Clinical Trial Protocol: PT003011-00

Study Title:	A Randomized, Phase IIIb, Three-period, Three-treatment, Double-blind, Multi-center, Crossover Study to Evaluate the 24-hour Lung Function Profile in Subjects with Moderate to Very Severe COPD after 4 Weeks of Treatment with PT003, Open-Label Spiriva® Respimat® (Tiotropium Bromide) as an Active Control, and Placebo
Study Number:	PT003011-00
Study Phase:	IIIb
Product Name:	Glycopyrronium and Formoterol Fumarate Inhalation Aerosol; PT003
IND Number:	107739
Indication:	Chronic Obstructive Pulmonary Disease (COPD)
Investigators:	Multi-center
Sponsor:	[redacted]
Sponsor Contact:	[redacted]

	Version Number	Date
Original Protocol	Version 1.0	[redacted]

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SYNOPSIS

Name of Sponsor:

[redacted]

Names of Finished Products:

Glycopyrronium and Formoterol Fumarate Inhalation Aerosol; PT003, Glycopyrronium and Formoterol Fumarate Metered Dose Inhaler (GFF MDI)

Placebo Metered Dose Inhaler (MDI) for Glycopyrronium and Formoterol Fumarate Inhalation Aerosol

Tiotropium Bromide Inhalation Solution; Spiriva® Respimat® (Spiriva)

Name of Active Ingredients:

Glycopyrronium and Formoterol Fumarate

Tiotropium Bromide

Study Title:
A Randomized, Phase IIIb, Three-period, Three-treatment, Double Blind, Multi-center, Crossover Study to Evaluate the 24-hour Lung Function Profile in Subjects with Moderate to Very Severe COPD after 4 Weeks of Treatment with PT003, Open-Label Spiriva® Respimat® (Tiotropium Bromide) as an active control and Placebo

Study Number: PT003011-00

Study Phase: IIIb

Study Objective(s):

Primary Objective:

To determine the 24-hour efficacy (lung function) profile of GFF MDI 14.4/9.6 µg twice daily (BID) relative to Placebo MDI BID in subjects with moderate to very severe COPD following chronic-dosing (4 Weeks).

Secondary Objective:

To determine the 24-hour efficacy (lung function) profile of GFF MDI 14.4/9.6 µg BID relative to Spiriva 5 µg once daily (QD) (open-label) in subjects with moderate to very severe COPD following chronic-dosing (4 Weeks).

Safety Objective(s):

To assess the safety of GFF MDI relative to Placebo MDI and Spiriva in subjects with moderate to very severe COPD based on adverse events (AEs), vital sign measurements, electrocardiograms (ECGs), and clinical laboratory evaluations.

Study Design:

This is a Phase IIIb, randomized, double-blind (GFF and Placebo MDIs), chronic-dosing (4 Weeks), three-period, three-treatment, multi-center, crossover study in subjects with moderate to very severe chronic obstructive pulmonary disease (COPD) to assess the efficacy and safety of GFF MDI 14.4/9.6 µg ex-actuator (dose delivered from the actuator [ie., mouthpiece] of the MDI) BID, relative to Spiriva Respimat (Spiriva) and Placebo MDI.

This is a multi-center study that will be conducted in approximately 10 sites in the United States. Across these sites, it is planned that approximately 80 subjects with moderate to very severe COPD will be randomized into one of six treatment sequences to provide an estimated 64 subjects to complete the study.

Serial spirometry will be performed over 24 hours on Day 29 of each Treatment Period in all randomized subjects (Visits 3, 5, and 7).

All treatment sequences will include GFF MDI 14.4/9.6 µg BID, Spiriva 5 µg QD (open-label; as an active control), and Placebo MDI BID. The design is balanced for period and first-order carryover effects within each block of the six treatment sequences.

Study Population:

Approximately 80 subjects with moderate to very severe COPD will be randomized into one of six treatment sequences to provide an estimated 64 subjects to complete the study.

Test Product, Dose, and Mode of Administration:

Investigational materials will be provided by Pearl Therapeutics as summarized in the table below.

Product Descriptions and Packaging of Clinical Supplies

Product Name and Dosage	Product Strength	Dose Form/Fill Count	Administration
Blinded Study Medications			
GFF MDI (PT003) 14.4/9.6 µg ex-actuator	GFF MDI 7.2/4.8 µg per actuation	1 MDI 120 inhalations	Taken as two inhalations as directed in the morning and evening
Placebo MDI	Formulation does not contain active ingredient	1 MDI 120 inhalations	Taken as two inhalations as directed in the morning and evening
Open-label Products			
Spiriva Respimat (tiotropium bromide) solution for inhalation[a] 5 µg ex-actuator	EU source: Spiriva® Respimat® Each inhalation contains 2.5 µg tiotropium per puff (2 puffs comprise one medicinal dose) and is equivalent to 3.124 µg tiotropium bromide monohydrate	1 Respimat Inhaler 60 inhalations	Taken as two inhalations as directed in the morning QD
Ventolin (albuterol sulfate) HFA inhalation aerosol 90 µg[b] ex-actuator	Ventolin® (albuterol sulfate) HFA inhalation aerosol Each inhalation contains 108 µg corresponding to 90 µg albuterol base per actuation	1 MDI 60 or 200 actuations	Taken as needed Supplies are open-label
Atrovent (ipratropium bromide) HFA inhalation aerosol 34 µg[c] ex-actuator	Atrovent® (ipratropium bromide) HFA Each inhalation contains 17 µg ex-actuator per actuation	1 MDI 200 actuations	Taken as two inhalations QID Supplies are open-label

Abbreviations: ex-actuator=dose delivered from the actuator (ie., mouthpiece) of the metered dose inhaler; GFF MDI=glycopyrronium and formoterol fumarate metered dose inhaler; HFA=hydrofluoroalkane; MDI=metered dose inhaler; NA=not applicable; QD=once daily; QID=four times daily; US=United States

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

Note: Glycopyrronium 14.4 µg in GFF MDI is equivalent to 18 µg of glycopyrronium bromide or glycopyrrolate.

[a] Active control

[b] Reversibility testing at Visit 1 (Visits 1a and/or 1b) and rescue medication during the study

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

Duration of Treatment:

Subjects will receive 4 weeks of study treatment with each of their assigned treatments for a total of three separate Treatment Periods. A Washout Period of at least 7 days (up to 21 days) will occur between the three Treatment Periods. The entire study is scheduled to take approximately 16-24 weeks for each individual subject from the time of Screening (Visit 1a) through follow-up (see Figure 1).

Efficacy Assessments:

The first day of treatment in each Treatment Period is Day 1. Each Treatment Period is planned to contain 28 days between the first and last dose corresponding to a span of 29 calendar days. Therefore, assessments collected on Day 29 (Visits 3, 5, and 7) will occur following 28 days of treatment.

Primary Efficacy Endpoint:

- Forced expiratory volume in 1 second (FEV_1) area under the curve from 0 to 24 hours (AUC_{0-24}) on Day 29

Secondary Efficacy Endpoints (Measured on Day 29, except as otherwise noted):

- FEV_1 AUC_{12-24}
- FEV_1 AUC_{0-12}
- Peak change from baseline in FEV_1 following the evening dose
- Peak change from baseline in FEV_1 following the morning dose
- Change from baseline in morning pre-dose trough FEV_1
- Change from baseline in morning pre-dose trough FEV_1 on Day 30
- Peak change from baseline in IC following the evening dose
- Peak change from baseline in IC following the morning dose

Other Efficacy Endpoints:

- Change from baseline in FEV_1 at each timepoint assessed on Days 1 and 29
- Peak change from baseline in FEV_1 on Day 1
- Forced vital capacity (FVC) AUC_{0-24}, AUC_{0-12}, and AUC_{12-24} on Day 29
- Peak expiratory flow rate (PEFR) AUC_{0-24}, AUC_{0-12}, and AUC_{12-24} on Day 29
- Morning pre-dose trough inspiratory capacity (IC) on Day 29
- Evening trough IC obtained 12-hours post-morning dose on Day 29
- Morning pre-dose trough IC on Day 30
- Peak change from baseline in FVC and PEFR on Days 1 and 29
- Peak change from baseline in IC on Day 1
- Change from baseline in average daily rescue Ventolin® HFA use over the Treatment Period

Safety Assessments:

- AEs
- Vital sign measurements
- 12-lead electrocardiograms (ECG)
- Clinical laboratory testing

Statistical Methods:

Primary Efficacy Analyses:

FEV_1 AUC_{0-24} is the area under the curve for the change from baseline in FEV_1 calculated using the trapezoidal rule and will be normalized by dividing the AUC by the length of follow up post-morning-dosing (typically 24 hours). Baseline FEV_1 is defined as the mean of available pre-dose values on the first day of each Treatment Period, ie., the mean of pre-dose values at Visits 2, 4, and 6, 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.

FEV_1 AUC_{0-24} on Day 29 will be analyzed using a mixed model with baseline FEV_1 and reversibility to albuterol as continuous covariates and period, treatment, smoking status at baseline, and inhaled corticosteroid use at baseline as unordered categorical covariates. The model will also include subject as a random effect to model correlation within a subject across the study.

The primary comparison of FEV_1 AUC_{0-24} on Day 29 will be for GFF MDI 14.4/9.6 µg BID relative to Placebo MDI and will be conducted based on the above model. A secondary comparison of FEV_1 AUC_{0-24} on Day 29 for GFF MDI 14.4/9.6 µg BID relative to Spiriva 5 µg QD will also be conducted.

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:

Power calculations were based on the properties of the primary endpoint, FEV_1 $AUC_{0-24,}$ on Day 29. The estimate of the within-subject standard deviation (SD) of FEV_1 AUC_{0-24} is based on FEV_1 AUC_{0-12} data from previous Pearl studies but is slightly larger since fewer observations are obtained during the second 12 hours. A within-subject SD of 140 mL is assumed. It is further assumed that approximately 20% of subjects will drop out, and a two-sided alpha level of 0.05 will be used. Under these assumptions, 80 randomized subjects will provide over 99% power to demonstrate a difference of 200 mL for GFF MDI 14.4/9.6 µg compared to Placebo MDI. The power to demonstrate a difference of 75 mL for GFF MDI 14.4/9.6 µg compared to Spiriva is approximately 90%.

Date of Original Approved Protocol: [redacted]

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	Adverse Event
ATS	American Thoracic Society
AUC_{x-y}	Area Under the Curve from Time x to Time y
BID	*Bis In Die*, Twice Daily
BMP	Basic Metabolic Panel
bpm	Beats Per Minute
BTPS	Body Temperature and Pressure Saturated
CBC	Complete Blood Count
CFR	Code of Federal Regulations
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
CT	Computerized Tomography
DBP	Diastolic Blood Pressure
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
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 (ie., 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
GOLD	Global Initiative for Chronic Obstructive Lung Disease
GP	Glycopyrronium
hCG	Human Chorionic Gonadotropin
HFA	Hydrofluoroalkane
HR	Heart Rate
IB	Investigator's Brochure
IC	Inspiratory Capacity
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
ICS	Inhaled Corticosteroid
ID	Identification
ie.	*Id Est,* That Is
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ISMPP	International Society for Medical Publications Professionals
ITT	Intent-to-Treat
IWRS	Interactive Web Response System
kPa	Kilopascal
L	Liter
LABA	Long-Acting β_2-Agonist
LAMA	Long-Acting Muscarinic Antagonist
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
OTC	Over-the-Counter
PEF	Peak Expiratory Flow
PEFR	Peak Expiratory Flow Rate
PFT	Pulmonary Function Test
PIN	Personal Identification Number
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
US	United States
VC	Vital Capacity

TRADEMARK INFORMATION

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Anoro	Respimat
Atrovent	Seebri
Eklira	Spiriva
Ellipta	Tudorza
Foradil	Ventolin
KoKo Spirometer	Ziploc

1 INTRODUCTION AND STUDY RATIONALE

Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity and mortality at a global level and recent statistics suggest it will become more prevalent as smoking frequencies rise and the population ages [Calverley, 2003; Feenstra, 2001; Ferrer, 1997; Murray, 1997; Sullivan, 2000]. In a systematic review and meta-analysis by Halbert and colleagues, the prevalence of physiologically defined COPD in adults aged ≥40 years was observed to be 9% to 10% [Halbert, 2003; Halbert, 2006]. The causes behind COPD are multi-factorial, where various risk factors and environmental stimuli have been identified and include smoking, air pollution, and occupational hazards.

COPD is a disease of the lungs characterized by airflow limitation that is not fully reversible. The chronic airflow limitation characteristic of COPD is caused by a mixture of small airways disease (obstructive bronchiolitis) and parenchymal destruction (emphysema) the relative contributions of which vary from person to person. The airflow limitation is progressive in nature and associated with abnormal inflammatory response of the lung to noxious particles or gases. This disease is characterized by premature loss of ventilator function as determined by a decline in forced expiratory volume in the first second of exhalation (FEV_1). Pathological inflammatory changes are characterized by elevations inactivated macrophages, neutrophils, elastases, and CD8 lymphocytes. These molecular and cellular changes cause the destruction of small airways and surrounding alveoli. As expiratory airflow (FEV_1 or forced vital capacity [FVC]) is a function of pressure against resistance, airflow in COPD is diminished due to a loss of elastic recoil and airway constriction.

