12.1.1 PROTOCOL AND PROTOCOL AMENDMENTS

This appendix includes the following approved original protocol:

- Original Protocol – [redacted]

Clinical Trial Protocol: PT003016-00

Title:	An Open-Label, Multi-Center, Dose Indicator Study of Glycopyrronium and Formoterol Fumarate (GFF) Metered Dose Inhaler (MDI) in Adult Subjects with Moderate to Very Severe Chronic Obstructive Pulmonary Disease (COPD)
Study Number:	PT003016-00
Study Phase:	IIIb
Product Name:	Glycopyrronium and Formoterol Fumarate Inhalation Aerosol; PT003
IND Number	107739
Indication:	COPD
Investigators:	Multicenter
Sponsor:	Pearl Therapeutics, Inc. [redacted]
Sponsor Contact	[redacted]

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

Confidentiality Statement

SYNOPSIS

Sponsor: Pearl Therapeutics, Inc.
Names of Finished Products: Glycopyrronium and Formoterol Fumarate Inhalation Aerosol; PT003
Name of Active Ingredients: Glycopyrronium Formoterol Fumarate
Title: An Open-Label, Multi-Center, Dose Indicator Study of Glycopyrronium and Formoterol Fumarate (GFF) Metered Dose Inhaler (MDI) in Adult Subjects with Moderate to Very Severe Chronic Obstructive Pulmonary Disease (COPD)
Study Number: PT003016-00
Study Phase: IIIb
Primary Objective: The primary objective of this study is to evaluate the performance of the dose indicator over the life of GFF MDI under normal subject handling conditions.
Safety Objective: To assess the safety of GFF MDI based on reported adverse events (AEs), vital sign measurements, ECGs, and clinical laboratory evaluations.
Study Design: This is an open-label, multi-center study to evaluate the accuracy, reliability and functionality of GFF MDI dose indicator in adult subjects with moderate to very severe COPD over a 4-week Treatment Period. This multi-center study will be conducted at approximately 10 sites, contributing approximately 15 subjects per site. Across these sites, it is planned that approximately 125 subjects who have an established clinical history and classification of moderate to very severe COPD will be enrolled and that at least 100 subjects will complete the study. The entire study period is scheduled to take approximately 6 weeks for each subject. The study is anticipated to run for approximately 6 months.
Number of Subjects: Approximately 125 subjects with moderate to very severe COPD will be enrolled to provide at least 100 subjects who complete the study.
Test Product, Dose, and Mode of Administration: Subjects will administer two actuations of GFF MDI by oral inhalation, twice daily (BID), approximately 12 hours apart.

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

Product Name & Dose	Product Strength	Dosage Form/ Fill Count	Administration
Study Medication			
GFF MDI 14.4/9.6 µg ex-actuator	GFF MDI 7.2/4.8 µg per actuation Each inhalation contains 9.0 µg of glycopyrronium bromide corresponding to 7.2 µg glycopyrronium per actuation	1 MDI 120 inhalations	Taken as 2 inhalations BID
Placebo			
Placebo MDI†	Formulation does not contain active ingredient	1 MDI 120 inhalations	Taken as 2 inhalations BID
Open-label Products			
Albuterol Sulfate inhalation aerosol‡ 90 µg	US source: Ventolin® HFA Each inhalation contains 108 µg corresponding to 90 µg albuterol base per actuation	1 MDI 60 or 200 actuations	Taken as directed Supplies are open-label
Ipratropium Bromide HFA inhalation aerosol§ 34 µg ex-actuator	US source: Atrovent HFA 17 µg per actuation	1 MDI 200 actuations	Taken as 2 inhalations Supplies are open-label QID

GFF MDI = Glycopyrronium and Formoterol Fumarate Metered Dose Inhaler; HFA= hydrofluoroalkane; MDI = Metered Dose Inhaler.

†Will be used during the Screening Period to assess compliance

‡ Will be used as rescue medication during the study

§ Will be used QID for COPD maintenance therapy during the Screening Period.

Duration of Treatment:

Each eligible subject entered into the study will receive study treatment for 4 weeks. The planned study duration is approximately 6 weeks, comprising of a 7- to 14-day Screening Period and a 4-week Treatment Period.

Study Endpoints:

Primary Dose Indicator Endpoint

Percentage of devices where the number of actuations as counted at the end of the study using the dose indicator reading is consistent (± 20 actuations) with the number of actuations reported by the subject.

Secondary Dose Indicator Endpoints

- Percentage of devices where the number of actuations as counted at the end of the study using the dose indicator reading is consistent (± 20 actuations) with the number of actuations used as estimated by the change in MDI weight
- Percentage of devices where the number of actuations as counted at the end of the study using the lab-advanced dose indicator reading is consistent (± 20 actuations) with the number of actuations used as reported by the subject
- Percentage of devices where the number of actuations as counted at the end of the study using the lab-advanced dose indicator reading is consistent (± 20 actuations) with the number of actuations used as estimated by the change in MDI weight
- Percentage of devices where the dose indicator actuation count is >20 less than the subject-reported actuation count (undercount)
- Number of correct advances (±2 actuations) of the dose indicator based on subject reported use
- Percentage of correct advances (±2 actuations) = 100 x (correct advances/total advances) based on subject reported use
- Number of correct advances (±4 actuations) of the dose indicator based on subject reported use
- Percentage of correct advances (±4 actuations) = 100 x (correct advances/total advances)

Other Dose Indicator Endpoints

- Percentage of consistent (± 20 actuations) devices at each visit for:
  - The dose indicator reading compared to the number of actuations reported by the subject
  - The dose indicator reading compared to the number of actuations used as estimated by the change in MDI weight
  - The lab-advanced dose indicator reading compared to the number of actuations reported by the subject
  - The lab-advanced dose indicator reading compared to the number of actuations used as estimated by the change in MDI weight

Safety Endpoints

The safety endpoints for this study will include AEs, vital sign measurements, ECGs, and clinical laboratory evaluations.

