber Plus VHC) with 90% confidence intervals (CIs) will be produced.

9.3.3 Other Efficacy Analyses

Descriptive statistics will be tabulated by treatment for FVC AUC_{0-12} and PEFR AUC_{0-12}, the peak changes from baseline in FEV_1, FVC, and PEFR on Day 1 and Day 8, changes from baseline in morning pre-dose trough FEV_1, FVC, and PEFR on Day 8, and changes from baseline in FEV_1, FVC, and PEFR at each time point assessed on Day 1 and Day 8. Baseline for these tabulations will implement the same definition as for the baseline covariate in the mixed model analysis of FEV_1 AUC_{0-12}.

9.3.4 Safety Analysis

9.3.4.1 Adverse Events

Adverse events during each Treatment Period will be summarized by the number of subjects experiencing an event. They will be tabulated at the level of the Medical Dictionary for Regulatory Activities (MedDRA) preferred term, and the MedDRA system organ class. The version of MedDRA current at the time of database lock will be used for the final analysis of data. Tabulations will be broken down by severity, seriousness, AEs leading to discontinuation, and by relationship to study drug. No hypothesis tests will be performed. Tables will show the overall incidence of AEs, and the incidence for each treatment.

9.3.4.2 Clinical Laboratory Measurements

Summary statistics (mean, median, standard deviation [SD], and range) of change from baseline values will be tabulated for each treatment and each assessment time. For clinical laboratory measurements, baseline will be defined as the last available value prior to dosing on Day 1 of each Treatment Period. Potentially clinically significant values will be identified and summarized.

Shift tables relative to the normal reference ranges will be produced using the categories defined by the Common Terminology Criteria for Adverse Events Version 4.03 grades. For these shift tables, for each treatment, the subject's pre-dose grade will be cross-tabulated by the subject's maximum post-baseline grade during the treatment; also, the subject's maximum post-baseline grade during treatment will be tabulated for all baseline grades combined.

Potentially clinically significant changes from test day baseline in serum potassium (>0.5 mmol/L reduction from baseline and serum potassium <3.5 mmol/L) and values (<3.5 mmol) will be listed and tabulated by treatment. Similarly, potentially clinically significant blood glucose values (>11.1 mmol/L) will also be listed and tabulated by treatment.

9.3.4.3 Vital Signs

Summary statistics (mean, median, SD, and range) for measured values and change from baseline will be tabulated by vital sign parameter and treatment for each scheduled assessment time. For vital signs, baseline will be defined as the average of the values prior to dosing on Day 1 of each Treatment Period. In addition, potentially clinically significant values will be identified and summarized.

9.3.4.4 12-Lead Electrocardiograms

Summary statistics (mean, median, SD, and range) for absolute values and change from baseline will be tabulated by ECG parameter and treatment for each scheduled assessment time. For ECG parameters, baseline values will be defined as the last value obtained prior to dosing on Day 1 of each Treatment Period. In addition, potentially clinically significant values will be identified and summarized.

9.4 Randomization

Subjects will be randomly assigned using an IWRS to treatment sequence AB or BA in a 1:1 ratio where A= GFF MDI BID with Aerochamber Plus VHC and B= GFF MDI BID without Aerochamber Plus VHC, respectively. All subjects who complete the study will receive both treatments.

9.5 Experimental Design

This study will be conducted as a two-period, two-treatment, crossover design. The experimental design was chosen to be balanced with respect to period and first-order carryover effects.

9.6 Sample Size

The sample size was determined based on precision in estimating the secondary endpoints, AUC_{0-12} and C_{max} of glycopyrronium and formoterol. Glycopyrronium and formoterol are both highly variable with intra-subject coefficients of variation of approximately 55% and 40%, respectively. Assuming a 15% dropout rate, randomization of N=60 subjects provides this study with ~19% precision in estimating the glycopyrronium GMR (GFF MDI with Aerochamber Plus VHC / GFF MDI without Aerochamber Plus VHC). That is, assuming an observed GMR of 1.05, the upper bound of the 90% CI would be 1.25.

Statistical power was also calculated for the primary endpoint, FEV_1 AUC_{0-12}, on Day 8. The estimate of the within-subject standard deviation (SD) of FEV_1 AUC_{0-12} is based on FEV_1

AUC_{0-12} data from previous Pearl studies. A within-subject SD of 0.130 L and a mean response of 1.490 L in FEV_1 AUC_{0-12} for GFF MDI BID without Aerochamber Plus VHC are assumed. If approximately 15% of subjects will drop out, and a two-sided alpha level of 0.05 will be used, 60 randomized subjects will provide >99% probability to demonstrate equivalence of GFF MDI with Aerochamber compared to GFF MDI without Aerochamber.

9.7 Data Validation and Transformation

In general, spirometry measures follow a normal distribution. However, under certain circumstances (e.g., during a COPD exacerbation unrelated to treatment), extreme and atypical values can arise. Such values may disproportionately affect model-based estimates of the fixed effect and variance parameters. Prior to data base lock and unblinding, the FEV_1 AUC_{0-12} data will be examined as part of data quality management. This will include production of normal probability plots, kernel density estimates, and normal order outlier statistics. If a single or small number of extreme values are identified, such outliers may be removed from the analysis if determined to be erroneous. Otherwise, nonparametric methods or data transformations (e.g. logarithmic or normal rank transformation) will be considered.