Pharmacologic therapy for COPD is used to reduce symptoms, reduce the frequency and severity of exacerbations, and improve health status and exercise tolerance. Bronchodilators are the mainstay of pharmacologic treatment of COPD. The principal bronchodilator treatments are short-acting beta agonists (SABAs), long-acting beta agonists (LABAs),short acting muscarinic antagonists, long-acting muscarinic antagonists (LAMAs) and methylxanthines used as monotherapy or in combination. In subjects with significant symptoms but low risk of exacerbations regular treatment with LABAs is more effective in the management of COPD than SABAs. In subjects with a high risk of exacerbations regardless of the number of symptoms, a fixed combination of an inhaled corticosteroid/LABA or a LAMA is recommended [Global Initiative for Chronic Obstructive Lung Disease (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. Ten Phase IIb studies were conducted which supported the dose selection for ongoing Phase III studies as well as 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 COPD. GP MDI has been evaluated in eight studies conducted by Pearl, including a single dose, single center, healthy volunteer study in Australia and seven multi-center studies in subjects with COPD conducted in the US, Australia, and New Zealand. This program has assessed the safety and efficacy of GP MDI across a wide range of doses from 115.2 µg down to 0.5 µg. Across these eight studies, approximately 350 subjects with mild to severe COPD were exposed to one or more doses of GP MDI. The lower end of the dose response curve has been adequately characterized in two chronic-dose, dose-ranging studies (Studies PT001002 and PT001003), and the findings from these two studies and the previous Phase II studies support GP MDI 14.4 µg BID as the most appropriate dose to be evaluated in Phase III clinical studies.

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].

Pearl Therapeutics conducted three studies to confirm dose selection and safety for FF MDI. These include studies: PT0050801, PT0031002, and PT003005. Results demonstrated dose proportionality of FF MDI 9.6 µg and bioequivalence to Foradil. In terms of safety, results showed no substantial differences between the FF MDI treatment groups to placebo or to Foradil 12 µg, and there were no important trends noted for FF MDI at any dose.

Pearl is developing its combination product, GFF MDI, in parallel with the individual agents. Eight different doses of GFF MDI have been evaluated in five studies conducted by Pearl, including a single dose, single center, healthy volunteer study in Australia, and four multicenter studies in subjects with COPD conducted in the US, Australia, and New Zealand. The studies in subjects with COPD included three Phase IIb studies of 1-week duration and one cardiovascular safety study of 2 weeks duration. The GFF MDI doses that have been studied include the following dosing combinations: 57.6/9.6 µg, 28.8/9.6 µg, 28.8/7.2 µg, 14.4/9.6 µg, 7.2/9.6 µg, 3.7/9.6 µg, 2.0/9.6 µg, and 1.0/9.6 µg. Throughout this

Phase IIb program, over 300 subjects with COPD have been exposed to one or more doses of GFF MDI. A detailed description of the study designs and results can be obtained in the Investigator's Brochure (IB).

1.1 Study Rationale

A previous study, (PT0010801) evaluated spirometry over 24 hours following a single dose of GP MDI in subjects with mild to moderate COPD. In PT0010801, GP MDI 14.4, 28.8, 57.6, and 115.2 µg demonstrated superior efficacy compared to placebo for peak FEV_1, the primary endpoint, and for FEV_1 AUC_{0-24}. Similarly, the current study is being conducted to determine the 24-hour lung function profile of GFF MDI 14.4/9.6 µg administered BID relative to Placebo MDI, in part, to describe the benefit in early morning and evening lung function conferred by the BID dosing regimen.

The purpose of this study is to provide efficacy and safety data for GFF MDI in subjects with moderate to very severe COPD. This study will determine the 24-hour efficacy (lung function) profile of GFF MDI 14.4/9.6 µg BID relative to Placebo MDI based on FEV_1 area under the curve from 0 to 24 hours (AUC_{0-24}), following chronic dosing (4 weeks). Spiriva Respimat (Spiriva) 5 µg once daily (QD) (open-label) is included as an active control.

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of this study is to:

Determine the 24-hour efficacy (lung function) profile of GFF MDI 14.4/9.6 µg BID relative to Placebo MDI in subjects with moderate to very severe COPD following chronic dosing (4 weeks).

2.2 Secondary Objective

The secondary objective of this study is to:

Further characterize the 24-hour efficacy (lung function) profile of GFF MDI 14.4/9.6 µg BID relative to Spiriva 5 µg QD (open-label) in subjects with moderate to very severe COPD following chronic dosing (4 weeks).

2.3 Other Objectives

2.3.1 Safety Objective

The safety objective of this study is:

To assess the safety of GFF MDI relative to Placebo MDI and Spiriva in subjects with moderate to very severe COPD based on adverse events (AEs), vital sign measurements, electrocardiograms (ECGs), and clinical laboratory evaluations.

3 STUDY ENDPOINTS

3.1 Efficacy Endpoints

The first day of treatment in each Treatment Period is Day 1 (Visits 2, 4, and 6). Each Treatment Period is planned to contain 28 days between the first and last dose corresponding to a span of 29 calendar days. Therefore, assessments collected on Day 29 (Visits 3, 5, and 7) will occur following 28 days of treatment.

3.1.1 Primary Efficacy Endpoint

- FEV_1 AUC_{0-24} on Day 29

3.1.2 Secondary Efficacy Endpoints (Measured on Day 29, except as otherwise noted)

- FEV_1 AUC_{12-24}
- FEV_1 AUC_{0-12}
- Peak change from baseline in FEV_1 following the evening dose
- Peak change from baseline in FEV_1 following the morning dose
- Change from baseline in morning pre-dose trough FEV_1 on Day 29
- Change from baseline in morning pre-dose trough FEV_1 on Day 30
- Peak change from baseline in IC following the evening dose
- Peak change from baseline in IC following the morning dose

3.1.3 Other Efficacy Endpoints

- Change from baseline in FEV_1 at each timepoint assessed on Days 1 and 29
- Peak change from baseline in FEV_1 on Day 1
- Forced vital capacity (FVC) AUC_{0-24}, AUC_{0-12}, and AUC_{12-24} on Day 29
- Peak expiratory flow rate (PEFR) AUC_{0-24}, AUC_{0-12}, and AUC_{12-24} on Day 29
- Morning pre-dose trough inspiratory capacity (IC) on Day 29
- Evening trough IC obtained 12-hours post-morning dose on Day 29
- Morning pre-dose trough IC on Day 30
- Peak change from baseline in FVC and PEFR on Days 1 and 29
- Peak change from baseline in IC on Day 1

- Change from baseline in average daily rescue Ventolin® HFA use over the Treatment Period

3.2 Safety Endpoints

- AEs and serious AEs (SAEs)
- Vital sign measurements
- 12-Lead electrocardiograms ECG
- Clinical laboratory testing

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

This is a Phase IIIb, randomized, double-blind (GFF and Placebo MDIs), chronic dosing (4 Weeks), three-period, three-treatment, multi-center, crossover study in subjects with moderate to very severe COPD to assess the efficacy and safety of GFF MDI 14.4/9.6 µg ex-actuator (dose delivered from the actuator [ie., mouthpiece] of the MDI) BID, relative to Spiriva 5 µg [Spiriva® Respimat®, 2014]and Placebo MDI.

It is planned that approximately 80 subjects with moderate to very severe COPD will be randomized into one of six treatment sequences to provide approximately 64 subjects to complete the study. All treatment sequences will include GFF MDI 14.4/9.6 µg BID, Spiriva 5 µg QD (open-label; as an active control), and Placebo MDI BID. The design is balanced for period and first-order carryover effects within each block of the six treatment sequences (see Appendix 7).

Subjects will receive 4 weeks of study treatment with each of their assigned treatments for a total of three separate Treatment Periods. A Washout Period of at least 7 days (up to 21 days) will occur between each Treatment Period. The entire study period is scheduled to take approximately 16-24 weeks for each individual subject from the time of Screening (see Figure 1). The study is anticipated to run for approximately 9 months and should not exceed 12 months.

Prior to or at the Screening Visit (Visit 1a), all subjects are to sign an Informed Consent Form (ICF) prior to the conduct of any Screening assessments. The Investigator or designee will obtain a medical history, physical examination, and any required documentation in order to determine eligibility for participation (inclusion/exclusion criteria; Section 5). Reversibility of FEV_1 60 minutes following four puffs of Ventolin® HFA [Ventolin, 2012] will be assessed at Screening to characterize the subject population, but will not be used to determine eligibility to participate in the study. Subjects who are not using a prohibited medication and meet all other entry criteria will return to the clinic up to 28 days after Screening for Visit 2 (Randomization Visit). For more details on Visit 1 procedures, refer to Section 8.1.

An eDiary will be issued at Screening (Visit 1a) for use as a practice during the Screening Period to assess the subject's compliance and understanding of how to use the eDiary to maintain a daily record of their study drug dosing as well as to establish a baseline for rescue medication use (see Section 7.1.2). Subjects who fail to demonstrate proper eDiary compliance prior to Randomization (Visit 2) must be screen failed.

Subjects who meet all entry criteria but are using certain prohibited COPD medications (eg., oral β_2-agonists, LABAs, LAMAs, LABA/LAMA, corticosteroid/LABA combination products, cromoglycate or nedocromil inhalers, leukotriene antagonists [eg., zafirlukast, montelukast, zileuton], inhaled corticosteroid (ICS)/LABA, or tiotropium [Spiriva], glycopyrronium bromide [eg., Seebri®], and aclidinium [eg., Tudorza™, Elkira®],

umeclidinium [Incruse® Ellipta®] will discontinue these medications for the duration of the study and be switched to Sponsor-provided Atrovent® HFA [Atrovent, 2012], administered QID (see Section 5.4).

In order to allow for an adequate washout of previous maintenance medications, subjects will undergo a Washout Period of at least 7 days (at least 14 days if taking tiotropium or at least 7 days prior to Screening if taking phosphodiesterase inhibitors) but not greater than 28 days duration prior to returning to the clinic for Visit 2 (Randomization; see Section 5.4).

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.

At Visit 2 (Randomization Visit; Day 1 of Treatment Period 1), subjects will return to the clinic before 10:00 am. Site personnel will confirm that subjects meet the compliance requirement of ≥70% subject completion of eDiary assessments in the last 7 days preceding the Randomization Visit prior to being randomized. Subjects who continue to meet entry inclusion/exclusion criteria and remain eligible for participation in the study will be randomized into one of six pre-defined treatment sequences (all possible treatment sequences to which a subject can be randomized are shown in Appendix 7). All subjects will receive three treatments (GFF MDI 14.4/9.6 µg BID, Spiriva 5 µg QD, and Placebo MDI BID) for 28 days with a Washout Period of 7 to 21 days in between each Treatment Period. For more details on Visit 2 procedures, refer to Section 8.3.

The subject, clinical site personnel, and Pearl will be unaware of the treatment sequence assigned to a subject; it will not be possible to differentiate between GFF and Placebo MDIs since they will be identical in all aspects. Randomization will be centralized, through the use of an Interactive Web Response System (IWRS). The GFF and Placebo MDIs will be administered BID, and Spiriva will be administered QD.

Subjects will be trained on how to read the dose indicator. See Appendix 8 for instructions on how to read the dose indicator.

During Visit 2 (Randomization Visit; Day 1 of Treatment Period 1), subjects will be dispensed Treatment Period 1 study drug according to their assigned treatment sequence and will administer their first dose in the clinic under site personnel supervision. Before sites dispense the first dose and prior to any study procedures being performed, site staff must confirm the subject meets all protocol-specific requirements and ensure adequate washout (6 hours or longer) of all inhaled medications (including ICS, and rescue medication).

Subjects will be required to remain at the clinic until completion of all Day 1 protocol-defined assessments up to and including the 4-hour post-dose timepoint (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 4 weeks at home until Visit 3. Subjects will utilize an eDiary in which they will be asked to maintain a daily record of their study drug dosing and rescue medication use.

On Visit 3 (Day 29 and Day 30 of Treatment Period 1), subjects will again return to the clinic before 10:00 am for administration of the final dose of Treatment Period 1 study drug under site personnel supervision before 10am. Site personnel must review eDiary data prior to dosing study drug in the clinic and will return the eDiary to the subject. Subjects will undergo Day 29 and Day 30 protocol-defined assessments up to and including the 24-hour post-dose assessments (see Table 8-3). Study drug will be collected, and subjects will be discharged from the clinic and undergo a study drug Washout Period of at least 7 days (up to 21 days), while on Sponsor-provided Atrovent HFA MDI, administered QID, prior to initiating the next treatment in their assigned treatment sequence. For more details on Visit 3 procedures, refer to Section 8.4.

Following the Washout Period, subjects will repeat a similar pattern of visits for the next two treatments in their assigned sequence as follows:

Visit 4 (Day 1 of Treatment Period 2): Subject eDiaries will be reviewed and returned to the subjects. Subjects will be dispensed Treatment Period 2 study drug according to their assigned treatment sequence and will administer their first dose in the clinic under site personnel supervision before 10 am. Subjects will undergo all protocol-defined assessments (see Table 8-2), be discharged from the clinic, and continue study drug administration for 28 days until Visit 5. For more details on Visit 4 procedures, refer to Section 8.5.

Visit 5 (Day 29 of Treatment Period 2): Subject eDiaries will be reviewed and returned to the subjects. Subjects will administer their final dose of Treatment Period 2 study drug in the clinic under site personnel supervision before 10 am. Subjects will undergo all protocol-defined assessments up to and including the 24-hour post-dose assessments (see Table 8-3). Study drug will be collected, and subjects will be discharged from the clinic and undergo a study drug Washout Period of at least 7 days (up to 21 days) while on Sponsor-provided Atrovent HFA MDI, administered QID, prior to initiating the next treatment in their assigned treatment sequence. For more details on Visit 5 procedures, refer to Section 8.6.