Statistical Methods:

The primary assessment of dose indicator accuracy for each device will be based on a comparison of the number of actuations used according to the dose indicator as inferred from the electronic case report form (eCRF) with the number of actuations reported by the subject using the eDiary. The two counts will be considered to be in agreement when the dose indicator count is within ±20 actuations of the diary count. The dose indicator count will also be compared to the weight-based actuation count. Agreement will be achieved when the dose indicator count is within ±20 actuations of the weight-based count. Supportive analyses will include comparisons of the lab-advanced count to the subject-reported and weight-based counts. For each pairwise comparison, the overall number and percentage of devices with agreement will be calculated and summarized. As a subset to the primary analysis, the number and percentage of devices for which the dose indicator undercounts the number of actuations by more the 20 counts as compared to the subject-reported count will also be tabulated. The sample size of approximately 125 enrolled subjects was chosen to ensure adequate subject experience using the GFF MDI with integrated dose indicator and provide a satisfactory estimate of the percent of devices with agreement between the dose indicator and subject-reported counts.
Draft Synopsis Date: [redacted]

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	Adverse event
BID	bis in die, Twice Daily
CFR	Code of Federal Regulations
CHF	Congestive Heart Failure
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eDiary	Electronic Diary
eg	Exempli gratia, for example
ERS	European Respiratory Society
FDA	Food and Drug Administration
FEV1	Forced Expiratory Volume In 1 Second
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GFF MDI	Glycopyrronium and Formoterol Fumarate MDI
GP MDI	Glycopyrronium MDI
HFA	Hydrofluroalkane
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ICMJE	International Committee of Medical Journal Editors
ICS	Inhaled Corticosteroid
ie	Id est, that is
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITT	Intention-to-treat
IWRS	Interactive Web Response System

L	Liter
LABA	Long-acting Beta Agonist
LAMA	Long-acting Muscarinic Antagonist
LTOT	Long Term Oxygen Therapy
MDI	Metered Dose Inhaler
MedDRA	Medical Dictionary for Regulatory Activities
mL	Milliliter
Msec (ms)	Millisecond
NHANES III	Third National Health and Nutrition Examination Survey
PFT	Pulmonary Function Test
PIN	Personal identification number
PRN	pro re nata, As Needed
QID	quater in die; Four Times Daily
SABA	Short-acting Beta Agonist
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOP	Standard Operating Procedure
TNF α	Anti-tumor Necrosis Factor α
US	United States

Definition of Special Terms

Ex-actuator	Dose Delivered from the Actuator (ie, mouthpiece) of the MDI

TRADEMARK INFORMATION

Trademarks Not Owned By Pearl Therapeutics

Atrovent

Combivent

Spiriva

Ventolin

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%-10% (Halbert, 2003 and 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 not only a smoker's disease with familial origins, but one that worsens with age.

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 ventilatory 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 in activated 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 (GOLD, 2014).

Combivent® [salbutamol sulfate and ipratropium bromide] is a short-acting fixed dose combination of a SABA and short acting muscarinic antagonist indicated for the treatment of COPD and is administered as two inhalations four times daily. Published studies (van Noord 2005; van Noord , 2006; Vogelmeier, 2008) have shown that the complementary mechanisms of action of a LABA (formoterol fumarate) and a LAMA (tiotropium bromide) significantly improved bronchodilation in COPD subjects compared to the individual agents.

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.

Formoterol fumarate (FF) is a potent and selective LABA approved in many countries worldwide for use in asthma and COPD. When inhaled, FF acts locally in the lung as a bronchodilator. Formoterol fumarate stimulates β2 adrenoreceptors in the airways, inducing airway smooth muscle relaxation and reducing or preventing bronchoconstriction.

Pearl Therapeutics is developing a combination product, Glycopyrronium and Formoterol Fumarate Inhalation Aerosol (hereafter referred to as GFF MDI), as a maintenance bronchodilator treatment in patients with COPD in parallel with individual agents. Nine different doses of GFF MDI (115.2/38.4 µg ; 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) have been evaluated in six studies, including two single dose, single center, healthy volunteer studies, and four multicenter studies in COPD subjects. The chronic dosing Phase IIb studies included three studies of 1-week duration and one cardiovascular safety study of 2-week duration. Throughout the Phase IIb program, more than 300 subjects with COPD have been exposed to one or more doses of GFF MDI. Three ongoing, multicenter, Phase III studies are currently being conducted evaluating more than 4000 subjects with COPD. Please refer to the GFF MDI, GP MDI, and FF MDI Investigator Brochure for additional information and study results.

Pearl Therapeutics has recently changed the naming convention for GFF MDI to make reference to the active moiety – glycopyrronium – instead of the bromide salt form previously used (glycopyrronium bromide, also known as glycopyrrolate). There have been no changes made to formulation of GFF MDI, just a change in how the strength/dose is expressed. All references to strengths/doses of GFF MDI in this protocol are based on the mass of glycopyrronium. In all completed clinical studies, Pearl Therapeutics expressed the strengths/doses of GFF MDI based on the mass of glycopyrrolate (glycopyrronium bromide), which is the bromide salt form of the active material. The dose of glycopyrronium (14.4 µg) in GFF MDI is equivalent to 18 µg of glycopyrrolate (glycopyrronium bromide). A more detailed description of the studies and results, as well as ongoing Phase III programs, can be obtained in the Investigator Brochure (IB).

1.1 Study Rationale

In the FDA's 2003 guidance, Integration of Dose-Counting Mechanisms into MDI Drug Product, it states that documentation of dose counter functionality, reliability, and accuracy would ideally be derived from assessments in clinical trials including, where possible, Phase-III trials. In order to meet FDA expectations, Pearl Therapeutics has been performing a count accuracy assessment of inhalers from their Phase III clinical studies, Study PT003006 and Study PT003007. All metered dose inhaler (MDI) product types first used by subjects in these clinical studies, GFF MDI; Glycopyrronium (GP MDI); FF MDI; and Placebo, are being tested using information from the electronic case report form (eCRF) and the electronic diary (eDiary). The number of actuations as reported by the subjects are calculated and compared to the number of actuations used as derived from the dose indicator reading.

Discrepancies greater than +/- 20 counts will be deemed inaccurate. From a preliminary blinded review of these data, Pearl Therapeutics has recognized that further alignment in their methodology and approach was needed, and has planned to conduct this focused study in order to obtain more accurate assessments of the dose indicator. The additional testing to be conducted in this study will include advancing the dose indicator to the next decrement in order to obtain an accurate dose indicator count and to estimate the number of doses taken based on MDI weight. This protocol outlines the sampling and testing plans for obtaining additional dose indicator accuracy data.

2 STUDY OBJECTIVE

The primary objective of this study is to evaluate the performance of the dose indicator over the life GFF MDI under normal handling conditions.

2.1 Safety Objectives

To assess the safety of GFF MDI based on reported adverse events (AEs), vital sign measurements, ECGs, and clinical laboratory evaluations.

3 STUDY ENDPOINTS

3.1 Primary Dose Indicator Endpoint

Percentage of devices where the number of actuations as counted at the end of the study using the dose indicator reading is consistent (± 20 actuations) with the number of actuations reported by the subject.