9.8 Analysis Plan

All analyses will be specified in a detailed Statistical Analysis Plan (SAP) that will include table and data listing shells with mock graphical representations. The SAP will be signed before database lock and unblinding.

9.9 Study Populations

The following analysis populations are defined in this study:

- The **ITT Population** is defined as all subjects who are randomized to treatment. Subjects will be analyzed according to the treatment assigned per the sequence randomization regardless of the treatment actually received.

- The **mITT Population** is a subset of the ITT Population including subjects who received treatment and have post-treatment efficacy data from both Treatment Periods. Data judged to be impacted by major protocol deviations will be determined prior to unblinding and excluded. Statistical tabulations and analyses will be by randomized treatment, but data obtained after subjects receive an incorrect treatment will be excluded from the affected periods.

- The **PK Population** is defined as all randomized and treated subjects who have sufficient data to reliably calculate at least one PK parameter. Statistical analyses and tabulations will be by the treatment actually received.

- The **Safety Population** is defined as all subjects who are randomized to treatment and receive at least one dose of the study treatment. Statistical analyses and tabulations will be by the treatment actually received.

- The **Not Randomized Population** is defined as subjects who did not receive a randomization number and therefore did not receive a dose of study treatment (e.g., subjects who were screen failures or stopped participation prior to having been randomized).

Analyses will be performed as follows:

Demographics will be summarized for the ITT, mITT, Safety, and the Not Randomized Populations. Extent of exposure will be summarized for the Safety Population. The Safety Population will be used to summarize safety.

Efficacy analyses will be performed for the mITT and ITT Populations, with the mITT Population being considered the primary population for these analyses.

9.10 Handling of Missing Data

Pre-dose spirometry values will use the average of the non-missing -60 and -30 minute values. In subjects missing either of these pre-dose assessments, the value will be calculated from the single measurement. In subjects missing both pre-dose values, morning pre-dose trough FEV_1 at that visit will not be calculated.

9.11 Statistical Software

Data processing, statistical screening, descriptive reporting and analysis of the efficacy and safety data will be performed using [redacted]. Graphs may also be produced using [redacted].

10 ADMINISTRATIVE CONSIDERATIONS

10.1 Regulatory Authority Approval

Pearl 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). These standards respect the following guidelines:

- Guideline for GCP E6 (R1): Consolidated Guideline (ICH of Technical Requirements for the Registration of Pharmaceuticals for Human Use, May 1996).
- US CFR dealing with clinical studies (21 CFR parts 50, 54, 56, and 312).
- Declaration of Helsinki, concerning medical research in humans (Ethical Principles for Medical Research Involving Human Subjects) http://www.wma.net/en/10home/index.html.
- Any additional regulatory requirements.

The Investigator (or Pearl, where applicable) is responsible for ensuring that this protocol, the site's ICF, and any other information that will be presented to potential subjects (e.g., 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.

Pearl 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 Pearl 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 and Pearl 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. A copy of the signed ICF will be provided to the subject. The original will be retained by the Investigator.

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 Pearl. Pearl 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 Pearl that information furnished to the Investigator by Pearl 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 Pearl (or representative), IRB/IEC, or Regulatory Agency representatives may consult and/or copy study documents in order to verify worksheet/CRF 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/CRF information, the subject/patient will be identified by unique code only, full names/initials will be masked prior to transmission to Pearl. In addition, the Investigator agrees to treat all subject/patient data used and disclosed in connection with this study in accordance with all applicable privacy laws (i.e., Health Insurance Portability and Accountability Act), rules, and regulations.

10.6 Quality Control and Assurance

Pearl is responsible for implementing and maintaining quality control and quality assurance systems with written SOP to ensure that studies 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 Pearl.

10.8 Study Monitoring

In accordance with applicable regulations, GCP, and Pearl 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 concerns. 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 Pearl.
- 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 Pearls' Quality Assurance auditors, and authorized representatives of the 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 Pearls' Quality Assurance auditors and by all applicable regulatory authorities. The period of time these documents must be maintained is governed by applicable regulations. Pearl or its designee will inform the Investigator when these documents may be destroyed. Pearl or its designee must be notified in writing *at least 6 months* prior to the intended date of disposal of any study record related to this protocol to allow Pearl to make alternate storage arrangements.

10.10 Financial Disclosure

The Principal Investigator or sub-Investigators named on the Form FDA 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 Final Report

Shortly after completion of the Investigator's participation in the study, the Investigator will submit a written report to Pearl.

10.12 Publication Policy

A study site may not publish results of a study until after a coordinated multicenter publication has been submitted for publication or until one year after the study has ended, whichever occurs first. Therefore, the study site will have the opportunity to publish the results of the study, provided that "THE SPONSOR" has had the opportunity to review and comment on the study site's proposed publication prior to its being submitted for publication with the prior advice of "LEGAL" (intellectual property council) and with proper regard to the protection of subjects' identities.