Visit 6 (Day 1 of Treatment Period 3): Subject eDiaries will be reviewed and returned to the subjects. Subjects will be dispensed Treatment Period 3 study drug according to their assigned treatment sequence and will administer their first dose in the clinic under site personnel supervision before 10 am. Subjects will undergo all protocol-defined assessments up to and including the 4-hour post-dose assessments (see Table 8-2), be discharged from the clinic, and continue study drug administration for 28 days until Visit 7. For more details on Visit 6 procedures, refer to Section 8.5.

Visit 7 (Day 29 of Treatment Period 3): will serve as the final clinic visit. Subjects will administer the final dose of study drug at the clinic under site supervision before 10 am. Subjects will complete all post-study assessments, including a final physical examination and recording of any AEs, and will then be discharged from the study. A telephone follow-up will be performed within 7 to 14 days following Visit 7. For more details on Visit 7 procedures, refer to Section 8.6.

Refer to Table 8-3 for the study procedures and assessments to be performed at Visit 7.

General Guidance for Treatment Visits 2 to 7 (in-clinic):

- At the start of each treatment visit, prior to any study procedures being performed, site personnel must confirm the subject withheld all COPD medications (including randomized study medication, ICS and rescue medication, eg., Ventolin HFA) for at least 6 hours, by confirming the last time of dosing for all COPD medication(s).
  - **Note**: Subjects who inadvertently took COPD medication(s) within 6 hours of the start of study procedures must be rescheduled as soon as is practical but within the specified visit window.
  - **Note:** Before the in-clinic dose is administered, the site must confirm the subject meets all other protocol-specified requirements (eg., FEV_1 baseline criteria; see Section 7.1.1.2).
- 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 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 consistent with their in-clinic dosing time.
  - Subjects will be required to take their study drug BID in the morning between 06:00 and 10:00 am (breakfast time) and in the evening between 06:00 and 10:00 pm (dinner time).
  - Subjects will be required to take their Spiriva QD in the morning between 06:00 and 10:00 am (breakfast time) and must not under any circumstances take another dose of Spiriva in the evening.
- 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 for blinded study medication.
  - 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 and 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 for BID treatment 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 dose of BID treatments the evening before (12±2 hours) prior to the scheduled visit.

- In the case of Spiriva, subjects should be reminded to withhold their Spiriva for at least 24 hours prior to pulmonary function tests (PFTs). (See below)
- To bring their study drugs with them to the clinic, to withhold all COPD medications (including randomized study medication, ICS, and rescue medication) for at least 6 hours prior to pulmonary function tests (PFTs).
- To bring their eDiary to the clinic visit
- 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 of 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 is discharged from the clinic. Site personnel should take every precaution to prevent 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 and return the medications to the subject at the end of the visit when all study procedures are completed.
- If a subject is experiencing severe symptoms and requires Ventolin HFA for relief of COPD symptoms at any time during a test day, site personnel must note the time and justification for use in the subject's chart and all subsequent spirometry and PEFR assessments should be stopped. However, 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 29 (4 weeks) following the initiation of each treatment arm. To accommodate scheduling conflicts, a window of 29±2 days is permitted (ie., Day 29 procedures must be done within a minimum of 27 days and a maximum of 31 days from Day 1).

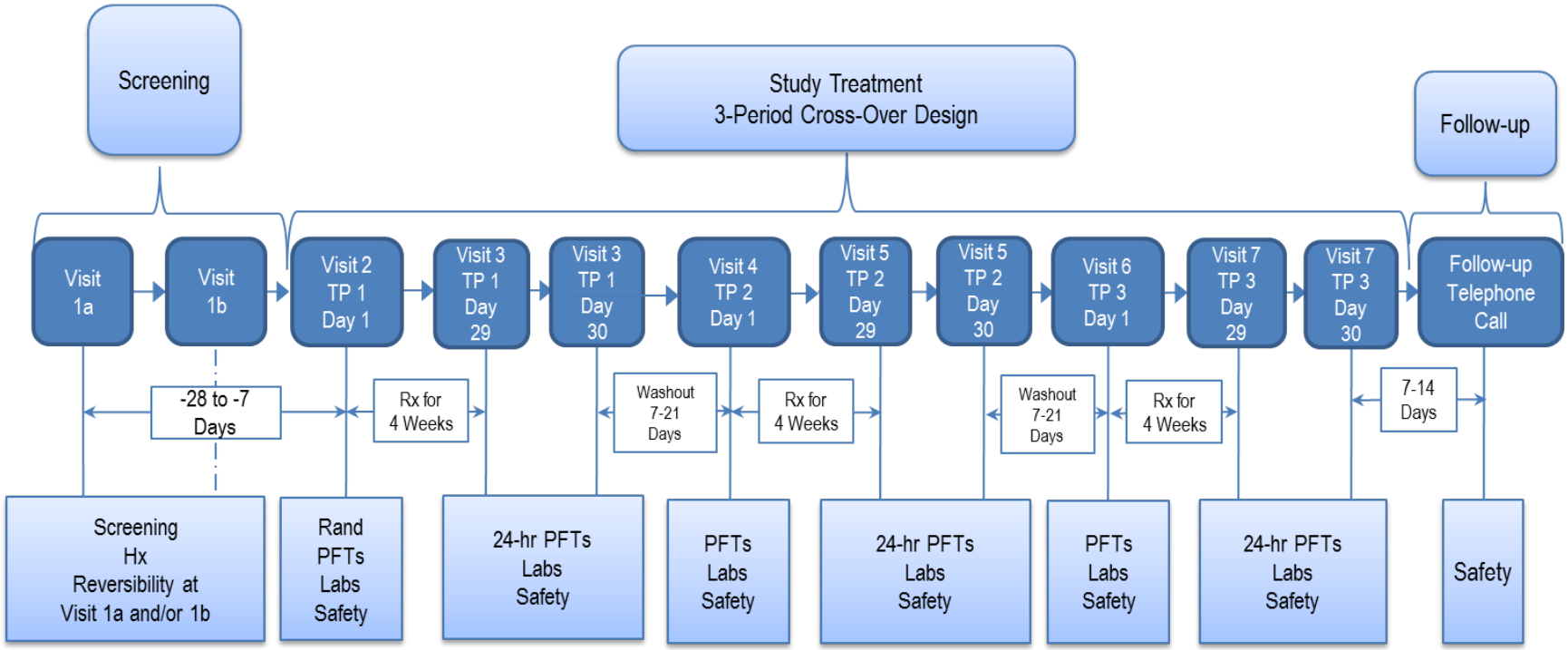
During each Treatment Period (between Visits 2 and 3, Visits 4 and 5, and Visits 6 and 7), subjects will be permitted to use Sponsor-provided Ventolin HFA on an as-needed basis for relief of COPD symptoms.

During the Washout Period, when subjects are not taking study drug (between Visits 3 and 4 and Visits 5 and 6), subjects will use the Sponsor-provided short-acting bronchodilator (Atrovent HFA) administered QID and may use 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.

Figure 1. Study Design



Hx = Medical History; PFT = Pulmonary Function Test; TP = Treatment Period

5 STUDY POPULATION SELECTION AND WITHDRAWAL CRITERIA

Approximately 80 subjects with moderate to very severe COPD will be enrolled to provide an estimated 64 subjects to complete the study. Subjects who withdraw from the study after receiving at least one treatment will not be replaced. Subjects who are re-evaluated will maintain one screening number throughout the study.

5.1 Inclusion Criteria

Subjects will be eligible to participate in the study if they meet all of the following criteria:

1. Give their signed written informed consent to participate
2. Are at least 40 years of age and no older than 80 at Visit 1a
3. A female is eligible to enter and participate in the study if she is of:
   - Non-child bearing potential (ie, 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 1a, and agrees to one of the following acceptable contraceptive methods used consistently and correctly as outlined below (ie, in accordance with the approved product label and the instructions of the physician for the duration of the study – from Visit 1a (Screening) until 14 days after Visit 7:
     - 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 (eg, 20 cigarettes per day for 10 years, or 10 cigarettes per day for 20 years represent 10 pack-years)].
6. Severity of Disease: Subjects with an established clinical history of COPD and severity defined as:
   - At Visit 1a (and 1b, if necessary), pre- and 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 also be ≥750 mL if FEV_1 <30% of predicted normal value.
   - At Visit 2, pre-bronchodilator FEV_1/FVC ratio of <0.70.
   - 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. Subject is willing and, in the opinion of the Investigator, able to adjust current COPD therapy as required by the protocol
8. Screening clinical laboratory tests must be acceptable to the Investigator.
9. Screening ECG must be acceptable to the Investigator.
10. Chest X-ray or computed tomography (CT) scan of the chest/lungs within 6 months prior to Visit 1a 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 1a.
11. 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 meeting any of the following criteria are to be excluded:

1. Significant diseases other than COPD, i.e., disease or condition which, in the opinion of the Investigator, may put the subject at risk because of participation in the study or may influence either the results of the study or the subject's ability to participate in the study.
2. Pregnancy: Women who are pregnant or lactating.
3. Respiratory
   a) Asthma: Subjects, who in the opinion of the Investigator, have a current diagnosis of asthma.
   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 (High Resolution CT evidence of bronchiectasis that causes repeated acute exacerbations), sarcoidosis, idiopathic interstitial pulmonary fibrosis (IPF), primary pulmonary hypertension, or 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 1a.

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

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

h) Spirometry Performance:
    a. Acceptability: Subjects who cannot perform acceptable spirometry, i.e., meet ATS/ERS acceptability criteria
    b. Repeatability: Subjects who cannot perform technically acceptable spirometry with at least three acceptable flow-volume curves with two or more meeting ATS repeatability criteria for FEV_1during the pre-bronchodilator assessments at Visit 1a/1b and at the post-bronchodilator assessment at Visit 1a/1b.

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

j) Subject use of any non-invasive positive pressure ventilation device (NIPPV). **Note:** Subjects using continuous positive airway pressure (CPAP) or bilevel positive airway pressure (BiPAP) for Sleep Apnea Syndrome are allowed in the study.

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

l) Pulmonary Rehabilitation: Subjects who have participated in the acute phase of a pulmonary rehabilitation program within 4 weeks prior to Visit 1a (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.

m) Subjects who have initiated or altered the dose regimen of intranasal corticosteroids, intranasal antihistamines, or a combination thereof within 7 days prior to Visit 1a or during the Screening Period (Visit 1a 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 1a). 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 (CHF NYHA Class III/IV)

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

1. Clinically significant conduction abnormalities [eg, left bundle branch block, Wolff-Parkinson-White syndrome or evidence of second degree (Mobitz Type II) or third degree atrioventricular (AV) block].
2. Clinically significant arrhythmias (eg, 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 (ie, selective beta 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, the atrial fibrillation must be confirmed by central reading.
3. 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 (eg, poorly defined termination of the T wave) at Visit 1a that remains elevated on repeat testing prior to Visit 2.
4. Ventricular rate <45 bpm
5. Pathological Q waves of ≤1 year
6. 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.
7. 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
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 ≤50 mL/minute using CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) formula (Levey, 2009) at Visit 1a and on repeat testing prior to Visit 2.

    Note: Subjects with overactive bladder syndrome, treated with oral anticholinergics, who have been on treatment for at least 1 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 AST, ALT, or total bilirubin ≥1.5 times upper limit of normal at Visit 1a and on repeat testing prior to Visit 2.
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 angle closure glaucoma will be excluded, regardless of whether or not they have been treated. Subjects with a diagnosis of open angle glaucoma -who have intraocular pressure controlled with medication(s) are eligible. All medications approved for control of intraocular pressures are allowed including topical ophthalmic non-selective β-blockers such as betaxolol, carteolol, levobunolol, metipranolol, or timolol.
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 1a (Screening) or during the Screening Period (between Visit 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 non-compliance with diary completion (ie, <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 (ie, studies that do not require change to medication or an additional intervention) is not exclusionary.
20. 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.
21. Previous Participation: Subjects who were previously enrolled in any trial conducted or sponsored by Pearl Therapeutics, Inc.

5.3 Subject Identification

All subjects who undergo screening will be assigned a unique screening identification (ID) 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.

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 Chronic Obstructive Pulmonary Disease Medications

The following medications used for the treatment of COPD are not permitted during 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. COPD Medications: Required Washout Periods, Pre Visit 2

Required Washout Period Prior to Visit 2:	
Class of medication	**Minimum washout period prior to Visit 2**
Long-acting anticholinergics	Tiotropium, 14 days; aclidinium[b], 2 days; glycopyrronium[b], 10 days; umeclidinium[b], 3 days
Short-acting anticholinergics	6 hours
LAMA/LABA	14 days
Fixed-combinations of long-acting β_2 agonists and inhaled corticosteroids[a]	7 days. At Visit 1a (Screening) these medications must be switched to the nearest equivalent dose of inhaled corticosteroid monotherapy
Fixed-combinations of short-acting β_2 agonists and short-acting anticholinergics	6 hours
Long acting β_2 agonists	48 hours; indacaterol[b], 15 days[c]
Short-acting β_2 agonists (including study rescue Ventolin HFA)	6 hours
Theophylline (Total daily dose $\geq$400 mg/day)*	7 days

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

[a]Please note that the washout periods for the LABA/ICS fluticasone furoate and vilanterol inhalation powder (Breo™ Ellipta™) and for the LABA indacaterol inhalation powder (Arcapta™ Neohaler™) are 5 days and 15 days, respectively.

[b.] Subject to approval in the respective countries.

[c.]Subjects treated with indacaterol at Screening (Visit 1a) will require an extension of the Screening Period by 1 additional day.