3.2 Secondary Dose Indicator Endpoints

- Percentage of devices where the number of actuations as counted at the end of the study using the dose indicator reading is consistent (± 20 actuations) with the number of actuations used as estimated by the change in MDI weight
- Percentage of devices where the number of actuations as counted at the end of the study using the lab-advanced dose indicator reading is consistent (± 20 actuations) with the number of actuations used as reported by the subject
- Percentage of devices where the number of actuations as counted at the end of the study using the lab-advanced dose indicator reading is consistent (± 20 actuations) with the number of actuations used as estimated by the change in MDI weight
- Percentage of devices where the dose indicator actuation count is >20 less than the subject-reported actuation count (undercount).
- Number of correct advances (±2 actuations) of the dose indicator based on subject reported use
- Percentage of correct advances (±2 actuations) = 100 x (correct advances/total advances) based on subject reported use
- Number of correct advances (±4 actuations) of the dose indicator based on subject reported use
- Percentage of correct advances (±4 actuations) = 100 x (correct advances/total advances)

3.3 Other Dose Indicator Endpoints

- Percentage of consistent (± 20 actuations) devices at each visit for:
  - The dose indicator reading compared to the number of actuations reported by the subject
  - The dose indicator reading compared to the number of actuations used as estimated by the change in MDI weight
  - The lab-advanced dose indicator reading compared to the number of actuations reported by the subject
  - The lab-advanced dose indicator reading compared to the number of actuations used as estimated by the change in MDI weight

3.4 Safety Endpoints

The safety endpoints for this study will include AEs, vital sign measurements, 12-Lead ECGs, and clinical laboratory test results.

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

This is an open-label, multi-center study to evaluate the accuracy, reliability and functionality of GFF MDI dose indicator in adult subjects with moderate to very severe COPD over a 4-week Treatment Period.

This multi-center study will be conducted at approximately 10 sites, contributing approximately 15 subjects per site. Across these sites, it is planned that approximately 125 subjects who have an established clinical history and classification of moderate to very severe COPD will be enrolled, and that at least 100 subjects will complete the study.

The entire study period is scheduled to take approximately 6 weeks for each individual subject. The study is anticipated to run for approximately 6 months.

4.1.1 Visit 1 - Screening Period (Day -14 to Day -1)

Prior to or at the Screening visit (Visit 1), all subjects will be required to sign an informed consent form prior to the conduct of any screening procedures. Subjects will be required to report to the clinic in the morning of Visit 1 and Visit 2.

Subject enrollment will be centralized through the use of an Interactive Web Response System (IWRS).

Subjects who meet all inclusion and exclusion entry criteria but are using certain prohibited COPD medications (eg., oral β_2-agonists, LABAs), cromoglycate or nedocromil inhalers, leukotriene antagonists (eg., zafirlukast, montelukast, zileuton), aclidinium, tiotropium, fixed-dose combination treatment with an inhaled corticosteroid (ICS), will discontinue these medications for the duration of the trial and be switched to Sponsor-provided Atrovent HFA MDI administered four times daily (QID) and Sponsor-provided rescue Ventolin HFA MDI to be used as needed to control symptoms. Refer to Section 5.4 for a list of prohibited COPD medications in this study.

Demographic information, medical/surgical history, physical examination, vital signs and lab assessments will be recorded. Pregnancy testing will be performed in female subjects, if applicable.

Subjects will be issued and trained on electronic diary (eDiary) use and instructed on how to record information during the Screening period.

A Sponsor-provided Placebo MDI will be issued, and subjects will be trained on its use and how to read and record information from the dose indicator during the Screening period. Appendix 1 provides instructions on MDI usage and cleaning. Appendix 4 provides instructions on how to read the dose indicator.

The Investigator or qualified designee will record the Placebo MDI dose indicator reading in the source/eCRF. Four priming shots will then be performed. (**Note:** The dose indicator reading should be recorded **prior to** the 4 priming shots). Based on weighing procedures in the User's Manual* of the Sponsor-provided scale, the Investigator or qualified designee will weigh the Placebo MDI (canister in the MDI without the cap in place) and record the weight in the source/eCRF.

***Note**: Sponsor will provide all sites with a scale and User's Manual, and will also provide procedural instructions for weighing and recording of the MDIs.

Under the supervision of site personnel, the subject will record the Placebo MDI dose indicator reading in their eDiary prior to dosing. Subjects will then administer two inhalations from the Placebo MDI and record the time of dosing, the number of actuations, and the dose indicator reading following dosing in their eDiary.

Subjects will use the Placebo MDI throughout the remainder of the Screening period and be instructed to take study medication twice daily, 2 puffs in the morning and 2 puffs in the evening approximately 12 hours apart, and record the dose indicator readings in their eDiary before and after each dose (two inhalations) until the subject returns to the clinic for their next visit.

During the Screening Period (between Visits 1 and 2), subjects will be issued Sponsor-provided Atrovent HFA MDI to be taken four times daily (QID), and Sponsor-provided rescue Ventolin HFA MDI, to be taken as needed to control symptoms.

4.1.2 Visit 2 - Study Treatment Period (Day 1)

At Visit 2, subjects will return to the clinic in the morning, return the Atrovent HFA used during the Screening period, and be reassessed for continued eligibility.

The Investigator or designee will assess the subject's COPD status and determine if any AEs have developed since the Screening visit. Safety assessments will continue throughout the study and be evaluated by the Investigator.

The Investigator or designee will check that the subject is using the eDiary correctly and will retrain the subject, as needed, to ensure compliance throughout the study. The subject's eDiary will be reviewed, and those subjects who are unable to meet the compliance requirement (>80% completion of diary assessments), will be considered a screen failure.

In addition, if the subject's reported count during Visit 1 (Screening) using the Placebo MDI is greater than an absolute difference of 6-actuations from the weight based count, the subject has not met compliance-based entry criteria and will be given one more opportunity to meet this compliance requirement, will be reissued a new Placebo MDI, and will be required to return to the clinic in 1 week (Visit 1b). If a subject fails to meet these criteria after the second attempt, they will be considered a screen failure.

Subjects eligible for entry into the Treatment period will be trained in the clinic on the proper cleaning techniques for the MDI using the Placebo MDI dispensed during the Screening period (see Appendix 1).

Subject enrollment will be centralized through the use of an IWRS, and a kit number will be assigned.

A Sponsor-provided GFF MDI will be issued, and subjects will be trained on its use, and how to read and record information from the dose indicator during the Treatment period (see Appendix 4).

The Investigator or qualified designee will record the GFF MDI dose indicator reading in the source/eCRF. Four priming shots will then be performed. (**Note:** The dose indicator reading should be recorded **prior to** the 4 priming shots). Based on weighing procedures in the User's Manual of the Sponsor-provided scale, the Investigator or qualified designee will weigh the Placebo MDI (canister in the MDI without the cap in place) and record the weight in the source/eCRF.

Under the supervision of site personnel, the subject will record the GFF MDI dose indicator reading in their eDiary prior to dosing. Subjects will then administer two inhalations from the GFF MDI, and record the time of dosing, the number of actuations, and the dose indicator reading following dosing in their eDiary.

Subjects will use the GFF MDI throughout the remainder of the study Treatment period and be instructed to take study medication twice daily, 2 puffs in the morning and 2 puffs in the evening approximately 12 hours apart, until their next clinic visit. Subjects will be instructed to record the time of dosing, the number of actuations, and the dose indicator readings (both before and after dosing) in their eDiary until the subject returns to the clinic for their next visit.