11 REFERENCE LIST

Aalbers R, Ayres J, Backer V, et al. Formoterol in patients with chronic obstructive pulmonary disease: a randomized, controlled 3-month trial. Eur Respir J. 2002;19(5):936-43.

Anderson, GP. Formoterol: Pharmacology, molecular basis of agonism, and mechanism of long duration of a highly potent and selective β-adrenoceptor agonist bronchodilator. Life Sciences. 1993;52(26):2145-60.

Atrovent Prescribing Information (US), Boehringer Ingelheim, 2012.

Berger WE, Nadel JA. Efficacy and safety of formoterol for the treatment of chronic obstructive pulmonary disease. Respir Med. 2008;102:173-88.

Campbell M, Eliraz A, Johansson G, et al. Formoterol for maintenance and as-needed treatment of chronic obstructive pulmonary disease. Respir Med. 2005;99(12):1511-20.

Campbell SC, Criner GJ, Levine BE, et al. Cardiac safety of formoterol 12 µg twice daily in patients with chronic obstructive pulmonary disease. Pulm Pharmacol Ther. 2007; 20(5):571-9.

Calverley P, Lee A, Towse L, van Noord J, Witek TJ, Kelsen S. Effect of tiotropium bromide on circadian variation in airflow limitation in chronic obstructive pulmonary disease. Thorax. 2003;58(10):855-60.

Casaburi R, Kukafka D, Cooper CB, Witek TJ Jr, Kesten S. Improvement in exercise tolerance with the combination of tiotropium and pulmonary rehabilitation in subjects with COPD. Chest. 2005;127:809–17.

Consolidated Standards of Reporting Trials (CONSORT) Statement 2010. Accessed on 17 July 2014. Available online at: http://www.consort-statement.org/consort-2010

Celli B, MaNee W, Agusti A, et al. Standards for the diagnosis and treatment of subjects with COPD: a summary of the ATS/ERS position paper. Eur Respir J 2004; 23:932-946.

Dahl R, Greefhorst LA, Nowak D, et al. Inhaled formoterol dry powder versus ipratropium bromide in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2001;164(5):778–84.

Feenstra TL, van Genugten ML, Hoogenveen RT, Wouters EF, Rutten-van Mölken MP. The impact of aging and smoking on the future burden of Chronic Obstructive Pulmonary Disease: a model analysis in the Netherlands. Am J Respir Crit Care Med. 2001;164(4):590-6.

Ferrer M, Alonso J, Morera J, et al. Chronic Obstructive Pulmonary Disease stage and health related quality of life. Ann Intern Med. 1997;127(12):1072-9.

Global strategy for the diagnosis, management, and prevention of COPD. Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2014. http://www.goldcopd.org. Accessed 14 March 2014.

Halbert RJ, Isonaka S, George D, Iqbal A. Interpreting COPD prevalence estimates: what is the true burden of disease? Chest. 2003;123(5):1684-92.

Halbert RJ, Natoli JL, Gano A, Badamgarav E, Buist AS, Mannino DM. Global burden of COPD: systemic review and meta-analysis. Eur Respir J. 2006;28(3):523-32.

Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150(9):604–12.

Leidy NK, Rennard SI, Schmier J, Jones MK, Goldman M. The Breathlessness, Cough, and Sputum Scale: the development of empirically based guidelines for interpretation. Chest. 2003;124(6):2182-91.

Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. Eur Respir J. 2005;26(2):319-38.

Moher D, Hopewell S, Schulz KF, et al. CONSORT 2010 Explanation and Elaboration: updated guidelines for reporting parallel group randomised trials. BMJ. 2010;340:c869. doi: 10.1136/bmj.c869.

Murray CJ, Lopez AD. Alternative projections of mortality and disability by cause 1990-2020: Global Burden of Disease Study. Lancet. 1997;349(9064):1498-504.

National Health and Nutrition Examination Survey (NHANES III), 2011. Accessed on 14 July 2014. Available online at: http://www.cdc.gov/niosh/topics/spirometry/nhanes.html

Niewoehner DE, Rice K, Cote C, Paulson D, Cooper JA Jr, Korducki L, Cassino C, Kesten S. Prevention of exacerbations of chronic obstructive pulmonary disease with tiotropium, a once-daily inhaled anticholinergic bronchodilator: a randomized trial. Ann Intern Med. 2005;143:317–326.

New York Heart Association NYHA 2011 NYHA Classification, the Stages of Heart Failure. Accessed on 14 July 2014. Available online at Heart Failure Society of America: http://www.abouthf.org/questions_stages.htm

R. Development Core Team. R: A language and environment for statistical computing. 2003. R Foundation for Statistical Computing, Vienna, Austria.

Rossi A, Kristufek P, Levine BE, et al. Comparison of the efficacy, tolerability, and safety of formoterol dry powder and oral, slow-release theophylline in the treatment of COPD. Chest. 2002 Apr;121(4):1058-69.

Sullivan SD, Ramsey SD, Lee TA. The economic burden of COPD. Chest. 2000;117:5S-9S.

Van Noord JA, Aumann JL, Janssens E, et al. Comparison of tiotropium once daily, formoterol twice daily and both combined once daily in subjects with COPD. Eur Respir J. 2005;26(2):214-22.