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

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

- 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 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 fluticasonse 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, mometasone or budesonide administered as a single agent BID, 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.
- 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, [eg, 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, and Visits 5 and 6), 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 (ie., between Visits 2 and 3, Visits 4 and 5, and Visits 6 and 7), subjects will receive study drug and are allowed Sponsor-provided Ventolin HFA to be used as needed for relief of COPD symptoms.
- The following respiratory medications are not permitted during this study (Table 5-2).

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). 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
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

Subjects requiring the following medications are prohibited from this study (Table 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

Prohibited Medications	Minimum cessation period prior to Visit 1 (Screening)
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 (eg, 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 must not ingest xanthine (caffeine)-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. Subjects should not consume grapefruits or grapefruit juice throughout the study.

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 3 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. Electronic cigarettes will be treated in the same manner as smoking is considered in the protocol.

5.7 Reasons and Procedures for Early Termination

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 values 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 ≥3 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 fail to meet FEV_1 Baseline Stability Criteria may be discontinued at the Investigator's discretion (See Section 7.1.1.2)

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 7.2.8).

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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 register 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 [redacted]. Each person accessing the IWRS system must be assigned an individual unique personal ID number (PIN). They must use only their assigned PIN to access the system and they must not share their assigned PIN with anyone.

6.2 Product Description

Investigational materials will be provided by Pearl as summarized in Table 6-1. Treatments will be blinded in terms of GFF MDI or Placebo MDI administered; these products are identical in form and function and indistinguishable from each other. Spiriva is open-label.

Table 6-1. Product Descriptions and Packaging of Clinical Supplies

Product Name and Dosage	Product Strength	Dose Form/Fill Count	Administration
Blinded Study Medications			
GFF MDI (PT003) 14.4/9.6 µg ex-actuator	GFF MDI 7.2/4.8 µg per actuation	1 MDI 120 inhalations	Taken as two inhalations as directed in the morning and evening
Placebo MDI	Formulation does not contain active ingredient	1 MDI 120 inhalations	Taken as two inhalations as directed in the morning and evening
Open-label Products			
Spiriva Respimat (tiotropium bromide) solution for inhalationa 5 µg ex-actuator	EU source: Spiriva® Respimat® Each inhalation contains 2.5 µg tiotropium per puff (2 puffs comprise one medicinal dose) and is equivalent to 3.124 µg tiotropium bromide monohydrate	1 Respimat Inhaler 60 inhalations	Taken as two inhalations as directed in the morning QD
Ventolin (albuterol sulfate) HFA inhalation aerosol 90 µg[b] ex-actuator	Ventolin (albuterol sulfate) HFA inhalation aerosol Each inhalation contains 108 µg corresponding to 90 µg albuterol base per actuation	1 MDI 60 or 200 actuations	Taken as needed Supplies are open-label
Atrovent (ipratropium bromide) HFA inhalation aerosol 34 µg[c] ex-actuator	Atrovent (ipratropium bromide) HFA Each inhalation contains 17 µg ex-actuator per actuation	1 MDI 200 actuations	Taken as two inhalations QID Supplies are open-label

Abbreviations: ex-actuator=dose delivered from the actuator (ie., mouthpiece) of the metered dose inhaler; GFF MDI=glycopyrronium and formoterol fumarate metered dose inhaler; HFA=hydrofluoroalkane; MDI=metered dose inhaler; NA=not applicable; QD=once daily; QID=four times daily; US=United States

Note: All study drugs will be administered by oral inhalation. Glycopyrronium 14.4 µg in GFF MDI is equivalent to 18 µg of glycopyrronium bromide or glycopyrrolate.

[a] Active control

[b] Reversibility testing at Visit 1 (Visits 1a and/or 1b) and rescue medication during the study

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

Placebo MDIs were created by Pearl in the image of the active test product.

For open-label Spiriva Respimat (tiotropium bromide, 5 µg) inhalers and cartridge will be provided. Manufacturer's instructions for study drug administration will be provided.

For open-label Atrovent HFA (ipratropium bromide, 34 µg), bulk commercial MDIs will be provided. Manufacturer's instructions for study drug administration will be provided.

For open-label Ventolin HFA (albuterol sulfate inhalation aerosol 90 µg) bulk commercial MDIs with dose counters will be provided. Manufacturer's instructions for study drug administration will be provided.

6.3 Primary Packaging and Labeling

Investigational materials will be packaged by Pearl as summarized in Table 6-1. Spiriva supplies will be provided as open-label Respimat inhalers and cartridges. Atrovent HFA and Ventolin HFA supplies will be supplied as open-label MDIs.

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

Open-label Supplies: Open-label Spiriva 5 µg will be provided as individually labeled Respimat inhalers with individually labeled Spiriva cartridges.

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:

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

6.4 Secondary Packaging and Labeling

Blinded investigational drug supplies, and open-label Spiriva, Atrovent HFA, and Ventolin HFA supplies will be provided in 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
Blinded	One MDI
Spiriva Respimat	One each Respimat inhaler and Spiriva cartridge
Atrovent HFA	One MDI
Ventolin HFA	One MDI

Abbreviations: HFA=hydrofluoroalkane; MDI=metered dose inhaler

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

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

6.5 Emergency Unblinding of Treatment Assignment

The IWRS should be used in order to unblind subjects and to unmask drug identity. When the Investigator contacts the system to unblind a subject, he/she must provide the requested subject identifying information and confirm the necessity to unblind the subject. Pearl will not provide a disclosure envelope with the clinical supplies. The Investigator or treating physician may unblind a subject's treatment assignment **only in the case of an emergency**, when knowledge of the study treatment is essential for the appropriate clinical management or welfare of the subject. Whenever possible, the Investigator must first discuss options with the Medical Monitor or appropriate study personnel **before** unblinding the subject's treatment assignment. If this is impractical, the Investigator must notify Pearl as soon as possible, but without revealing the treatment assignment of the unblinded subject, unless that information is important for the safety of subjects currently in the study. The date and reason for the unblinding must be recorded in the appropriate data collection tool.

6.6 Storage Requirements

Blinded supplies: Store blinded study supplies in a secured location as indicated on the package label.

Spiriva supplies: Store Spiriva supplies in a secured location as indicated on the package label.

Ventolin HFA supplies: Store Ventolin HFA supplies in a secured location as indicated on the package label.

Atrovent HFA supplies: Store Atrovent HFA supplies in a secured location as indicated on the package label.

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 this protocol or in the product label attached to the protocol. Documentation of temperature monitoring should be maintained.

6.7 Instructions for Preparation of Treatments for Administration and Dispensing

GFF and Placebo MDIs

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

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.

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

Spiriva Respimat (tiotropium bromide)

Bulk supplies of open-label Spiriva will be provided by Pearl and stored in a secured location within the clinic or pharmacy facilities.

Spiriva should be stored at room temperature by the subject. Spiriva should be primed per manufacturer's instructions prior to dispensing to subject. See Appendix 6 for the manufacturer's instructions on the administration of Spiriva. Study personnel will record number on the dose counter at the time of dispensing (following priming) and upon return.

Inhaler and cartridge will be contained in an individual visit treatment box. The visit treatment box 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. Write the subject number and treatment visit number on the label.

In addition, Respimat inhalers and individually sealed cartridges will be provided for emergency resupply needs.

The initial dose will be administered in the clinic under the supervision of study personnel. Subjects will be dispensed the Respimat device and cartridge to continue taking study drug once a day until the subject returns to the clinic. Two inhalations will be administered in the morning approximately 24 hours apart. See Appendix 4 for the manufacturer's instructions on the administration of tiotropium bromide (Spiriva Respimat 5 µg).

Atrovent HFA MDI (ipratropium bromide)

Individual Atrovent HFA MDIs will be contained in an individual visit treatment box. The visit treatment box 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. Write the subject number and treatment visit number on the label.

Atrovent HFA is a solution aerosol that does not require shaking. However, as with any other MDI, some coordination is required between actuating the canister and inhaling the medication. Atrovent HFA should be primed per manufacturer's instructions prior to dispensing to subject (ie., "prime" or actuate Atrovent HFA before using for the first time by releasing two test sprays into the air away from the face). In cases where the inhaler has not been used for more than 3 days, prime the inhaler again by releasing two test sprays into the air away from the face. Subjects should avoid spraying Atrovent HFA into their eyes.

As needed, subjects will be dispensed the MDI for COPD maintenance therapy during Screening (between Visits 1a and 2) and the Washout Periods (between Visits 3 and 4 and Visits 5 and 6) per the manufacturer's instruction, two puffs with each administration QID, approximately 6 hours apart. The MDI should be stored at room temperature by the subject, avoiding temperature extremes and storage in direct sunlight. See Appendix 5 for the manufacturer's instructions on the administration of Atrovent HFA.

Ventolin HFA (albuterol sulfate inhalation aerosol)

Bulk supplies of open-label Ventolin HFA will be provided by Pearl and stored in a secured location within the clinic or pharmacy facilities.

Ventolin HFA should be stored at room temperature by the subject. Ventolin HFA should be primed per manufacturer's instructions prior to dispensing to subject. See Appendix 6 for the manufacturer's instructions on the administration of Ventolin HFA. Study personnel will record number on the dose counter at the time of dispensing (following priming) and upon return.

6.8 Drug Accountability/Return of Clinical Supplies

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

Investigational clinical supplies must be received by a designated person at the study site, handled and stored safely and properly, and kept in a 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.

7 STUDY PROCEDURES

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

Note: Subjects unable to complete 24-hour spirometry should not be enrolled.

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, 4, and 6) and on Day 29 (Visits 3, 5, and 7) of each Treatment Period are provided in Table 8-2 and Table 8-3.

All assessments during Visits 2 through 7 are recommended to be conducted in the following order: vital signs, ECGs, clinical laboratory assessments, IC and spirometry.

7.1 Efficacy Assessments

7.1.1 Pulmonary Function Tests (Spirometry)

Forced expiratory spirometry maneuvers for derivation of FEV_1, FVC, and PEFR, and slow vital capacity maneuvers for IC determination will be assessed using a spirometer that meets or exceeds minimum performance recommendations of the ATS (Appendix 1).

On Day 1 of each Treatment Period (Visits 2, 4, and 6), 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 baseline FEV_1, FVC, and PEFR. Following study drug administration, spirometry will be obtained at 15 and 30 minutes, and 1, 2, and 4 hours post-dosing of study drug.

On Day 1 of the second and third Treatment Period (Visits 4 and 6) subjects must meet the FEV_1 baseline stability criteria (see Section 7.1.1.2) prior to dosing.

On Day 29 of each Treatment Period (Visits 3, 5, and 7), spirometry will be conducted 60 minutes and 30 minutes prior to morning study drug administration. Following study drug administration, spirometry will be obtained at 15 and 30 minutes, and 1, 2, 4, 8, 11.5, 12, 12.25, 12.5, 13, 14, 16, 22, 23.5, and 24 hours post-dosing of study drug. The 12-hour timepoint must be captured prior to the evening dosing; 24-hour timepoint must be captured prior to dosing with any medications on Day 30.

7.1.1.1 Characterization of Reversibility Criteria

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:

- Perform pre-bronchodilator pulmonary function tests within 60 minutes prior to administration of Ventolin HFA (albuterol)
- Administer four puffs of Ventolin HFA (albuterol)
- Perform post-bronchodilator PFT within 30-60 minutes after the administration of Ventolin HFA

7.1.1.2 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 and third treatment periods. As such, the baseline FEV_1 at Visits 4 and 6 must be within ±20% or 200 mL of the pre-dose FEV_1 obtained at the Randomization Visit (Visit 2).

At Visits 4 and 6, 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 (ie., 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 (eg., within 1 week), or the subject may be discontinued.

7.1.1.3 Inspiratory Capacity

On Days 1 and 29 of each Treatment Period (Visits 2 to 7); IC assessments will be conducted prior to study drug administration, and prior to any other spirometry assessments. The average of the two assessments on Day 1 of each Treatment Period will be used to establish the baseline IC. Specifically, IC data will be analyzed for secondary assessments.

On Day 1 of each Treatment Period (Visits 2, 4, and 6): IC assessments will be conducted 60 minutes and 30 minutes prior to study drug administration and at 1 and 2 hours post-dosing of study drug.

On Day 29 of each Treatment Period (Visits 3, 5, and 7): IC assessments will be conducted 60 minutes and 30 minutes prior to study drug administration and at 1, 2, 12, 13, 14, 22, and 24 hours post-dosing of study drug. All subjects will be instructed on the performance of the IC maneuver. Subjects must be tested in the seated position wearing a nose clip with no air leaks between the mouth and mouthpiece. Subjects should be relaxed with shoulders down and asked to breathe regularly for several breaths until the end-expiratory lung volume is stable (this usually requires at least five tidal maneuvers). They are then urged to take a deep breath to total lung capacity with no hesitation. From at least three

acceptable trials, the two largest IC measurements should agree within 5% or 100 mL, both of these IC values will be captured and analyzed.

7.1.1.4 Standardization of IC and Spirometry Collections

All PFTs include FEV_1, FVC, and PEFR, as well as all IC assessments, as defined in ATS/ERS guidelines and 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 PFTs 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 reproducibility 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.

The volume accuracy of the spirometer is to be checked daily using a 3 L syringe across three flow ranges (ie., low, medium, and high flows) 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, Miller, 2005). 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).

7.1.2 Subject eDiary Data Collection

Subjects will be provided with an eDiary to be completed BID to record their study drug dosing and rescue medication use.

Before issuing the eDiary to the subject, site personnel will be responsible for programming the eDiary and training the subject on eDiary use.