4.1.3 Visits 3, 4, 5 - Treatment Period (Day 8, Day 15, Day 22)

At each treatment visit (Visit 3, Visit 4, and Visit 5), subjects will return to the clinic and be reassessed for eligibility to continue in the study.

The Investigator or designee will review and record any worsening of COPD symptoms and AEs. Safety assessments will continue throughout the study and be evaluated by the Investigator.

Subject eDiary compliance will be reviewed by site personnel and eDiary dose indicator information will be recorded in the source/eCRF at each visit. The Investigator or qualified designee will ask the subject if cleaning has been performed, if any unrecorded sprays or actuations have occurred, if there are any problems with using the inhaler, and if any incidents have occurred (ie., dropping or unintentional disassembly).

Based on weighing procedures in the User's Manual of the Sponsor-provided scale, the Investigator or qualified designee will weigh the GFF MDI and record the MDI weight in the source/eCRF at each visit.

Subjects will be instructed to clean the GFF MDI weekly after the evening dosing on the day of Visits 3, 4, and 5. The number of actuations and dose indicator readings (before and after priming) following MDI cleaning will be recorded in their eDiary.

4.1.4 Visit 6 - Final Visit (Day 29)

Subjects will return to the clinic and be reassessed for eligibility. The Investigator or designee will review and record any worsening of COPD symptoms and AEs.

Subjects eDiary compliance will be reviewed by site personnel and eDiary dose indicator information will be recorded in the source/eCRF. Based on weighing procedures in the User's Manual of the Sponsor-provided scale, the Investigator or qualified designee will weigh the GFF MDI and record the MDI weight in the source/eCRF.

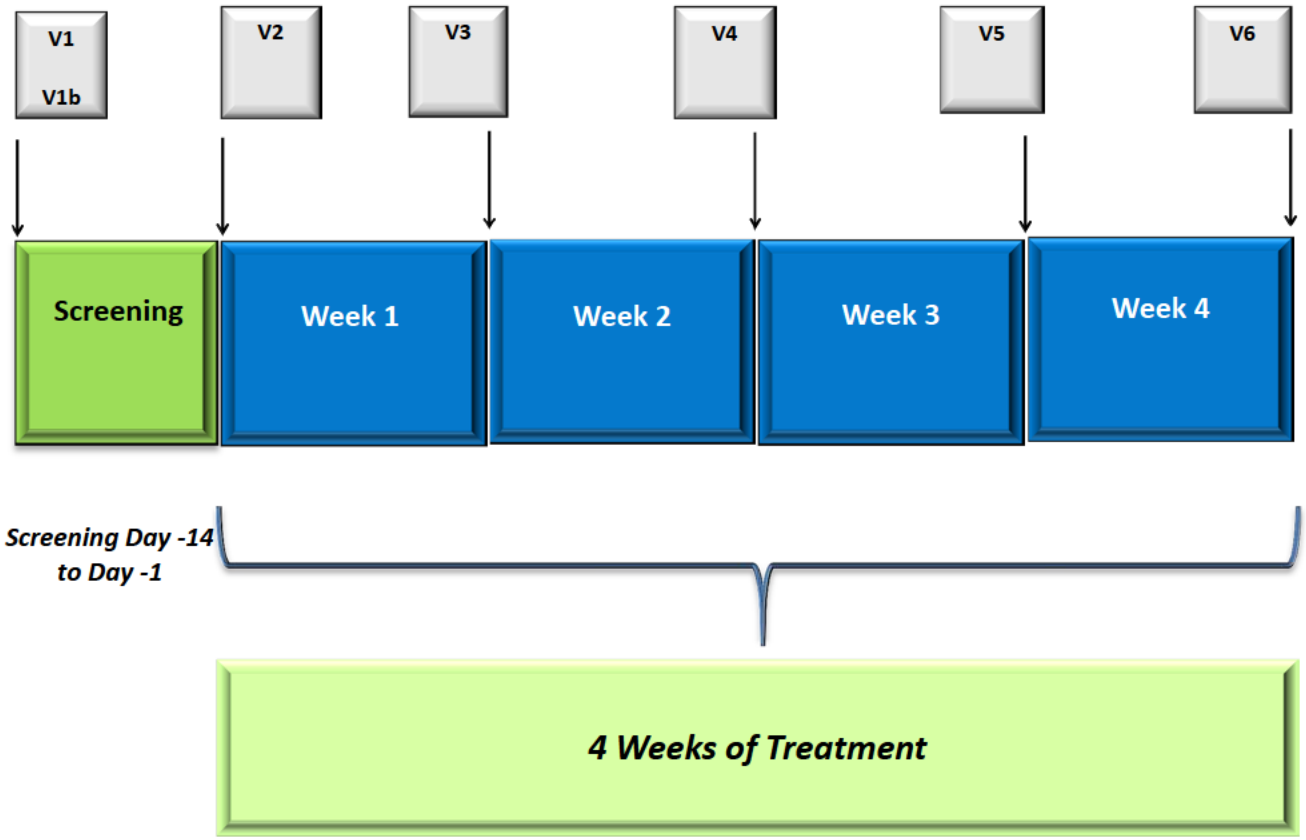
All study-related medication and supplies will be collected. After all study-related procedures have completed, subjects be returned to pre-study or appropriate maintenance COPD medications.

Any study discontinuations will be captured as an unscheduled visit.

For more details of each scheduled procedure and visit, refer to the Section 7, the Schedule of Events table (Table 8-1), and Sections 8.1 through 8.9.

A Study Flow Diagram is displayed in Figure 4-1.

Figure 4-1. Study Flow Diagram



5 STUDY POPULATION SELECTION AND WITHDRAWAL CRITERIA

5.1 Inclusion Criteria

Subjects eligible for enrollment in the study must 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 1.
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 1 and Visit 6, 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:
    - 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 a minimum 6 months 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. Severity of COPD Disease: A documented or demonstrated moderate to very severe COPD criteria at Screening:
    - FEV_1/FVC ratio of <0.70.
    - Post-bronchodilator FEV_1 must be $\geq 30\%$ and $<80\%$ predicted normal value calculated using the Third National Health and Nutrition Examination Survey (NHANES III) reference equations, and must also be greater than or equal to 750 mL.

    Note: Pulmonary function test assessments required during this study are to be conducted at the Investigator site using site equipment.