Van Noord JA, Aumann JL, Janssens E, et al. Effects of tiotropium with and without formoterol on airflow obstruction and resting hyperinflation in patients with COPD. Chest. 2006;129(3);509-17.

Ventolin (albuterol sulfate) inhalation aerosol HFA. Highlights of Prescribing Information (2012). Accessed on 15 July 2014. Available online at: https://www.gsksource.com/gskprm/htdocs/documents/VENTOLIN-HFA-PI-PIL.PDF

Vogelmeier C, Kardos P, Harari S, Gans SJ, Stenglein S, Thirlwell J. Formoterol mono- and combination therapy with tiotropium in patients with COPD: a 6-month study. Respir Med. 2008;102(11):1511-20.

12 APPENDICES

APPENDIX 1 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.

Series "ATS/ERS Task Force: Standardization of Lung Function Testing: Number 2 in Series. European Respiratory Journal 2005;26(2):319-338."

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 (i.e., 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 $L\text{-}s^{-1}$. The total resistance to airflow at 14.0 $L\text{-}s^{-1}$ must be <1.5 $cmH_2O\ L^{-1}s^{-1}$ (0.15 kPa $L^{-1}s^{-1}$). The total resistance must be measured with any tubing, valves, pre-filter, etc., included that may be inserted between the subject and the spirometer. Some devices may exhibit changes in resistance due to water vapor condensation, and accuracy requirements must be met under BTPS conditions for up to 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 versus volume provide more detail for the initial portion (first 1 s) of the FVC maneuver. Since this portion of the maneuver, particularly the peak expiratory flow (PEF), 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

	Instrument Display		Hardcopy Graphical Output
Parameter	**Resolution Required**	**Scale Factor**	**Resolution Required**
Volume[a]	0.050 L	5 mm-L^{-1}	0.050 L
Flow[a]	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

[a] 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 (i.e., 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 a 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 one 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 one 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 to 1,1 to 2, 2 to 3,…6 to 7 and 7 to 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 to 3, 1 to 4, 2 to 5, 3 to 6, 4 to 7 and 5 to 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 patient 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%.

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 (i.e., 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 A1-1, but must meet the recommendations for those that are measured. Accuracy and repeatability recommendations apply over the entire volume range of the instrument.

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

Test	Range/Accuracy (BTPS)	Flow Range ($L\text{-}s^{-1}$)	Time (s)	Resistance and Back Pressure	Test Signal
VC	0.5–8 L, ±3% of reading or ±0.050 L, whichever is greater	0-14	30		3-L Calibration syringe
FVC	0.5–8 L, ±3% of reading or ±0.050 L, whichever is greater	0-14	15	<1.5 cm H_2O L^{-1} s^{-1} (0.15 kPa $L^{-1}s^{-1}$)	24 ATS waveforms, 3-L Calibration syringe
FEV_1	0.5–8 L, ±3% of reading or ±0.050 L, whichever is greater	0-14	1	<1.5 cm H_2O L^{-1} s^{-1} (0.15 kPa $L^{-1}s^{-1}$)	24 ATS waveforms
Time Zero	The time point from which all FEV_t measurements are taken			Back extrapolation	

Abbreviations: ATS=American Thoracic Society; BTPS=body temperature and pressure saturated; FEV_1=forced expiratory volume in 1 second; FEV_t=forced expiratory volume in t seconds; FVC=forced vital capacity; VC=vital capacity

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 minutes), 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 2 SPIROMETRY ASSESSMENT CRITERIA

Acceptable Versus Usable Tests

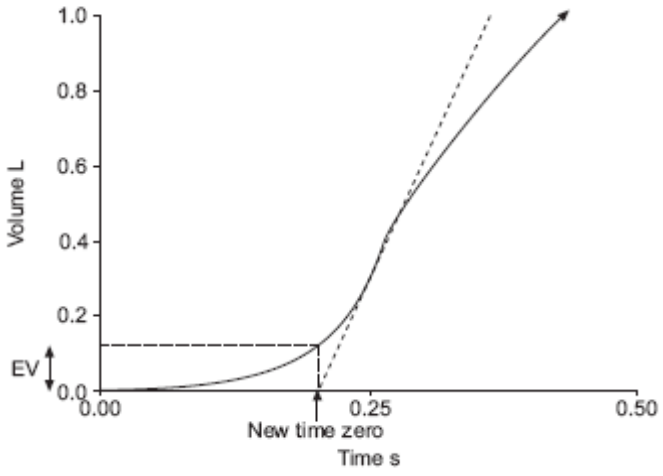
***Acceptable* Tests must meet the following seven criteria:**

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

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

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

Figure A2-1. Example of a Usable Spirogram



EV=back extrapolation volume

The expanded version of the early part of a subject's volume-time spirogram, illustrating back extrapolation through the steepest part of the curve, where flow is PEF, to determine the

new "time zero." Forced vital capacity -4.291 L; EV – 0.123 L (2.9% FVC): back extrapolation line through PEF.