Subjects will be issued and trained on eDiary use at the Screening Visit (Visit 1a). Subjects will be instructed to collect eDiary data during the Screening Period (between Visits 1a and 2). For the duration of the study including treatment and washout periods, subjects will continue to maintain a daily record of their study drug dosing and rescue medication use.

Site personnel will review the eDiary during the Screening Period to assess the subject's compliance and understanding of how to use the eDiary to maintain a daily record of their study drug dosing, and rescue medication use.

At the Randomization Visit (Visit 2), subjects must meet the compliance requirement of ≥70% subject completion of eDiary assessments in the last 7 days preceding the Randomization Visit to be randomized in the study. Subjects who fail to demonstrate proper eDiary compliance prior to Randomization must be screen failed.

At Visit 2 (Randomization Visit), subjects will continue to maintain daily eDiary records (morning and evening) until the end of the study.

Note: In-clinic dosing times will be documented in the source by the site staff and will not be entered by subjects into their eDiary.

At Visits 2 to 7, site personnel must review eDiary data prior to dosing study drug in the clinic.

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 eDiary entries have been recorded by the subject for compliance requirements. The subject should be reinstructed, as appropriate, on the importance of recording BID entries if missing entries are observed. If the subject demonstrates persistent eDiary compliance issues, the subject should be evaluated, at the Investigator's discretion, for further study continuation.

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. 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 four actuations, this should be recorded as four "puffs." Subjects requiring more than eight puffs per day on three 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 7, Day 29 of Treatment Period 3) and Premature Discontinuation (if applicable). A complete physical examination will include the following: general appearance, skin, head, eyes, ears, nose, throat, neck (including thyroid), lymph nodes, chest, heart, abdomen, extremities, and nervous system. Weight, assessed in ordinary indoor clothing with shoes removed will be recorded at the Screening (Visit 1a) and at the Final Visit (Visit 7) and Premature Discontinuation (if applicable). 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 the morning, and post-evening dose, if applicable. 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 timepoints 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 and temperature, as directed above:

- At Screening (Visits 1a):
- Baseline measures will be obtained
- **At Day 1 of each Treatment Period (Visits 2, 4, and 6):**
- 30 minutes *prior* to study drug administration and 30 minutes, and 4 hours *after* study drug administration
- **At Day 29 of each Treatment Period (Visits 3, 5, and 7):**
- 30 minutes *prior* to study drug administration; 30 minutes, and 11.5, 12.5 and 24 hours *after* study drug administration

7.2.3 12-Lead Electrocardiogram

Twelve-lead ECGs will be performed as described below:

Twelve-lead ECGs will be obtained during Screening (Visit 1a), at Visit 2, and at (Day 29 of each Treatment Period, Visits 3, 5, and 7), as follows:

- **At Visit 1a (Screening)**: Each subject will undergo a 12-lead ECG obtained at -30 minutes *prior* to study drug administration.
- **At Visit 2 (Randomization):** Each subject will undergo a 12-lead ECG obtained at -30 minutes *prior* to study drug administration.
- **At Visits 3, 5, and 7 (Day 29 of each Treatment Period):** Each subject will undergo a 12-lead ECG at -30 minutes *prior* to study drug administration.

Note: Baseline ECG values are defined as the last value obtained *prior* to dosing at Randomization (Visit 2). Electrocardiogram parameter assessments include: HR, PR interval, QRS axis, QRS interval, QT interval, and 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, the Investigator will make a determination on the suitability of continuing the subject in the study. Refer to Section 5.7 for specific criteria for QTcF that prompt subjects to be discontinued 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.

The decision to continue the treatment of any subject with prolonged QT or QTcF interval must be discussed and agreed upon by the Investigator and 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.

7.2.3.1 Standardization of ECG Data Collection

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]

[redacted] Feedback on the quality of the ECGs will be provided to the investigational site via a site qualification form.

7.2.4 Clinical Laboratory Tests

Clinical safety laboratory tests will be analyzed by a local or central laboratory according to standardized, validated assays. The laboratory will supply detailed instructions and all containers for blood investigations. Blood sample volumes will meet the laboratory's specification.

At the Screening Visit (Visit 1a):, hematology (complete blood count [CBC]) and chemistry (comprehensive metabolic panel [CMP]) will be obtained within 60 minutes prior to dosing (see Table 8-1). Please see the table below. For further information, refer to the Laboratory Manual for the assessments included in a CBC and CMP.

On Day 29 of each Treatment Period (Visits, 3, 5, and 7): Pre-dose: On Day 29 of Treatment Period 3 (Visit 7), a CMP will be collected within 60 minutes prior to dosing. Post-dose: At Visits 3, 5, and 7, a BMP will be obtained at 30 minutes and 2 hours post-dosing, respectively (see Table 8-1).(Creatinine clearance will be estimated by the CKD-EPI published formula at Visits 1a, 3, 5, and 7).

In women of childbearing potential, serum pregnancy testing will be performed at Screening (Visit 1a) and at the Final Visit (Day 29 of Treatment Period 3, Visit 7), and urine human chorionic gonadotropin (hCG) testing will be performed prior to the start of each Treatment Period (Visits 2, 4, 6).

The following clinical laboratory parameters will be assessed:

Hematology	
Hemoglobin	Mean corpuscular hemoglobin
Hematocrit	Mean corpuscular hemoglobin concentration
White blood cell count with differential	Mean corpuscular volume
Red blood cell count	
Platelet count	
Clinical Chemistry	
Liver Enzyme and Other Function Tests	**Other Clinical Chemistry**
Alanine aminotransferase[b]	Albumin[b]
Aspartate aminotransferase[b]	Blood urea nitrogen[a, b]
Alkaline phosphatase[b]	Calcium[a, b]
Bilirubin, total[b]	Chloride[a, b]
Gamma-glutamyl transferase[b]	Cholesterol[b]
	Bicarbonate[b]
	Creatinine[a, b]
	Glucose[a, b]
	Magnesium[b]
	Potassium[a, b]
	Phosphate[b]
	Protein, total[b]
	Sodium[a,b]
	Triglycerides[b]
Other Tests:	
Pregnancy test (women of childbearing potential only): Serum hCG at Screening and the Final/Premature Discontinuation Visit only and urine hCG at Visits 2, 4, and 6.	
Creatinine clearance will be estimated by the CKD-EPI published formula at Visits 1a, 3, 5, and 7)	

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.

7.2.5 Adverse Event Assessments

7.2.5.1 Performing Adverse Event Assessments

The Investigator is responsible for promptly documenting and reporting all AEs observed during the study in the subject's eCRF and on the AE Reporting Form. In addition, certain AEs (as described in Section 7.2.5.8) 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 from the study prematurely.

7.2.5.2 Adverse Event Definitions

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

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

Adverse events include, but are not limited to:

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

An AE does not include:

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

7.2.5.3 Pre-Randomization Adverse Events

Adverse events that occur between the time a 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 AE unless the event meets the definition of an SAE as defined below.

7.2.5.4 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 to be life-threatening; resulting in significant disability or incapacity; and requiring therapeutic intervention.

7.2.5.5 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.

7.2.5.6 COPD Exacerbations

All COPD exacerbations will be captured using a COPD Exacerbation eCRF and will not be reported as AEs unless considered an 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.

7.2.5.7 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). In such cases, the laboratory abnormality itself (e.g., elevated creatinine in a setting of renal failure) does not need to be recorded as an AE. 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 a 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.

7.2.5.8 Serious Adverse Events

DEFINITION

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 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.

REPORTING 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 Medical Monitor 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 a SAE to the Medical Monitor 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.

Post-study SAEs following the last dose of study drug must be reported to Pearl as described in Section 7.2.5.11.

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

7.2.5.9 Supplemental Investigation of Serious Adverse Events

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.

7.2.5.10 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.

7.2.5.11 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.

7.2.5.12 Institutional Review 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.

7.2.5.13 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.

7.2.6 Adverse Events of 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 7) 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 (ie., 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.

7.2.7 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.

7.2.8 Pregnancy

Any pregnancy that occurs from Screening until study completion must be reported to Pearl. To ensure subject safety, each pregnancy must be reported to Pearl within 14 days of learning of its occurrence. The pregnancy must be followed up to determine the outcome (including premature termination) and status of mother and child.

7.3 Termination of the Study

The study may be terminated prematurely with sufficient notice in advance by the Investigator for any reason as per the terms of the contract with Pearl. The reason should be communicated in writing to 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 time frame that is compatible with the subjects' wellbeing.

8 STUDY ACTIVITIES

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, 4, and 6) and on Day 29 (Visits 3, 5, and 7) 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		Treatment 3			
	Visit 1a	Visit 1b	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7		
Study Day[a]	**Up to-28**	**Up to-27**	**Day 1**	**Day 29 ±2Days**	**Day 1[a]**	**Day 29 ±2Days**	**Day 1[a]**	**Day 29 ±2Days**	**7-14 Days**	
Obtain Informed Consent	X									
Review Inclusion/Exclusion Criteria	X		X							
Verify Continued Eligibility		X		X	X	X	X	X		
Reversibility	X	X								
Demographics and Medical/Surgical History	X		X							
Smoking Status	X	X	X	X	X	X	X	X		
Prior/Concomitant Medications[b]	X		X	X	X	X	X	X	X	X
Inspiratory Capacity			X	X	X	X	X	X		
Spirometry[c]	X	X	X	X	X	X	X	X		
Physical Examination[d]	X							X		X
Vital Signs[e]	X		X	X	X	X	X	X		X
12-Lead ECG[f]	X		X	X		X		X		X
Pregnancy Test[g]	X		X		X		X	X		X
Clinical Laboratory Testing[g]	X			X		X		X		X
Chest X-ray[h]	X									
Adjust COPD Medications[i]	X							X		
COPD Exacerbations and Adverse Events	X	X	X	X	X	X	X	X	X	X
Inhalation Device Training[j]	X									
Study Drug Dispensing/Collection[k]	X[k]	X[k]	X	X	X	X	X	X		X
Study Drug Administration[l]			X	X	X	X	X	X		

Paradoxical Bronchospasm			X	X	X	X	X	X		
Issue eDiary and eDiary Training[n]	X									
Review of eDiary[o]			X	X	X	X	X	X		
Review/Record Dose Indicator Reading[p]			X	X	X	X	X	X		
Telephone Reminder[q]			X	X	X	X	X	X		
Telephone Contact									X	

Abbreviations: COPD=chronic obstructive pulmonary disease; CT= computerized tomography; ECG=electrocardiogram; eDiary=electronic diary; HFA= hydrofluoroalkane; IC=inspiratory capacity; ICS=inhaled corticosteroid; LABA=long-acting β_2-agonist

Note: Where data collection timepoints are concurrent, variables must be collected 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 1a (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 7.1.1 for spirometry assessments and specific timepoints to be performed at each treatment visit.

d. Includes evaluation of height and weight at Visit 1a (Screening) only.

e. Refer to Section 7.2.2 for vital sign assessments and specific timepoints to be performed at each treatment visit.

f. An ECG will be obtained at Screening (Visit 1a), on Day 1 of Treatment Period 1 (Visit 2), and on Day 29 of each Treatment Period (Visits 3, 5, and 7). Refer to Section 7.2.3 for ECG assessments and specific timepoints to beperformed at each treatment visit.

g. Refer to Section 7.2.4 for clinical laboratory assessments (hematology, chemistry and urinalysis) and specific timepoints to be performed at each treatment visit. A serum pregnancy test will be obtained at Screening (Visit 1a) and at Day 29 of Treatment Period 3 (Visit 7). On Day 1 of each Treatment Period (Visits 2, 4, and 6) a urine pregnancy test will be performed.

h. 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.

i. At Visit 1a (Screening), stop prohibited COPD medications and change COPD medications as specified in the protocol (ie., Sponsor-provided Atrovent HFA with or without ICS). At the end of Visit 7, return subject to pre-study or other appropriate inhaled maintenance COPD medications.

j. Sites may use Sponsor-provided Atrovent HFA or Ventolin HFA to train subjects on the use of MDIs.

k. 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) (ie., only if a subject meets the definition of COPD following spirometry assessments at Screening).

l. 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 if assigned to blinded treatment or 24±2 hours of the prior morning dosing time if assigned to Spiriva.

m. See Section 7.2.6 for definition of paradoxical bronchospasm.

n. Refer to Section 7.1.2 for details of eDiary review.

o. See Section 7.1.2 for guidance on subject eDiary use.

p. Refer to Appendix 8 for details and instructions on recording dose indicator readings.

q. 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 and eDiary to the visit, etc.).