6. 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)].
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. **Note**: ECGs required during this study are to be conducted at the Investigator site using site ECG equipment.
10. Chest X-ray or computed tomography (CT) scan of the chest/lungs within 6 months prior to Visit 1 must be acceptable to the Investigator. Subjects who have a chest X-ray (or CT scan) that reveals clinically significant abnormalities not believed to be due to the presence of COPD should not be included. A chest X-ray must be conducted if the most recent chest X-ray or CT scan are more than 6 months old at the time of Visit 1.
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, ie., 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 cause repeated acute exacerbations), sarcoidosis, idiopathic interstitial pulmonary fibrosis (IPF), primary pulmonary hypertension, or uncontrolled sleep apnea (ie., in the opinion of the Investigator severity of the disorder would impact the conduct of the study). **Note:** Allergic rhinitis is not exclusionary.
    d) Lung Volume Reduction: Subjects who have undergone lung volume reduction surgery, lobectomy or bronchoscopic lung volume reduction (endobronchial blockers, airway bypass, endobronchial valves, thermal vapor ablation, biological sealants, and airway implants) within 1 year of Visit 1.
    e) Hospitalization: Subjects who have been hospitalized due to poorly controlled COPD within 3 months prior to Visit 1 (Screening) or during the Screening Period (Visit 1 to Visit 2).

f) Poorly Controlled COPD: Subjects who have poorly controlled or worsening COPD prior to Visit 1 (Screening) or during the Screening Period (Visit 1 to Visit 2).

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

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

i) 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.

j) Change in smoking status (ie., start or stop smoking) during the study.

k) Pulmonary Rehabilitation: Subjects in the acute phase, 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.

4. Cardiac disease

a) Subjects who have unstable ischemic heart disease, left ventricular failure, or documented myocardial infarction within 12 months of enrollment. Subjects with a recent history of acute coronary syndrome, or who have undergone percutaneous coronary intervention or coronary artery bypass graft within the past three 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 (to be conducted at study site using site ECG machines):

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/minute.
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 1.
4. Ventricular rate <45 beats per minute (bpm)

5. Pathological Q waves of 1 year or less
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. **Note**: ECGs are to be conducted at the site by the Investigator using site equipment.

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

5. Neurological
   - Subjects with seizures requiring anticonvulsants within 12 months prior to Visit 1 (Screening). **Note:** Subjects treated with anticonvulsant medication for 12 months or more with no seizure events are eligible.
   - 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 1 or is altered at any point during the Screening Period (Visit 1 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 1 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 1.

      Note: Subjects with overactive bladder syndrome treated with oral anticholinergics that 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 Type 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 1.
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 glaucoma that, in the opinion of the Investigator, has not been adequately treated. All medications approved for control of intraocular pressures are allowed including topical ophthalmic non-selective beta-blockers such as betaxolol, carteolol, levobunolol, metipranolol, and timolol.
11. Drug Allergy: Subjects who have a history of hypersensitivity to β_2-agonists, glycopyrronium or other muscarinic anticholinergics, lactose/milk protein 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. Prohibited Medications: Subjects who, in the opinion of the Investigator, would be unable to abstain from protocol-defined prohibited medications during the Screening period (Visit 1) and treatment phases of this study (Refer to Section 5.4).
14. Non-compliance: Subjects unable to comply with study procedures including non-compliance with diary completion (ie., <80% completion of diary assessments), or discrepancies in MDI actuations vs. weight based count.
15. 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.
16. 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.
17. Subjects using prohibited medications (Refer to Table 5-2).
18. 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 1 (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.
19. 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.
20. Previous Participation: Subjects who were previously randomized in any trial conducted or sponsored by Pearl Therapeutics (PT001, PT003 and PT005) are not allowed to participate in this study. **Note**: Subjects who were screen failures and never randomized in any Pearl Therapeutics trials (PT001, PT003 and PT005) may be enrolled.

5.3 Subject Identification

All Subjects who undergo screening will be assigned a unique screening identification number at the Screening Visit (Visit 1).

5.4 Prior, Concomitant, and Prohibited Medications

All prescription and over-the-counter (OTC) medications taken by the subject within 30 days before Visit 1 (Screening) will be recorded as prior/concomitant medications in the eCRF. Any additions, deletions, or changes in the dose of these medications while in the study

should be entered in the eCRF. Any current ongoing medications, including OTC drugs and herbal supplements, will be allowed provided they are not prohibited by the protocol (Refer to 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 with indication, dose, dose regimen, and dates of drug administration.

5.4.1 Prohibited COPD Medications

The following medications used for the treatment of COPD are not permitted during this study. These medications must be discontinued at Visit 1 (Screening) and are not permitted during the Screening Period (Table 5-1).

Table 5-1. COPD Medications: Required Washout Periods, Pre Visit 1

Required Washout Period Prior to Visit 1:	
Class of medication	**Minimum washout period prior to Visit 1**
Long-acting anticholinergics	14 days
Short-acting anticholinergics	6 hours
LABA/LAMA	3 days
Fixed-combinations of LABA/ICS	7 days
Fixed-combinations of SABAs and short-acting anticholinergics	6 hours
LABA	48 hours (indacaterol 7 days)
SABAs (including study rescue Ventolin HFA)	6 hours
Phosphodiesterase-4 inhibitor	6 days
Theophylline (Total daily dose ≤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

*Theophylline is allowed if the total daily dose is ≤400 mg. Subjects taking roflumilast are allowed provided they have been on stable dose of therapy for at least 2 months prior to study initiation.

Note:

- Subjects who are steroid dependent and maintained on an equivalent of ≤ 5 mg oral prednisone per day or ≤ 10 mg oral prednisone every other day for at least 3 months prior to Visit 1 are eligible providing the dose of oral steroids remains stable during the screening period (Visit 1 to Visit 2).
- During the Treatment Period (Visit 2 to Visit 6), subjects may be treated with corticosteroids if required, and the usage indication can be discussed with the Medical Monitor.

Subjects who meet all entry criteria but are using one or more of the above listed prohibited COPD medications will have their maintenance therapy for COPD adjusted as follows:

- Subjects receiving a maintenance dose of an ICS as part of a fixed dose combination therapy containing fluticasone and salmeterol, mometasone and formoterol, budesonide and formoterol or fluticasone and formoterol must have been on the ICS component for at least 4 weeks prior to Visit 1 (Screening) and maintained on a stable dose for at least 4 weeks prior to Visit 1 (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 rescue Ventolin HFA to be administered as needed for control of symptoms.
- Subjects receiving a maintenance dose of an ICS that is not administered as a fixed-dose combination together with a LABA will be permitted to continue the ICS provided they have been maintained on a stable dose for at least 4 weeks prior to Visit 1 (Screening).
- All subjects treated with either a LABA (eg., salmeterol, formoterol, indacaterol, etc.) or currently marketed long- acting anti-muscarinic agent (LAMA) (tiotropium, aclidinium), 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 rescue Ventolin HFA to be administered as needed for control of symptoms.

Leukotriene antagonists (eg., zafirlukast, montelukast, and zilueton), cromoglycate, nedocromil, and ketotifen are permitted in this study.

5.4.2 Other Prohibited Medications

The following medications should be used under specific conditions during this study: intranasal corticosteroids, intranasal antihistamines or combination, thereof. Each concomitant drug must be individually assessed against all exclusion criteria. If in doubt, the Investigator should contact the Pearl Therapeutics' Medical Monitor before a subject is allowed to continued or a new medication is to be started.