Between-Maneuver Reproducibility Criteria

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

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

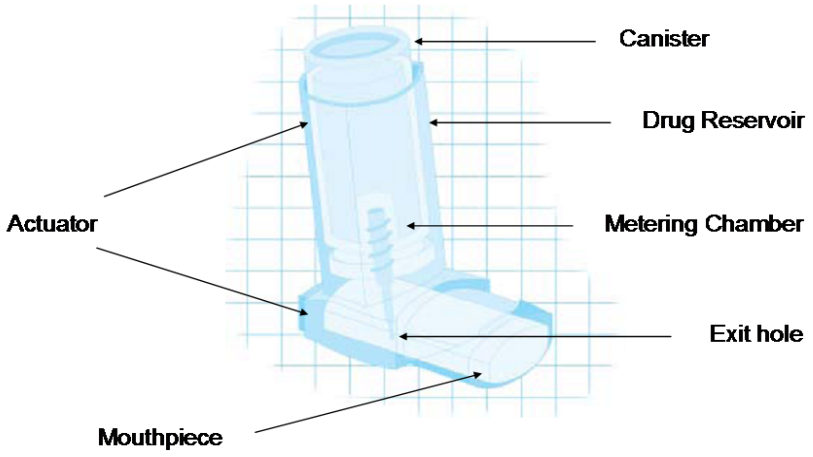
If these criteria are met, the spirometry testing for that time point may conclude. The highest FEV_1 and the highest FVC obtained at each testing time point (even if from different reproducible tracings), will be collected.