Table 8-2. Visit Procedures on Day 1 of Each Treatment Period (Visits 2, 4, and 6)

	Pre-dosing		Post-dosing				
Clinical Variable[a]	**-60 mins**	**-30 mins**	**15 min**	**30 min**	**1 hr**	**2 hr**	**4 hr**
Review of Electronic Diary Data	**X**[b]						
Vital Signs[c]		**X**		**X**			**X**
12- Lead ECG[d]		**X**					
Clinical Laboratory Testing[e]	**X**						
Spirometry (FEV_1, FVC, PEFR)[f]	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Inspiratory Capacity[g]	**X**	**X**			**X**	**X**	
Study Drug Collection[h]	**X**[b]						
Record Dose Indicator Reading[i]		X[b]					
Study Drug Collection/Dispensing[j]		**X**[b]					
Paradoxical Bronchospasm[k]			**X**	**X**			

Abbreviations: FEV_1=forced expiratory volume in 1 second; FVC=forced vital capacity; IC=inspiratory 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 timepoint to ensure that spirometry for IC, FEV_1, FVC, and PEFR assessments will be conducted as close to the specified timepoints as possible (ie., IC, FEV_1, FVC, and PEFR assessments need to be conducted within ±15 minutes of specified timepoints prior to study drug administration; ±5 minutes of specified timepoints for the first 60 minutes post study drug administration; ±15 minutes of specified timepoint 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 7.2.2 for vital signs assessments and specific timepoints to be performed at each treatment visit.
d. Refer to Section 7.2.3 for ECG assessments and specific timepoints to be performed at each treatment visit.
e. Refer to Section 7.2.4 for clinical laboratory assessments (hematology and chemistry) and specific timepoints to be performed at each treatment visit. On Day 1 of each Treatment Period (Visits 2, 4, and 6) a urine pregnancy test will be performed.
f. Spirometry will be collected at -60 and -30 minutes prior to dosing. Post-dose spirometry assessments on Day 1 (Visits 2, 4, and 6) will be obtained prior to dosing, and at 15 and 30 minutes, and at 1, 2, and 4 hours post-dosing.
g. Refer to Section 7.1.1.3 for IC assessments and specific timepoints to be performed at each treatment visit.
h. 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..
i. Site staff will record the dose indicator reading at each visit. The dose indicator reading recorded by the site staff will be dose indicator count observed prior to subject dosing. For new MDIs the recorded count will be the count following the priming of the device but before the subject dose. Refer to Appendix 8.
j. Please refer to Sections 8.3 and 8.5 for the sequence of events and study drug collection and dispensing. See Appendix 3 for Instructions for

k. Preparation of Treatments for Administration and Dispensing.
Please refer to Section 7.2.6 for definition of paradoxical bronchospasm.

Table 8-3. Visit Procedures on Day 29 of Each Treatment Period (Visits 3, 5, and 7)

Clinical Variable[a]	Pre-dosing		Post-dosing															
	-60 min	-30 min	15 min	30 min	1 hr	2 hr	4 hr	8 hr	11.5 hr	12hr	12.25 hr	12.5 hr	13 hr	14 hr	16 hr	22 hr	23.5 hr	24 hr
Review of Electronic Diary Data	X[b]																	
Vital Signs[c]		X		X					X			X						X
12- Lead ECG[d]		X																
Clinical Laboratory Testing[e]	X[e]			X		X												
Spirometry (FEV_1, FVC, PEFR)[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Inspiratory Capacity[g]	X	X			X	X				X			X	X		X		X
Study Drug Collection[h]	X																	
Record Dose Indicator Reading[i]		X[b]																
Study Drug Collection/Dispensing[j]		X																X
Paradoxical bronchospasm[k]			X	X														

Abbreviations: ECG=electrocardiogram: FEV_1=forced expiratory volume in 1 second; FVC=forced vital capacity; IC=inspiratory capacity; ICS=inhaled corticosteroid(s); PEFR=peak expiratory flow rate; QTcF=QT corrected using Fridericia's formula

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 timepoint to ensure that spirometry for IC, FEV_1, FVC, and PEFR assessments will be conducted as close to the specified timepoints as possible (ie., IC, FEV_1, FVC, and PEFR assessments need to be conducted within ±15 minutes of specified timepoints prior to study drug administration; ±5 minutes of specified timepoints for the first 60 minutes post study drug administration; ±15 minutes of specified timepoint 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 7.2.2 for vital signs assessments and specific timepoints to be performed at each treatment visit.
d. Refer to Section 7.2.3 for ECG assessments and specific timepoints to be performed at each treatment visit.
e. Refer to Section 7.2.4 for clinical laboratory assessments (hematology and chemistry) and specific timepoints to be performed at each treatment visit. A serum pregnancy test will be obtained at Screening (Visit 1) and at Day 29 of Treatment Period 3 (Visit 7).
f. Spirometry will be collected at -60 and -30 minutes prior to dosing. Post-dose spirometry assessments will be obtained on Day 29 (Visits 3, 5, and 7) at 15 and 30 minutes, and 1, 2, 4, 8, 11.5, 12, 12.25, 12.5, 13, 14, 16, 22, 23.5 and 24 hours post-dosing.
g. Refer to Section 7.1.1.3 for IC assessments and specific timepoints to be performed at each treatment visit.
h. 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).

i. Site staff will record the dose indicator reading at each visit. The dose indicator reading recorded by the site staff will be dose indicator count observed prior to subject dosing. For new MDIs the recorded count will be the count following the priming of the device but before the subject dose. Refer to Appendix 8.
j. Dispense study drug to subject following completion of all post-dose assessments. See Appendix 8 for Instructions for Preparation of Treatments for Administration and Dispensing.
k. Please refer to Section 7.2.6 for definition of paradoxical bronchospasm.

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 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 IC and spirometry assessments (FEV_1, FVC, and PEFR) (Refer to Section 7.1.1.3).
- 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 IC and 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, ie., 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 7.2.5.8).
- Dispense subject eDiary and provide instructions on eDiary completion.
- 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. Screen fail subject if he/she has not met the eDiary compliance requirement (see Section 7.1.2).
- 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).
- Record COPD exacerbations and AEs, if any.
- Perform all pre-dose assessments (see Table 8-1).
- Obtain vital signs (HR and SBP/DBP after the subject has been in the supine position for 5 minutes, and oral or tympanic temperature).
- Obtain a 12-lead ECG (refer to Section 7.2.3)
- Perform urine pregnancy test
- Perform IC and spirometry assessments (FEV_1, FVC, and PEFR) (Refer to Section 7.1.1.3).
- Obtain subject randomization number and treatment assignment 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 6.7 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.
- The subject is to be considered randomized after receiving a randomization number from the IWRS.
- 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 Visits 3 and 5 (Day 29 of Treatment Periods 1, 2)

- Review subject eDiary and dose indicator reading.
- Confirm subject's eligibility to continue.
- 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 all previously dispensed study medications.
- Record COPD exacerbations and AEs, if any.
- Perform all pre-dose assessments for morning dose (see Table 8-1).
- Obtain vital signs (HR and SBP/DBP after the subject has been in the supine position for 5 minutes, and oral or tympanic temperature).
- Perform IC and spirometry assessments (FEV_1, FVC, and PEFR) (Refer to Section 7.1.1.3).
- Prior to dosing, site personnel will use IWRS to assign subjects to a new kit of blinded study drug or open-label Spiriva for in-clinic dosing.
- Record dose indicator reading (refer to Appendix 8).
- Refer to Section 6.7 for detailed instructions for preparation of treatments for administration.
- Record dose indicator reading (refer to Appendix 8).
- Administer in-clinic study drug from the new assigned kit at the visit.
- Perform all post-dose assessments for morning dose (see Table 8-3).
- Perform all pre-dose assessments for evening dose (see Table 8-1).

- Obtain vital signs (HR and SBP/DBP after the subject has been in the supine position for 5 minutes, and oral or tympanic temperature).
- Perform evening pre-dose IC and spirometry assessments (FEV_1, FVC, and PEFR) (Refer to Section 7.1.1.3).
- Subject will administer the evening dose of newly dispensed blinded study drug at the clinic under site supervision (not for Spiriva).
- Perform all post-dose assessments for evening dose (see Table 8-3).
- Collect study drug.
- At the conclusions of Visit 3 and 5, schedule Visits 4 and 6 (to follow a Washout Period of at least 7 days but no longer than 21 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 Visits 4 and 6 (Day 1 of Treatment Periods 2 and 3, Respectively)

- Review subject eDiary.
- Confirm subject's eligibility to continue.
- 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 7.1.1.2).
- Perform all pre-dose assessments (see Table 8-1).
- Obtain vital signs (HR and SBP/DBP after the subject has been in the supine position for 5 minutes, and oral or tympanic temperature).
- Perform a urine pregnancy test, if applicable
- Perform IC and spirometry assessments (FEV_1, FVC, and PEFR) (Refer to Section 7.1.1.3).
- Obtain subject treatment assignment 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 6.7 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 8).
- Perform all post-dose assessments (see Table 8-1).
- Schedule the next visit and ensure that the subject has an adequate supply of study drug and rescue Ventolin HFA.

8.6 Visit 7 (Day 29 of Treatment Period 3)

- Review subject eDiary
- 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 all previously dispensed study medications.
- Record COPD exacerbations and AEs, if any.
- Perform IC and spirometry assessments (FEV_1, FVC, and PEFR).
- Obtain vital signs (HR and SBP/DBP after the subject has been in the supine position for 5 minutes, and oral or tympanic temperature).
- Obtain a 12-lead ECG (refer to Section 7.2.3)
- 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.
- Perform serum pregnancy test
- 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).
- Perform all pre-dose assessments (see Table 8-1)
- Prior to dosing, site personnel will use IWRS to assign subjects to a new kit of blinded study drug or open-label Spiriva for in-clinic dosing.
- Record dose indicator reading (refer to Appendix 8).
- Refer to Section 6.7 for detailed instructions for preparation of treatments for administration.

- Administer in-clinic study drug from the new assigned kit at the visit.
- Perform all post-dose assessments (see Table 8-1).
- Perform all pre-dose assessments for evening dose (see Table 8-1).
- Obtain vital signs (HR and SBP/DBP after the subject has been in the supine position for 5 minutes, and oral or tympanic temperature).
- Perform evening pre-dose IC and spirometry assessments (FEV_1, FVC, and PEFR) (Refer to Section 7.1.1.3).
- Subject will administer the final dose of newly dispensed blinded study drug at the clinic under site supervision (not for Spiriva).
- Perform all post-dose assessments (see Table 8-3).
- Collect subject eDiary.
- Collect study drug.
- Return subject to pre-study or appropriate inhaled 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:

- Review eDiary data.
- 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 child bearing potential.
- Collect subject eDiary.
- Collect all study drug.
- 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 a double-blind (GFF and Placebo MDIs), chronic dosing (4 weeks), three-period, three-treatment, crossover design evaluating the following three treatments in approximately 80 subjects:

- GFF MDI 14.4/9.6 µg BID
- Placebo MDI BID
- Spiriva 5 µg QD

The primary objective of this study is to determine the 24-hour efficacy (lung function) profile of GFF MDI 14.4/9.6 µg BID relative to Placebo MDI following chronic dosing (4 weeks) in subjects with moderate to very severe COPD.

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 28 days between the first and last dose corresponding to a span of 29 calendar days. Therefore, assessments collected on Day 29 and Day 30 (Visits 3, 5, and 7) will occur following 28 days of treatment.

Since pre-dose values are known to be variable and an isolated timepoint may not accurately reflect the true baseline, the following baseline will be used for statistical analyses unless otherwise specified: the mean of available pre-dose values on the first day of each Treatment Period, ie., the mean of pre-dose values at Visits 2, 4, and 6, where the mean of the -60 and -30 minute value for each visit day is obtained and then all visit means are averaged. Note that all spirometry and eDiary-based endpoints will utilize changes from baseline and that area under the curve (AUC) assessments will be normalized by dividing the AUC by the length of follow up post-dosing (typically 24 hours for AUC over a full day or 12 hours for AUC assessed during a single dosing interval).

9.2.1.1 Primary Efficacy Endpoint

- FEV_1 AUC_{0-24} on Day 29

9.2.1.2 Secondary Efficacy Endpoints measured on Day 29, except as otherwise noted

- FEV_1 AUC_{12-24}
- FEV_1 AUC_{0-12}

- Peak change from baseline in FEV_1 following the evening dose
- Peak change from baseline in FEV_1 following the morning dose
- Change from baseline in morning pre-dose trough FEV_1 on Day 29
- Change from baseline in morning pre-dose trough FEV_1 on Day 30
- Peak change from baseline in IC following the evening dose
- Peak change from baseline in IC following the morning dose

9.2.1.3 Other Efficacy Endpoints

- Change from baseline in FEV_1 at each timepoint assessed on Days 1 and 29
- Peak change from baseline in FEV_1 on Day 1
- Forced vital capacity (FVC) AUC_{0-24}, AUC_{0-12}, and AUC_{12-24} on Day 29
- Peak expiratory flow rate (PEFR) AUC_{0-24}, AUC_{0-12}, and AUC_{12-24} on Day 29
- Morning pre-dose trough inspiratory capacity (IC) on Day 29
- Evening trough IC obtained 12-hours post-morning dose on Day 29
- Morning pre-dose trough IC on Day 30
- Peak change from baseline in FVC and PEFR on Days 1 and 29
- Peak change from baseline in IC on Day 1
- Change from baseline in average daily rescue Ventolin® HFA use over the Treatment Period

9.2.2 Safety Endpoints

- AEs and serious AEs (SAEs)
- Vital sign measurements
- 12-Lead ECG
- Clinical laboratory testing

9.3 Analysis

9.3.1 Primary Efficacy Analysis

FEV_1 AUC_{0-24} is the area under the curve for the change from baseline in FEV_1 calculated using the trapezoidal rule and will be normalized by dividing the AUC by the length of follow up post-morning-dosing (typically 24 hours). Baseline FEV_1 is defined as the mean of available pre-dose values on the first day of each Treatment Period, ie., the mean of pre-dose

values at Visits 2, 4, and 6, 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.

FEV_1 AUC_{0-24} on Day 29 will be analyzed using a mixed model with baseline FEV_1 and reversibility to Ventolin HFA as continuous covariates and period, treatment, smoking status at baseline, 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 ($p<0.10$).

The primary comparison of FEV_1 AUC_{0-24} on Day 29 will be for GFF MDI 14.4/9.6 µg BID relative to Placebo MDI and will be conducted based on the above model. A secondary comparison of FEV_1 AUC_{0-24} on Day 29 for GFF MDI 14.4/9.6 µg BID relative to Spiriva 5 µg QD will also be conducted. The modified Intent-to-Treat (mITT) Population will be considered the primary analysis population, and the Intent-to-Treat (ITT) Population will be considered supportive.