Subjects requiring the following medications are prohibited from this study (Table 5-2). Subjects who recently discontinued use of these medications may be considered for study enrollment providing they have met the minimum washout period prior to Visit 1 (Screening). These medications are prohibited throughout the course of the study, and, should a subject require use of any of the listed medications, they should be discontinued.

Table 5-2. 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

Table 5-2. Prohibited Medications

Prohibited Medications	Minimum cessation period prior to Visit 1 (Screening)
Other investigational drugs	30 days or 5 half-lives whichever is longer
Non-selective beta-blocking agents	7 days
Cardiac antiarrhythmics Class Ia, III	7 days, amiodarone 3 months
Anticonvulsants for seizure disorder	Allowed if stable dose for 12 months and free of seizures for 1 year
Anticonvulsants for other indications	Allowed if stable dose for at least 3 months and the Investigator confirms there have been no seizures within the past 12 months.
Tricyclic antidepressants	14 days
Monoamine oxidase inhibitors	14 days
Anti-tumor necrosis factor α (TNF α) antibodies (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 1) to the end of Visit 6 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.

5.6 Smoking Status

Current and former smokers are permitted.

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 Therapeutics at any time or for any reason. 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, regardless of the cause, should undergo the assessments outlined in Section 8.8 on the date of discontinuation. Subjects who suffer a moderate exacerbation will remain in the study and continue to take their assigned study drug unless the Investigator decides that it is in the best interest of the subject to discontinue early from the study. Any subject who suffers a severe exacerbation (requiring hospitalization) will be discontinued. Subjects who suffer more than two moderate COPD exacerbations will be discontinued from the study.

An 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 or more days, is beyond normal day-to-day variations, is acute in onset and may warrant a change in regular medication. The severity of 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 requires treatment with systemic steroids and/or antibiotics, and do not result in hospitalization or death.
- Severe: exacerbations that result in hospitalization or death.

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

- Initiation of maintenance therapy with any prohibited medications as listed in Table 5-2
- Initiation of maintenance therapy with a marketed LABA (eg., salmeterol, formoterol, indacaterol, olodaterol, vilanterol) administered alone or in combination with an ICS or a marketed LAMA (eg., tiotropium, aclidinium, umeclidinium).

If a female subject becomes pregnant during the course of the study, the subject will be discontinued (see Section 7.2.8).

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

6.1 Subject Information

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

6.2 Product Descriptions

Investigational materials will be provided by Pearl Therapeutics as summarized in Table 6-1.

Table 6-1. Product Descriptions

Product Name & Dose	Product Strength	Dosage Form/ Fill Count	Administration
Study Medication			
GFF MDI 14.4/9.6 µg ex-actuator	GFF MDI 7.2/4.8 µg per actuation Each inhalation contains 9.0 µg of glycopyrronium bromide corresponding to 7.2 µg glycopyrronium per actuation	1 MDI 120 inhalations	Taken as 2 inhalations BID
Placebo			
Placebo MDI†	Formulation does not contain active ingredient	1 MDI 120 inhalations	Taken as 2 inhalations BID
Open-label Products			
Albuterol Sulfate inhalation aerosol‡ 90 µg	US source: Ventolin® HFA Each inhalation contains 108 µg corresponding to 90 µg albuterol base per actuation	1 MDI 60 or 200 actuations	Taken prn as directed, Supplies are open-label
Ipratropium Bromide HFA inhalation aerosol§ 34 µg ex-actuator	US source: Atrovent HFA 17 µg per actuation	1 MDI 200 actuations	Taken as 2 inhalations. Supplies are open-label QID

GFF MDI = Glycopyrronium and Formoterol Fumarate Metered Dose Inhaler; HFA= hydrofluoroalkane; MDI = Metered Dose Inhaler.

†Will be used during the screening period to assess compliance

‡ Will be used as rescue medication during the study

§ Will be used QID for COPD maintenance therapy during the screening period.

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

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

6.3 Primary Packaging and Labeling Information

Investigational materials will be packaged by Pearl Therapeutics which will include GFF MDI, Atrovent HFA and Ventolin HFA supplied as open-label MDIs.

GFF MDI and Placebo MDI Supplies: Each MDI will be labeled with a single label. The MDI actuator will be labeled with a single label. The foil pouch will be labeled with a single label.

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

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

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

6.4 Secondary Packaging and Box-labeling Information

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

Table 6-2. Description of Boxes

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

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

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

6.5 Emergency Unblinding of Treatment Assignment

Not applicable.

6.6 Storage Requirements

GFF MDI and Placebo MDI Supplies: Clinical supplies should be kept in a secured location at room temperature (Store at 20° - 25°C; excursions permitted to 15°C - 30°C). Do not refrigerate or freeze.

Ventolin HFA supplies: Store between 15° and 25°C (59° and 77°F). Store the inhaler with the mouthpiece down. For best results, the inhaler should be at room temperature before use. Do not use or store near heat or open flame. Exposure to temperatures above 120 °F (49 °C) may cause bursting. Never throw into a fire or incinerator.

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

The clinical supplies storage area at the site must be monitored by the site staff for temperature consistency with the acceptable storage temperature range specified in this

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

6.7 Instructions for Preparation of Treatments for Administration and Dispensing

6.7.1 GFF MDI and Placebo MDI

Individual GFF MDI and Placebo MDI 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 onto the IWRS confirmation report.

All MDI devices must be primed before the first use. Priming involves releasing a certain number of sprays (4) into the air before the first use of the inhaler. Shaking and priming the inhaler fills a chamber inside the canister with the correct dose and mix of medication so that the inhaler is ready to use.

The MDI must be primed in a separate room from the subject treatment area. Each dose will consist of 2 puffs from the MDI. Subjects will be dispensed the MDI and instructed to continue taking study medication twice daily, 2 puffs in the morning and 2 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. Refer to Appendix 1 for instructions on the administration and cleaning of the GFF and Placebo MDIs.

6.7.2 Atrovent HFA (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 identification (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 onto the IWRS confirmation report.

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 2 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 2 test sprays into the air away from the face. Subjects should avoid spraying Atrovent HFA into their eyes.

Subjects will be dispensed the Atrovent HFA for COPD maintenance therapy during screening period (between Visit 1 and 4) per the manufacturer's instruction, 2 puffs with each administration four times a day, approximately 6 hours apart. The MDI should be stored at room temperature by the subject, avoiding temperature extremes and storage in direct sunlight. Refer to Appendix 2 for the manufacturer's instructions on the administration of Atrovent HFA.

6.7.3 Ventolin HFA (Albuterol Sulfate)

Open-label Ventolin HFA will be provided by Pearl Therapeutics 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. Refer to Appendix 3 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(s) allow the study drug to be used other than as directed by this protocol.

Investigational clinical supplies must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secure 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 Therapeutics, the amount dispensed to and returned by the subject, and the amount remaining at the conclusion of the study. Study medication should be handled in accordance with Good Pharmacy Practices (ie., gloves should always be worn by study personnel if directly handling tablets or capsules that are returned). 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 Therapeutics.