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

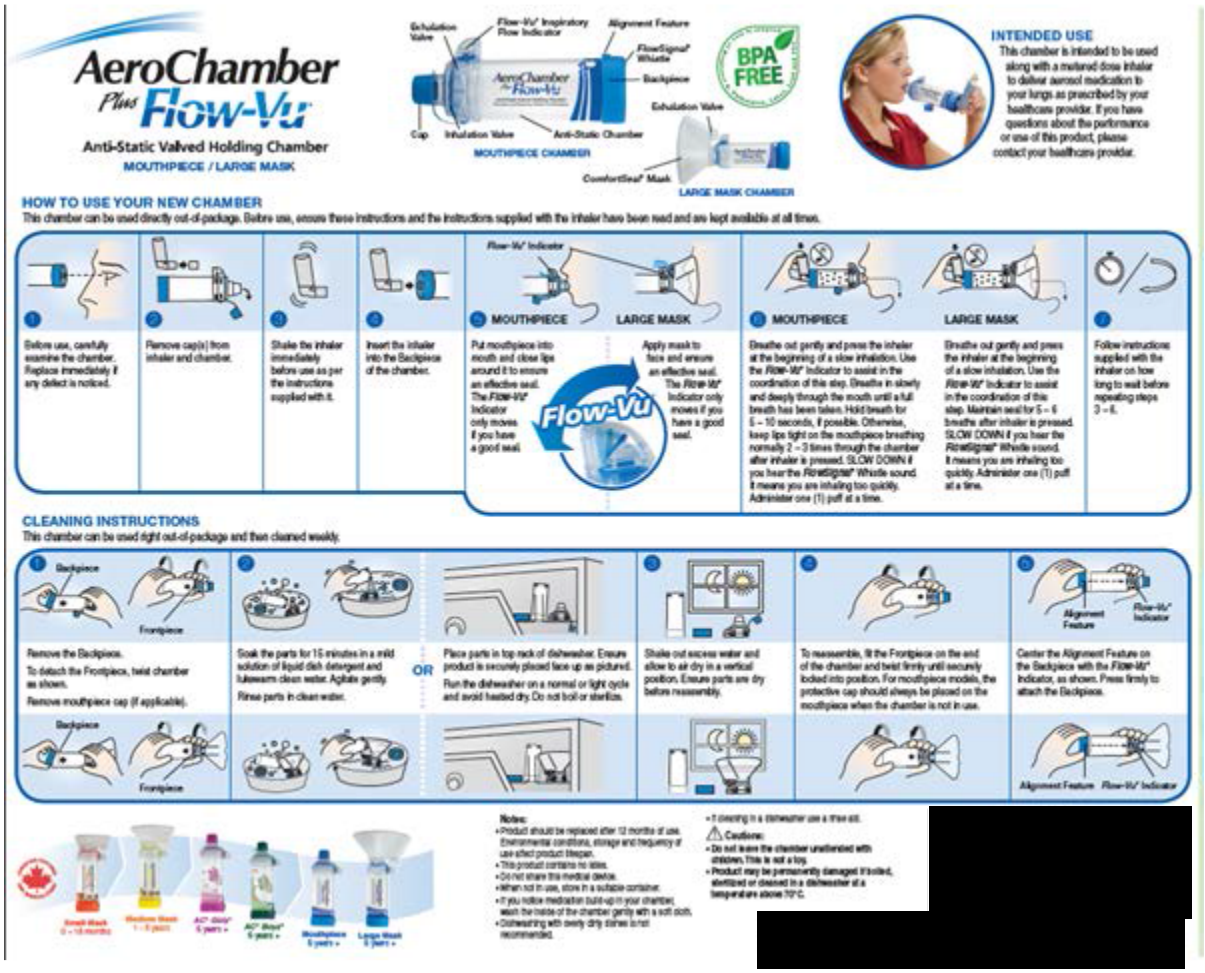
APPENDIX 3 SUBJECT INSTRUCTIONS FOR USE OF GFF MDI DEVICES

1. The inhaler should be stored at room temperature.
2. Take the cap off the mouthpiece of the actuator.
3. Inspect the front of the inhaler and make sure there is nothing inside the mouthpiece of the inhaler. Make sure the canister is fully and firmly inserted into the actuator.
4. All MDIs must be primed before the first use. Priming involves releasing a certain number of sprays (four) into the air before the first use of the inhaler. Shaking and priming the inhaler fills a chamber inside the canister with the correct dose and mix of medication so that it is ready to use. To prime the inhaler, gently shake the inhaler for 5 to 10 seconds and then spray once into the air away from yourself and others. Wait approximately 30 seconds and repeat the process three more times.
5. Gently shake the inhaler for 5 to 10 seconds before each spray.
6. Breathe out fully through your mouth, expelling as much air from your lungs as possible. Tilt your head back slightly, place the mouthpiece into your mouth, holding the inhaler with the mouthpiece down, and closing your lips around it. To allow the medication to enter your lungs, keep your tongue flat on the floor of your mouth.
7. While breathing in deeply and slowly through your mouth, fully depress the top of the metal canister with your index finger. Immediately after the spray is delivered, release your finger from the canister. When you have breathed in fully, remove the inhaler from your mouth and close your mouth.
8. Hold your breath as long as possible, up to 10 seconds, and then breathe normally.
9. If you are taking more than one puff, repeat steps 5 to 7, with gentle shaking for 5 to 10 seconds prior to each spray.
10. Put the cap back on the mouthpiece after every time the inhaler is used.

METERED DOSE INHALER SCHEMA



APPENDIX 4 AEROCHAMBER PLUS FLOW-VU INSTRUCTIONS FOR USE



APPENDIX 5 INSTRUCTIONS FOR USE OF ATROVENT HFA INHALATION AEROSOL MDI DEVICE

You do not have to shake the **ATROVENT HFA** Inhalation Aerosol canister before using it.

ATROVENT HFA Inhalation Aerosol should be "primed" two times before taking the first dose from a new inhaler or when the inhaler has not been used for more than 3 days. To prime, push the canister against the mouthpiece (see Figure 1), allowing the medicine to spray into the air. **Avoid spraying the medicine into your eyes while priming ATROVENT HFA Inhalation Aerosol**.

1. Insert the metal canister into the clear end of the mouthpiece (see Figure 1). Make sure the canister is fully and firmly inserted into the mouthpiece. The **ATROVENT HFA** Inhalation Aerosol canister is for use only with the **ATROVENT HFA** Inhalation Aerosol mouthpiece. Do not use the **ATROVENT HFA** Inhalation Aerosol canister with other mouthpieces. This mouthpiece should not be used with other inhaled medicines.

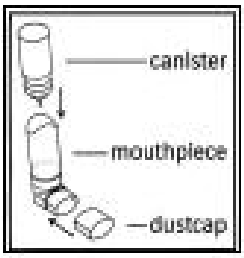


Figure 1

2. Remove the **green** protective **dust** cap. If the cap is not on the mouthpiece, make sure there is nothing in the mouthpiece before use. For best results, the canister should be at room temperature before use.
3. ***Breathe out (exhale) deeply*** through your mouth. Hold the canister upright as shown in Figure 2, between your thumb and first two fingers. Put the mouthpiece in your mouth and close your lips. Keep your eyes closed so that no medicine will be sprayed into your eyes. **Atrovent HFA** (ipratropium bromide HFA) Inhalation Aerosol can cause blurry vision, narrow-angle glaucoma or worsening of this condition or eye pain if the medicine is sprayed into your eyes.

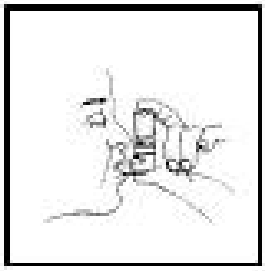


Figure 2

4. ***Breathe in (inhale) slowly*** through your mouth and at the same time firmly press once on the canister against the mouthpiece as shown in Figure 3. Keep breathing in deeply.

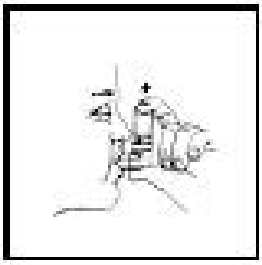


Figure 3

5. ***Hold your breath*** for ten seconds and then remove the mouthpiece from your mouth and breathe out slowly, as in Figure 4. **Wait at least 15 seconds and repeat steps 3 to 5 again.**

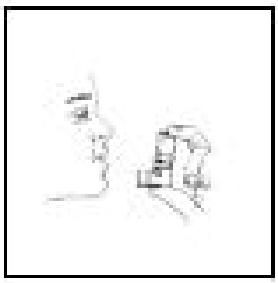


Figure 4

6. Replace the green protective dust cap after use.
7. **Keep the mouthpiece clean**. It is very important to keep the mouthpiece clean. At least once a week, wash the mouthpiece, shake it to remove excess water and let it air dry all the way (see the instructions below).
   - Mouthpiece Cleanin

-
- g Instructions:
- **Step A.** Remove and set aside the canister and dust cap from the mouthpiece (see Figure 1).
- **Step B.** Wash the mouthpiece through the top and bottom with warm running water for at least 30 seconds (see Figure 5). Do not use anything other than water to wash the mouthpiece.