9.3.2 Secondary Efficacy Analysis

9.3.2.1 FEV_1 AUC_{12-24}

FEV_1 AUC_{12-24} following chronic dosing on Day 29 will be calculated similarly to FEV_1 AUC_{0-24} and analyzed in a similar fashion.

9.3.2.2 FEV_1 AUC_{0-12}

FEV_1 AUC_{0-12} following chronic dosing on Day 29 will be calculated similarly to FEV_1 AUC_{0-24} and analyzed in a similar fashion.

9.3.2.3 Peak Change in FEV_1

Peak change from baseline in FEV_1 following the morning dose on Day 29 is defined similarly to the peak change following the evening dose and will be identified from all non-missing change values up through and including the 12-hour time point, provided that there are at least 2 non-missing values during the first 2 hours post-dose. Peak change in FEV_1 following the morning dose on Day 29 will be analyzed in a similar fashion to FEV_1 AUC_{0-24}.

Peak change from baseline in FEV_1 following the evening dose on Day 29 is defined as the change at the highest value of FEV_1 post- the evening dose, or after 12-hours post-dosing for subjects taking Spiriva on Day 29. The peak change from baseline in FEV_1 will be identified from all non-missing change values up through and including the 24-hour time point, provided that there are at least 2 non-missing values during the first 2 hours post-dose. Note that peak change following the evening dose will be calculated over the same time period for FEV_1 after treatment with Spiriva 5 µg QD even though an evening dose is not administered. Peak change in FEV_1 following the evening dose on Day 29 will be analyzed in a similar fashion to FEV_1 AUC_{0-24}.

9.3.2.4 Peak Change in IC

Peak change from baseline in IC following the morning dose on Day 29 is defined similarly to the peak change following the evening dose and will be identified from all non-missing change values up through and including the 12-hour time point, provided that there are at least 2 non-missing values during the first 2 hours post-dose.

Peak change from baseline in IC following the evening dose on Day 29 is defined as the change at the highest value of IC post the evening dose or after 12-hours post-dosing for subjects taking Spiriva on Day 29. The peak change from baseline in IC will be identified from all non-missing change values up through and including the 24-hour time point, provided that there are at least 2 non-missing values during the first 2 hours post-dose. Note that peak change following the evening dose will be calculated over the same time period for IC after treatment with Spiriva 5 µg QD even though an evening dose is not administered.

Baseline IC is defined as the mean of available pre-dose values on the first day of each Treatment Period, ie., the mean of pre-dose values at Visits 2, 4, and 6, 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.

Peak change in IC following the evening (morning) dose on Day 29 will be analyzed in a similar fashion to FEV_1 AUC_{0-24}.

9.3.2.5 Morning Pre-dose Trough FEV_1

The change from baseline in morning pre-dose trough FEV_1 on Day 29 and Day 30 will each be analyzed in a similar fashion to FEV_1 AUC_{0-24}.

9.3.3 Other Efficacy Analysis

The other efficacy endpoints will be analyzed using a similar model as the primary and secondary endpoints as appropriate.

9.3.4 Control of Type I Error

Type I error will be strictly controlled at the two-sided 0.05 level for the primary endpoint, FEV_1 AUC_{0-24}, for the two comparisons of primary interest (GFF MDI to Placebo MDI and GFF MDI to Spiriva), across the secondary endpoints for comparisons of GFF MDI to Placebo MDI, and within each secondary endpoint across the two comparisons of primary interest. Comparisons of Spiriva to Placebo MDI will not be strictly controlled. For the primary endpoint, the comparison of GFF MDI to Spiriva will only be interpreted inferentially if the comparison of GFF MDI to Placebo MDI is significant. If these comparison are both significant, then Type I error will be controlled for the comparison of GFF MDI to Placebo MDI across the secondary endpoints using a sequential approach. For each secondary endpoint, if the comparison of GFF MDI to Placebo MDI is significant, then the comparison of GFF MDI to Spiriva will be interpreted inferentially.

9.3.5 Safety Analysis

9.3.5.1 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.

9.3.5.2 Paradoxical Bronchospasm

Paradoxical bronchospasm will be considered an AE of special interest, and will be tabulated separately. Bronchospasm will be summarized by the number of subjects experiencing the event during scheduled assessment periods on a test day and during the particular treatment period. Tabulations for bronchospasms will differ from those for general AEs, since paradoxical bronchospasm with onset during a treatment period will be included while onset during a washout or follow-up period will be excluded. Bronchospasm with onset outside a treatment period will be listed separately. No hypothesis tests will be performed.

9.3.5.3 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.

9.3.5.4 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.

9.3.5.5 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 to one of six treatment sequences using an IWRS in a 1:1:1:1:1:1 ratio. Each sequence will include exactly one of the three treatment groups included in this study per Treatment Period. All subjects will receive GFF MDI 14.4/9.6 µg, Spiriva 5 µg, and Placebo MDI.

The six treatment sequences are shown below where A is GFF MDI 14.4/9.6 µg, B is Spiriva 5 µg, C is Placebo MDI:

ABC	BAC	CAB
ACB	BCA	CBA

9.5 Experimental Design

The experimental design was chosen to be balanced with respect to period and first-order carryover effects.

9.6 Sample Size Consideration

Power calculations were based on the properties of the primary endpoint, FEV_1 AUC_{0-24}, on Day 29. The estimate of the within-subject SD of FEV_1 AUC_{0-24} is based on FEV_1 AUC_{0-12} data from previous Pearl studies but is slightly larger since fewer observations are obtained during the second 12 hours. A within-subject SD of 140 mL is assumed. It is further assumed that approximately 20% of subjects will drop out, and a two-sided alpha level of 0.05 will be used. Under these assumptions, 80 randomized subjects will provide over 99% power to demonstrate a difference of 200 mL for GFF MDI 14.4/9.6 µg compared to Placebo MDI. The power to demonstrate a difference of 75 mL for GFF MDI 14.4/9.6 µg compared to Spiriva is approximately 90%.

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 changes from baseline in spirometry measures 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 will be removed from the analysis. Otherwise if the data are highly skewed, data transformations such as the logarithmic transformation or normal rank transformation will be considered. If outliers are removed, sensitivity analyses including those values will be reported.

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. Treatment is assigned as randomized 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 at least two 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 **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 (eg., 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. Weekly averages for eDiary-based parameters will use all non-missing values.

Peak FEV_1 will be included in the ITT analyses as long as there is one non-missing post-dose value and in the mITT analyses as long as there are at least two non-missing FEV_1 datapoints during the first 2 hours post-dose.

For the mITT analyses, FEV_1 AUC_{0-24} will be calculated if there are at least two non-missing datapoints during the first 2 hours post-dose and there is at least one non-missing value at 4 hours post-dose or later. Peak FEV_1 will be calculated if there are at least two non-missing datapoints missing during the first 2 hours post-dose.

9.11 Statistical Software

Data processing, statistical screening, descriptive reporting and analysis of the efficacy and safety data will be performed using SAS (Version 9.2 or higher). Graphs may also be produced using R® [R. Development Core Team, 2003].

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/30publications/10policies/b3/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 (eg., advertisements or information that supports or supplements the ICF) are reviewed and approved by the appropriate IRB/IEC. The Investigator agrees to allow the IRB/IEC direct access to all relevant documents. The IRB/IEC must be constituted in accordance with all applicable regulatory requirements.

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 Confidentiality

10.4.1 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.

10.4.2 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 (ie., Health Insurance Portability and Accountability Act), rules, and regulations.

10.5 Quality Control and Assurance

Pearl is responsible for implementing and maintaining quality control and quality assurance systems with written SOPs 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.

10.6 Data Management

Data management procedures and information for this protocol will be provided by Pearl.

10.7 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 10.8. 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.

10.8 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 records related to this protocol to allow Pearl to make alternate storage arrangements.

10.9 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.

10.10 Investigator's Final Report

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

11 REFERENCE LIST

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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 (ie., 37°C), ambient pressure, saturated with water vapor, body temperature and pressure saturated [BTPS]) with an accuracy of at least ±3% of reading or ±0.050 L, whichever is greater, with flows between 0 and 14 $L\text{-}s^{-1}$. 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 (ie., both display methods are provided for interpretations and no hand measurements are performed), the time scale requirement is reduced to 10 mm-s^{-1} from the usually required minimum of 20 mm-s^{-1} (Table A1-1). The rationale for this exception is that the flow–volume curve can provide the means for quality assessment during the initial portion of the FVC maneuver. The volume-time curve can be used to evaluate the latter part of the FVC maneuver, making the time scale less critical.

Validation

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

Quality Control

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

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

Table A1-2. Summary of Equipment Quality Control

Test	Minimal Interval	Action
Volume	Daily	Calibration check with a 3-L syringe
Leak	Daily	2 cmH_2O (0.3 kPa) constant pressure for 1 minute
Volume Linearity	Quarterly	1-L increments with a calibrating syringe measured over the entire volume range
Flow Linearity	Weekly	Test at least three different flow ranges
Time	Quarterly	Mechanical recorder check with stop watch
Software	New versions	Log installation date and perform test using "known" subject

Calibration is the procedure for establishing the relationship between sensor-determined values of flow or volume and the actual flow or volume. A calibration check is different from calibration and is the procedure used to validate that the device is within calibration limits, eg., ±3% of true. If a device fails its calibration check, then 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%.

VC AND IC MANEUVERS

Equipment

For measurements of VC and IC, the spirometer or flow meter must comply with the requirements for FVC (as described previously) and be capable of accumulating volume for ≥30 s. Expiratory maneuvers or, ideally, both inspiratory and expiratory maneuvers should

be included in the display of VC maneuver. Regardless of whether the inspiratory or expiratory maneuver is used for deriving measurements, a display of the entire recorded VC maneuver must be provided. The maximal expiratory volume must be assessed to determine whether the subject has obtained a plateau in the expiratory effort. For display of the slow VC, the time scale may be reduced to 5 mm-s^{-1}.

TECHNICAL CONSIDERATIONS

Minimal recommendations for spirometry systems

Accurate results require accurate equipment. Spirometer equipment recommendations apply to all spirometers and are minimal requirements. In some circumstances, it may be appropriate to exceed these requirements (ie., in some research/surveillance applications). Instrumentation recommendations should be followed to provide accurate spirometric data and information that is comparable from laboratory to laboratory and from 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 timepoint 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

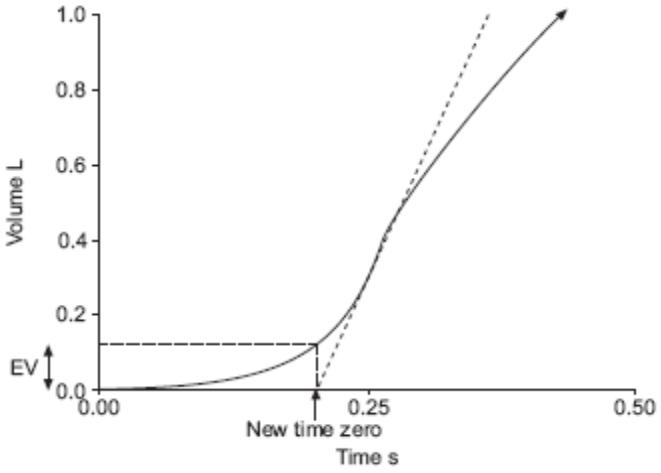
***Acceptable* Tests must meet the following seven criteria:**

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, ie., the volume-time curve shows no change in volume (<0.025 L) for ≥ 1s, and the subject has tried to exhale for at least 6 seconds

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

Usable spirometry tracings are those that only meet criteria 1 and 2. When this occurs, repeat testing up to eight attempts 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

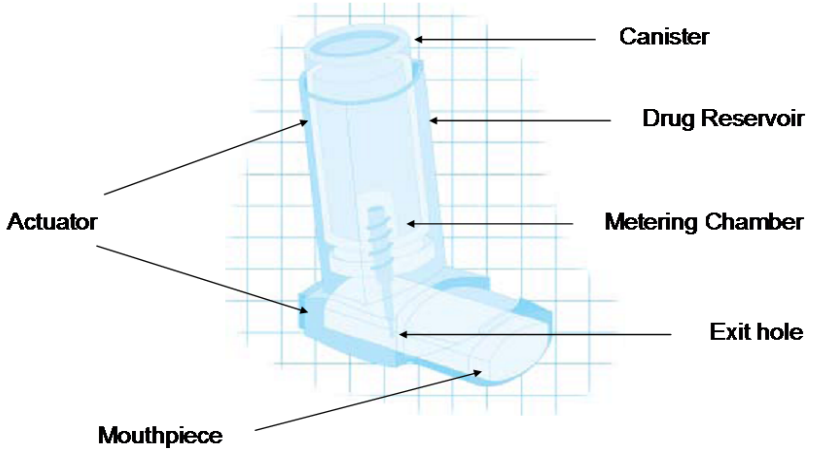
If these criteria are met, the spirometry testing for that timepoint may conclude. The highest FEV_1 and the highest FVC obtained at each testing timepoint (even if from different reproducible tracings), will be collected.

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

Appendix 3 Subject Instructions for Use of GFF MDI and Placebo 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

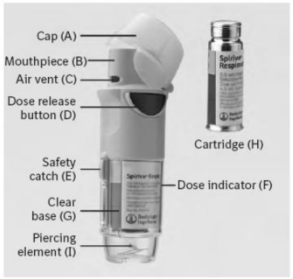


Appendix 4 Instructions for Use of Spiriva Respimat Inhaler

How to use your Spiriva Respimat inhaler
This leaflet explains how to use and care for your Spiriva Respimat Inhaler.
Please read and carefully follow these instructions. See also section 3.
How to take Spiriva Respimat Inhaler on the other side of this leaflet.