Sites should check with the Pearl Therapeutics 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 deemed eligible to continue with the study. Any deviation from this must be discussed with the Clinical Monitor.

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

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

7 STUDY PROCEDURES

A schedule of procedural events is provided in Table 8-1.

7.1 Dose Indicator Assessments

7.1.1 Recording of Dose Indicator Reading

The GFF MDI and Placebo MDI are fitted with a dose indicator to track the use of the MDI. Accuracy, reliability and functionality of the dose indicator will be evaluated in all subjects enrolled throughout the treatment period (Visits 3-6 [Days 8-29]). Subjects will be trained by site personnel and instructed to record the dose indicator reading (before and after dosing) in their eDiary.

At Visit 1 through Visit 6, or at a Premature Discontinuation Visit, if applicable, site personnel will record the dose indicator reading of the Placebo MDI or GFF MDI in the source/eCRF source.

If the subject's reported count during Visit 1 (Screening period) using the Placebo MDI is greater than an absolute difference of 6-actuations from the weight based count, the subject has not met compliance-based entry criteria and will be given one more opportunity to meet this compliance requirement, will be reissued a new Placebo MDI, and will be required to return to the clinic in 1 week. If a subject fails to meet these criteria after the second attempt, they will be considered a screen failure.

At Visit 2 through Visit 6, the site staff will compare the dose indicator reading entered in the subject eDiary with the dose indicator reading recorded by the site staff in the source/eCRF. For major discrepancies (ie., >20 puff difference), the site staff will review the major discrepancy with the subject and document the reason for any major discrepancy in the appropriate study source and source/eCRF. If appropriate, site staff will re-train the subject on the proper recording of dose indicator reading and/or proper use of the MDI.

7.1.2 MDI Weighing Procedures

All sites will be provided with a scale and User's Manual, and will also be provided with procedural instructions for weighing and recording of the MDIs.

The Investigator or a qualified designee will weigh the Placebo MDI (used during Screening period to Visit 2) and GFF MDI (used from Visit 2 through Visit 6), based on the weighing procedures detailed in the User's Manual of the Sponsor-provided scale, and record the MDI weight in the source/eCRF.

7.1.3 Subject Electronic Diary Data Collection

Subjects will be provided with an eDiary to record time of study medication administration, the number of actuations used (including priming shots before and after cleaning), and dose indicator readings (both before and after dosing), to be completed twice daily.

Before issuing the eDiary to the subject, site personnel will be responsible for programming the eDiary and training subjects on eDiary use at Visit 1 (Screening). Subjects will be instructed to begin collecting information during the Screening Period.

Electronic Diary Compliance Requirement: Subject participation may be terminated at any time during the study for the following reason:

- Chronic failure, in the judgment of the Investigator, to comply with eDiary compliance, despite documentation at the site of repeated efforts to reinforce compliance. As defined for this study, compliance requires >80% subject completion of eDiary assessments. The Sponsor may also instruct a site to discontinue a subject based on consistent noncompliance.
- Subjects who are unable to meet the compliance requirement (>80% subject completion of eDiary assessments) will be considered a screen failure.

In-clinic dosing times and dose indicator readings will be documented in the eCRF by the site staff.

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

7.1.4 Medication Compliance

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

7.2 Safety Assessments

The safety assessments include physical examination findings, medical and surgical history, vital signs, ECGs, clinical laboratory tests in addition to recording of AEs.

7.2.1 Medical/Surgical History and Physical Examination

Medical history, including specific cardiovascular history details, will be collected at Visit 1 (Screening) and updated during the Screening Period. The number of COPD exacerbations requiring oral steroids and/or oral antibiotics, or hospitalization within 12 months of Visit 1 (Screening) will be collected. A complete physical examination will be performed at Visit 1 (Screening) and at Visit 6 (Final Visit) or at the Premature Discontinuation Visit, if applicable. A complete physical examination will include evaluation of 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 Visit 1 (Screening) and Visit 6 (Final Visit) only. Height will be recorded at Visit 1 (Screening) only

7.2.1.1 Pregnancy Test

A serum pregnancy test will be performed at the study site in women of child-bearing potential and pre-menopausal women who are not surgically sterile, at Visit 1 (Screening) and at the Last Visit (Visit 6) or at the Premature Discontinuation Visit, if applicable. If the test is positive, the subject must be discontinued from the study. The pregnancy test should be performed prior to any ECG or blood collection for laboratory assessments.

7.2.2 Vital Sign Measurements

Heart rate, systolic blood pressure (SBP), diastolic blood pressure (DBP), and temperature will be obtained at Visit 1 (Screening) and at the Last Visit (Visit 6), or at the Premature Discontinuation Visit, if applicable. Assessments may be obtained in either the supine or seated position for 5 minutes.

7.2.3 12-Lead Electrocardiogram

If applicable, an ECG will be obtained at the Visit 1 (Screening), Visit 2, and at the Final Visit (Visit 6), or at the Premature Discontinuation Visit. ECGs will be performed at the Investigator sites using site equipment. The ECG parameters that will be assessed include heart rate, PR interval, QRS axis, QRS interval, and QT/QTcF interval.

7.2.4 Clinical Laboratory Tests

Clinical safety laboratory tests will be analyzed by a central laboratory according to standardized, validated assays. The laboratory will supply detailed instructions and all containers for blood and urine investigations. Blood sample volumes will meet the laboratory's specification. All clinical laboratory tests will be obtained at Visit 1 (Screening) and at the Final Visit (Visit 6), or at the Premature Discontinuation Visit, if applicable.

The central laboratory will supply procedures for the preparation and collection of these samples.

Table 7-1. Lab Parameters

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 Blood Chemistry	
Liver Enzyme and Other Function Tests	**Other Clinical Blood Chemistry**
Alanine aminotransferase	Albumin
Aspartate aminotransferase	Calcium[a]
Alkaline phosphatase	Chloride[a]
Bilirubin, total	Cholesterol
Gamma-glutamyl transferase	Bicarbonate
	Creatinine[a]
	Glucose[a]
	Magnesium
	Potassium[a]
	Phosphate
	Protein, total
	Sodium[a]
	Triglycerides
Other Tests:	
Pregnancy test (women of childbearing potential only): serum (human chorionic gonadotropin) at Visit 1 (Screening) and Final Visit (Visit 6) only.	
Creatinine clearance will be estimated by the CKD-EPI formula.	

Abbreviations: CKD-EPI=Chronic Kidney Disease Epidemiology Collaboration (according to National Kidney Disease Education Program)

[a] Parameters included in the Basic Metabolic Panel.

7.2.4.1 Hematology

Hematology will be measured at Visit 1 (Screening) and at the Last Visit (Visit 6), or the Premature Discontinuation Visit, if applicable.