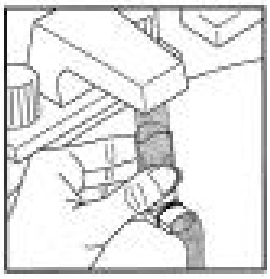


Figure 5

- **Step C.** Dry the mouthpiece by shaking off the excess water and allow it to air-dry all the way.
- **Step D.** When the mouthpiece is dry, replace the canister. Make sure the canister is fully and firmly inserted into the mouthpiece.
- **Step E.** Replace the green protective dust cap.
- **If the mouthpiece becomes blocked,** and little or no medicine comes out of the mouthpiece, wash the mouthpiece as described in Steps A to E under the **"Mouthpiece Cleaning Instructions."**

8. **Keep track of the number of sprays used. Discard the canister after 200 sprays.** Even though the canister is not empty, you cannot be sure of the amount of medicine in each spray after 200 sprays.

APPENDIX 6 INSTRUCTIONS FOR USE OF VENTOLIN HFA INHALER

The Parts of Your VENTOLIN HFA Inhaler

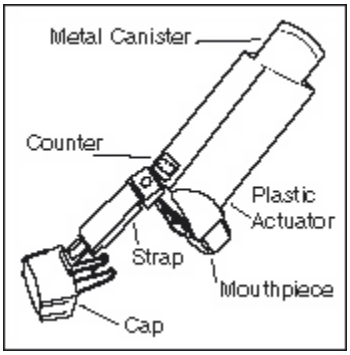


Figure 1

There are two main parts to your VENTOLIN HFA inhaler:

1. The metal canister that holds the medicine and
2. The blue plastic actuator that sprays the medicine from the canister (see Figure 1).
    a. The inhaler also has a cap that covers the mouthpiece of the actuator.
    b. The strap on the cap will stay attached to the actuator.
    c. 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.

The counter starts at 204, the number will count down by 1 each time you spray the inhaler. The counter will stop counting at 000.

Never 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.

Do not use the actuator with a canister of medicine from any other inhaler. In addition, do not use a VENTOLIN HFA canister with an actuator from any other inhaler.

How to Use Your VENTOLIN HFA

Before using your VENTOLIN HFA:

1. Take the inhaler out of the foil pouch. Safely throw away the pouch and the drying packet that comes inside the pouch. The counter should read 204. *The inhaler should be at room temperature before you use it.*
2. Check each time to make sure the canister fits firmly in the plastic actuator. Also, look into the mouthpiece to make sure there are no foreign objects there, especially if the strap is no longer attached to the actuator or if the cap is not being used to cover the mouthpiece.

Priming your VENTOLIN HFA:

1. You must prime the inhaler to get the right amount of medicine. Prime the inhaler before you use it for the first time, if you have not used it for more than 14 days, or if it has been dropped.
    1. To prime the inhaler, take the cap off the mouthpiece of the actuator.
    2. Then shake the inhaler well, and spray it into the air away from your face.
    3. Shake and spray the inhaler like this 3 more times to finish priming it.
    4. The counter should now read 200, or 60 if you have a sample or institutional canister.

Instructions for taking a dose from your VENTOLIN HFA:

Read through the 6 steps below before using VENTOLIN HFA. If you have any questions, ask your study doctor.

1. Take the cap off the mouthpiece of the actuator. **Shake the inhaler well** before each spray.
2. Hold the inhaler with the mouthpiece down (see Figure 2). **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.
3. **Push the top of the canister all the way down while you breathe in deeply and slowly through your mouth** (see Figure 3). Right 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.

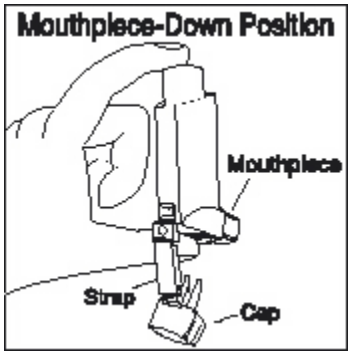


Figure 2

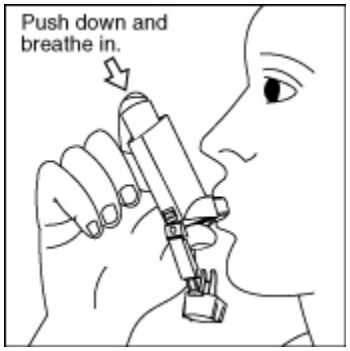


Figure 3

1. **Hold your breath as long as you can**, up to 10 seconds, then breathe normally.
2. If your doctor has prescribed more sprays, wait 1 minute and **shake** the inhaler again. Repeat steps 2 through 4.
3. Put the cap back on the mouthpiece after every time you use the inhaler, and make sure it snaps firmly into place.