The Spiriva Respimat Inhaler releases medication slowly and gently, making it easy to inhale it into your lungs.

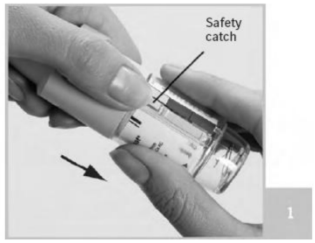
The Spiriva Respimat Inhaler enables you to inhale the medicine contained in a cartridge. The full cartridge provides 60 puffs (30 medicinal doses). **You will need to use this inhaler only ONCE A DAY,** if possible at the same time of the day. **Each time you use it take TWO PUFFS.** There is enough medicine for 30 days when it is used according to the directions for use. In the box you will find the Spiriva Respimat inhaler and the Spiriva Respimat cartridge. Before the Spiriva Respimat inhaler is used for the first time, the cartridge provided must be inserted.



Spiriva Respimat Inhaler and the Spiriva Respimat cartridge

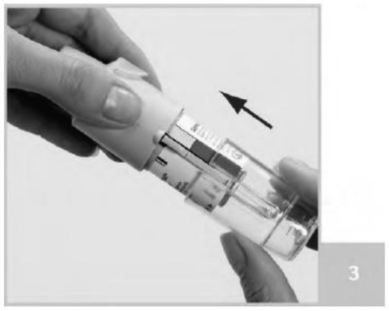
1) Inserting the cartridge

The following steps 1–6 are necessary before first use:



1. With the green cap (A) closed, press the safety catch (E) while pulling off the clear base (G).

2. Take the cartridge (H) out of the box. Push the **narrow** end of the cartridge into the inhaler until it clicks into place. The cartridge should be pushed **firmly** against a firm surface to ensure that it has gone all the way in (2b). The cartridge will not be flush with the inhaler, you will still see the silver ring of the lower end of the cartridge.
Do not remove the cartridge once it has been inserted into the inhaler.

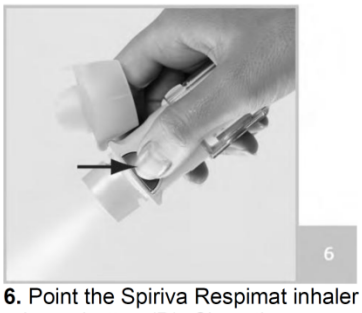


3. Replace the clear base (G). Do not remove the clear base again.

2) <u>To prepare the Spiriva Respimat inhaler for first-time use</u>

4. Hold the Spiriva Respimat inhaler upright, with the green cap (A) closed. Turn the base (G) in the direction of the red arrows on the label until it **clicks** (half a turn).

5. Open the green cap (A) until it snaps fully open.



6. Point the Spiriva Respimat inhaler towards the ground. Press the dose release button (D). Close the green cap (A).

Repeat steps 4, 5 and 6 until a cloud is visible.

Then repeat steps 4, 5 and 6 three more times to ensure the inhaler is prepared for use.

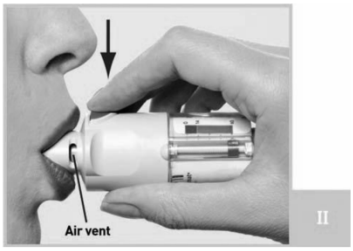
Your Spiriva Respimat inhaler is now ready to use.

These steps will not affect the number of doses available. After preparation your Spiriva Respimat inhaler will be able to deliver your 60 puffs (30 medicinal doses).

Daily use of your Spiriva Respimat inhaler

You will need to use this inhaler only ONCE A DAY. Each time you use it take TWO PUFFS.

I Hold the Spiriva Respimat inhaler upright, with the green cap (A) closed, to avoid accidental release of dose. Turn the base (G) in the direction of the red arrows on the label until it clicks (half a turn).



II Open the green cap (A) until it snaps fully open. Breathe out slowly and fully, and then close your lips around the end of the mouthpiece without covering the air vents (C). Point your Spiriva Respimat inhaler to the back of your throat.

While taking in a slow, deep breath through your mouth, press the dose release button (D) and continue to breathe in slowly for as long as you can. Hold your breath for 10 seconds or for as long as comfortable.

III Repeat steps I and II so that you get the full dose.
You will need to use this inhaler only ONCE A DAY.

Close the green cap until you use your Spiriva Respimat inhaler again.

If Spiriva Respimat inhaler has not been used for more than 7 days release one puff towards the ground. If Spiriva Respimat inhaler has not been used for more than 21 days repeat steps 4 to 6 until a cloud is visible. Then repeat steps 4 to 6 three more times.

When to get a new Spiriva Respimat inhaler

The Spiriva Respimat inhaler contains 60 puffs (30 medicinal doses). The dose indicator shows approximately how much medication is left. When the pointer enters the red area of the scale, there is, approximately, medication for 7 days left (14 puffs). This is when you need to get a new Spiriva Respimat inhaler prescription.

Once the dose indicator has reached the end of the red scale (i.e. all 30 doses have been used), the Spiriva Respimat inhaler is empty and locks automatically. At this point, the base cannot be turned any further.

At the latest, three months after use the Spiriva Respimat inhaler should be discarded even if not all medication has been used.

What if…

What if...	Reason	What to do
I can't turn the base easily.	a) The Spiriva Respimat inhaler is already prepared and ready to use. b) The Spiriva Respimat inhaler is locked after 60 puffs (30 medicinal doses).	a) The Spiriva Respimat inhaler can be used as it is. b) Prepare and use your new Spiriva Respimat inhaler.
The cap is fully pulled off and apart from the inhaler.	While opening the cap it was pulled too hard.	The cap can easily be attached again.
I can't press the dose release button.	The clear base has not been turned.	Turn the clear base until it **clicks**. (half a turn)
The clear base springs back after I have turned it.	The clear base was not turned far enough.	Prepare the Spiriva Respimat inhaler for use by turning the clear base until it **clicks**. (half a turn)
I can turn the clear base past the point where it clicks.	Either the dose release button has been pressed, or the clear base has been turned too far.	With the green cap **closed**, turn the base until it **clicks**. (half a turn)

How to care for your inhaler

Clean the mouthpiece including the metal part inside the mouthpiece with a damp cloth or tissue only, at least once a week. Any minor discolouration in the mouthpiece does not affect the performance of your Spiriva Respimat inhaler.

If necessary, wipe the outside of your Spiriva Respimat inhaler with a damp cloth.

Further information

The Spiriva Respimat inhaler must not be disassembled after inserting the cartridge and replacing the clear base.

Do not touch the piercing element inside the base.

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.

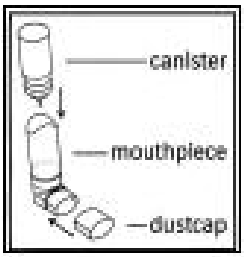


Figure 1

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.

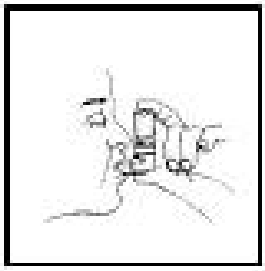


Figure 2

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.

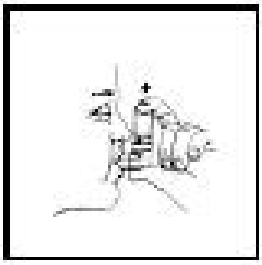


Figure 3

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.**

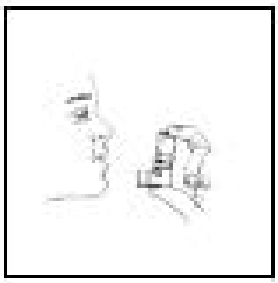


Figure 4

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 Cleaning 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.

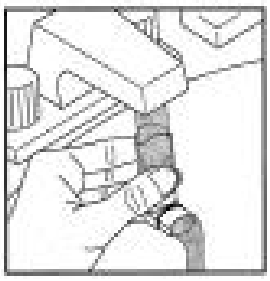


Figure 5

- **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

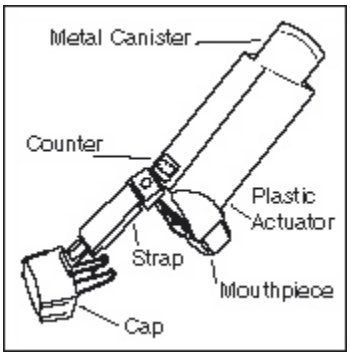


Figure 1

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.

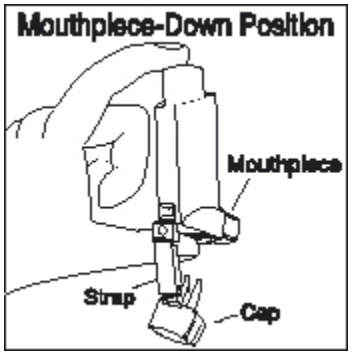


Figure 2

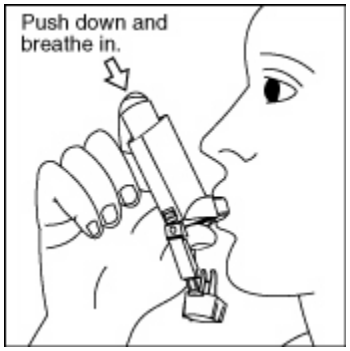


Figure 3

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).

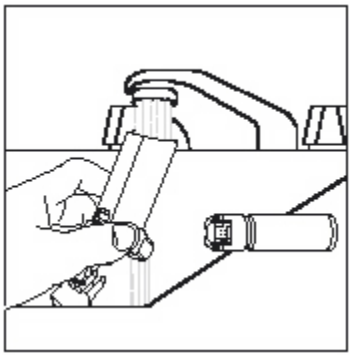


Figure 4

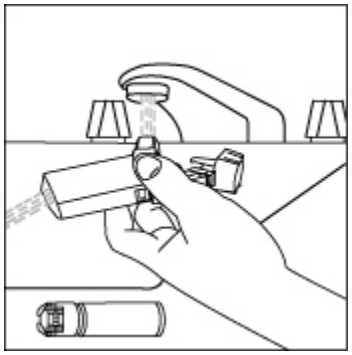


Figure 5

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).

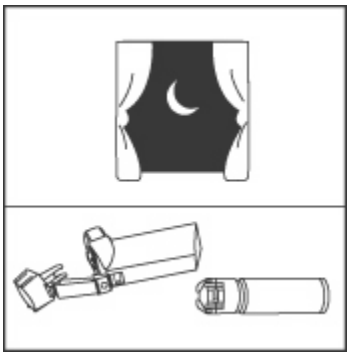


Figure 6

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.

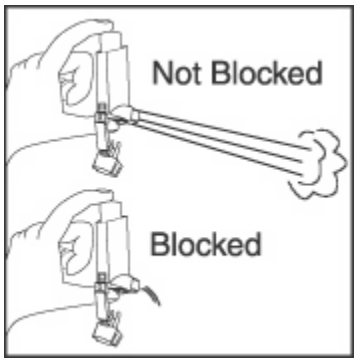


Figure 7

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 Treatment Sequences

The six planned treatment sequences are shown in Table A8-1 where A is GFF MDI 14.4/9.6 µg, B is Spiriva 5 µg, and C is Placebo MDI 9.6 µg.

Table A8-1. Planned Treatment Sequences

Sequence	Treatment Period		
	1	2	3
ABC	GFF MDI 14.4/9.6 µg	Spiriva 5 µg	Placebo MDI
ACB	GFF MDI 14.4/9.6 µg	Placebo MDI	Spiriva 5 µg
BAC	Spiriva 5 µg	GFF MDI 14.4/9.6 µg	Placebo MDI
BCA	Spiriva 5 µg	Placebo MDI	GFF MDI 14.4/9.6 µg
CAB	Placebo MDI	GFF MDI 14.4/9.6 µg	Spiriva 5 µg
CBA	Placebo MDI	Spiriva 5 µg	GFF MDI 14.4/9.6 µg

Abbreviations: ex-actuator= dose delivered from the actuator (ie., mouthpiece) of the metered dose inhaler; GFF MDI=glycopyrronium and formoterol fumarate metered dose inhaler; MDI=metered dose inhaler.
Note: Spiriva inhalation solution 5 µg (tiotropium bromide) ex-actuator used as an active control.

Appendix 8 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 9 Sponsor Signatory

Study Title: A Randomized, Phase IIIb, Three-period, Three-treatment, Double-blind, Multi-center, Crossover Study to Evaluate the 24-hour Lung Function Profile in Subjects with Moderate to Very Severe COPD after 4 Weeks of Treatment with PT003, Open-Label Spiriva® Respimat® (Tiotropium Bromide) as an Active Control, and Placebo

Study Number: PT003011-00

Final Date: [redacted]

Signature [redacted]

Name: [redacted]

Title: [redacted]

Appendix 10 Investigator's Agreement and Signature Page

Study Title: A Randomized, Phase IIIb, Three-period, Three-treatment, Double-blind, Multi-center, Crossover Study to Evaluate the 24-hour Lung Function Profile in Subjects with Moderate to Very Severe COPD after 4 Weeks of Treatment with PT003, Open-Label Spiriva® Respimat® (Tiotropium Bromide) as an Active Control, and Placebo

Study Number: PT003011-00

Final Date: [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: _____