When to Replace Your VENTOLIN HFA

1. **When the counter reads 020**, you should refill your prescription or ask your doctor if you need another prescription for VENTOLIN HFA.
2. **Throw the inhaler away** when the counter reads 000 or 6 months after you have taken the inhaler out of the foil pouch, whichever happens first. You should not keep using the inhaler when the counter reads 000 because you will not receive the right amount of medicine.
3. **Do not use the inhaler** after the expiration date, which is on the packaging it comes in.

How to Clean Your VENTOLIN HFA

It is very important to keep the plastic actuator clean so the medicine will not build-up and block the spray. Do not try to clean the metal canister or let it get wet. The inhaler may stop spraying if it is not cleaned correctly.

Wash the actuator at least once a week.

Cleaning instructions:

1. 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.
2. Wash the actuator through the top with warm running water for 30 seconds (see Figure 4). Then wash the actuator again through the mouthpiece (see Figure 5).

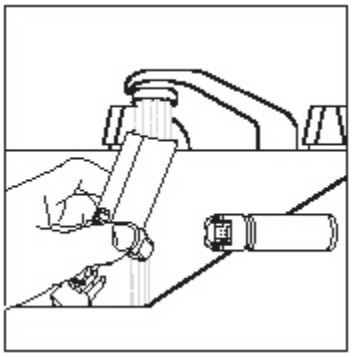


Figure 4

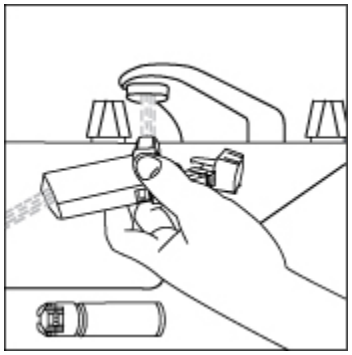


Figure 5

3. 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 step 2.
4. Let the actuator air-dry completely, such as overnight (see Figure 6).

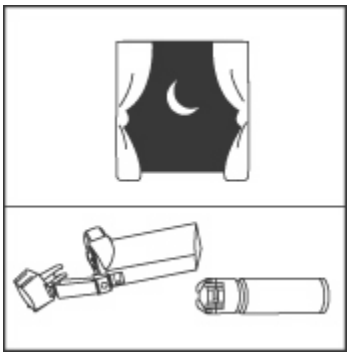


Figure 6

5. When the actuator is dry, put the canister in the actuator and make sure it fits firmly. Shake the inhaler well and spray it once into the air away from your face. (The counter will count down by 1.) Put the cap back on the mouthpiece.

If your actuator becomes blocked:

Blockage from medicine build-up is more likely to happen if you do not let the actuator air-dry completely. If the actuator gets blocked so that little or no medicine comes out of the mouthpiece (see Figure 7), wash the actuator as described in cleaning steps 1 to 5.

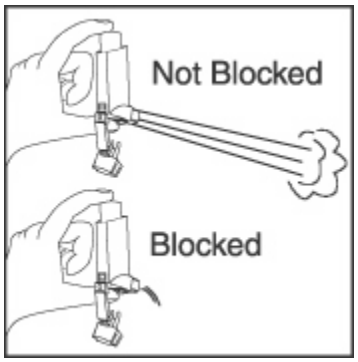


Figure 7

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 canister in the actuator and make sure it fits firmly. Shake the inhaler well and spray it once into the air away from your face. Then take your dose as prescribed. Then clean and air-dry it completely.

Storing Your VENTOLIN HFA

Store at room temperature with the mouthpiece down. Keep out of reach of children.

Contents Under Pressure: Do not puncture. Do not use or store near heat or open flame. Exposure to temperatures above 49°C (120°F) may cause bursting. Never throw into fire or incinerator.

APPENDIX 7 DOSE INDICATORY DISPLAY READING INSTRUCTIONS

For the purposes of this study, when recording the dose indicator display value, review the indicator display at the top of the MDI and record the number of inhalations remaining that matches the chart below:

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 8 SPONSOR SIGNATORY

Study Title: A Randomized, Phase III, Two-period, Open-label, Chronic-dosing (7 Days), Multi-center, Crossover Study to Assess the Efficacy of PT003 in Subjects with Moderate to Very Severe COPD with and without a Valved Holding Chamber

Study Number: PT003013-01

Final Date: [redacted]

Signature: [redacted] Date: [redacted]

Name: [redacted]

Title: [redacted] Pearl Therapeutics, Inc.

APPENDIX 9 INVESTIGATOR'S AGREEMENT AND SIGNATURE PAGE

Study Title: A Randomized, Phase III, Two-period, Open-label, Chronic-dosing (7 Days), Multi-center, Crossover Study to Assess the Efficacy of PT003 in Subjects with Moderate to Very Severe COPD with and without a Valved Holding Chamber

Study Number: PT003013-01

Final Date: Version 2.0, [redacted]

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 Institutional Review Board/Independent Ethics Committee, 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 comply with Good Clinical Practice 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 electronic Case Report Forms (eCRFs). The eCRFs will be provided to the Sponsor in a timely manner at the completion of the study, or as otherwise specified by the Sponsor.
- To allow authorized representatives of Pearl or regulatory authority representatives to conduct on-site visits to review, audit and copy study documents. I will personally meet with these representatives to answer any study-related questions.

Signature:_____ Date:_____

Name:_____

Affiliation: _____