7.2.4.2 Clinical Chemistry

Clinical chemistry will be measured at Visit 1 (Screening) and at the Last Visit (Visit 6), or the Premature Discontinuation Visit, if applicable.

7.2.5 COPD Exacerbations

Site personnel will evaluate whether the subject has experienced a worsening of their COPD that meets the definition of a COPD exacerbation since their last visit. An exacerbation will be defined as a change in the patient's baseline dyspnea, cough, and/or sputum (increase in volume or change in color towards purulence) that lasts 3 or more days, is beyond normal day-to-day variations, is acute in onset and may warrant a change in regular medication.

All COPD exacerbations will be reported as AEs unless considered an SAE.

7.2.6 Adverse Events

7.2.6.1 Performing Adverse Events Assessments

The Investigator is responsible for promptly documenting and reporting all AEs observed during the study in the subject's case report form and on the AE Reporting Form. If the AE is "alarming," the Investigator must report the AE immediately to Pearl Therapeutics. In addition, certain AEs (as described in Section 7.2.6.8) are classified as "serious" and must be reported no later than 24 hours after the Investigator recognizes/classifies the event as a serious adverse event to Pearl Therapeutics or its designee.

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

7.2.6.2 Adverse Event Definitions

The following definitions of terms are guided by the International Conference on Harmonization (ICH) and the US Code of Federal Regulations [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 adverse event (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 adverse event 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 leads to the procedure is an AE (eg., bleeding esophageal varices, dental caries).
- Overdose of either study drug or concurrent medication without any clinical signs or symptoms.
- Non-clinically significant abnormal laboratory values. (If accompanied by signs/symptoms, the signs or symptoms are considered an AE).

7.2.6.3 Pre-Study Initiation Adverse Events

Adverse events that occur between the time subject signs the informed consent form for the study and the time when that subject is randomized into the study will be summarized as medical history and not as a treatment emergent adverse event unless the event meets the definition of an SAE, defined, as follows:

7.2.6.4 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.

7.2.6.5 Relationship

The relationship of each adverse event 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.

7.2.6.6 COPD Exacerbations

COPD exacerbations are expected events in subjects with moderate to very severe COPD. All COPD exacerbations will be reported as AEs unless considered an SAE.

7.2.6.7 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 (eg., elevated BUN and creatinine in the setting of an adverse event of renal failure, or decreased hemoglobin in a case of bleeding esophageal varices). In such cases, the laboratory abnormality itself (eg., elevated creatinine in a setting of renal failure) does not need to be recorded as an AE. However, isolated laboratory abnormalities should be reported as AEs if they are considered to be clinically significant by the Investigator.

Criteria for a "clinically significant" laboratory abnormality are:

- 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)
- 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 normal range (eg., < or > normal reference range), the Investigator should indicate whether the value is clinically significant or not clinically significant for the subject.

7.2.6.8 Serious Adverse Events

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

- Death
- A life-threatening adverse event

- In patient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect.

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

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

An AE is considered "life-threatening' if, in the view of the Investigator or Sponsor, its occurrence places the subject 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 Pearl Therapeutics' Medical Monitor or designee. All SAEs must be reported to Pearl Therapeutics no later than 24 hours after the Investigator recognizes/classifies the event as a serious adverse event. 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 may 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 Therapeutics as described in Section 7.2.6.10.

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.

7.2.6.9 Supplemental Investigations 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 Therapeutics. 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 Therapeutics.

7.2.6.10 Post-Study Follow-Up of Adverse Events

All AEs, including a worsening of clinically significant laboratory values or physical examination findings compared with baseline values, must be followed until the event resolves, the condition stabilizes, the event is otherwise explained, or the subject is lost-to-follow-up.

Adverse events ongoing at the Final Visit will be followed for as long as necessary to adequately evaluate the subject's safety or until the event stabilizes or resolves. If resolved, a resolution date should be documented on the case report form or reported to Pearl Therapeutics if the case report forms have been locked. The Investigator is responsible to ensure that follow-up includes any supplemental investigations as may be indicated to elucidate the nature and/or causality of the AE. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals as is practical.

7.2.6.11 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 SAEs occurring up to 14 days following the last dose of study drug must be reported to Pearl Therapeutics, whether or not the event is attributable to study drug. All SAEs must be reported to Pearl Therapeutics no later than 24 hours after the Investigator recognizes/classifies the event as an SAE.

7.2.6.12 IRB/IEC Notification of Serious Adverse Events

The Investigator is responsible for promptly notifying her/his investigational research board/independent ethics committee (IRB/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 he/she receives from Pearl Therapeutics. Documentation of the submission to the IRB/IEC must be retained for each safety report. The Investigator is also responsible for notifying Pearl Therapeutics if their IRB/IEC requires revisions to the informed consent form or other measures based on its review of an SAE report.

7.2.6.13 Health Authority Safety Reports

Pearl Therapeutics 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 Therapeutics 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 Therapeutics-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.

7.2.7 Overdose

An overdose is defined as a dose greater than the high dose level evaluated in this study as described in Section 6.2 (Product Descriptions) that results in clinical signs and symptoms. In the event of an overdose of study medication, 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, adverse events, and other significant data pertaining to the study drug(s) being used in this study.

7.2.8 Pregnancy

To ensure subject safety, each pregnancy in a female subject from Visit 1 (Screening) until study completion must be reported to Pearl Therapeutics within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the Investigator to Pearl Therapeutics Safety Department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the Pearl Therapeutics study drug of any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

7.2.9 Use of Steroids during the Study

At each visit, subjects will be asked whether they have been administered oral, intramuscular or intravenous corticosteroids since last visit. Use of oral, intramuscular or intravenous corticosteroids for the management of COPD exacerbations or other condition is not a reason for early termination. Use of corticosteroids should be documented. Subjects who are being treated for a COPD exacerbation with oral corticosteroids or have been treated for a COPD exacerbation with oral corticosteroids within 14 days of the scheduled visit will be allowed in the study under close medical supervision and at the discretion of the Investigator.

Subjects treated with oral, intramuscular, or intravenous corticosteroids for other indications will follow their visit schedule. If a subject requires intraocular corticosteroids this should be fully documented and the Investigator should make a determination as to the suitability of the subject continuing in the study.

7.3 Termination of the Study

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

Pearl Therapeutics 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 Therapeutics, in a time frame that is compatible with the subjects' well-being.

8 STUDY ACTIVITIES

A time and events schedule is provided in Table 8-1.

Table 8-1. Schedule of Events

Procedures	Screening Period		Treatment Period				
	Visit 1	**Visit 1b[a] (optional)**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**
Study Day[b]	**Days -14 to -1**	**Day -7**	**Day 1**	**Day 8 ±2 Days**	**Day 15 ±2 Days**	**Day 22 ±2 Days**	**Day 29 ±2 Days**
Obtain Informed Consent[c]	X						
Review Inclusion/ Exclusion Criteria[d]	X		X	X	X	X	X
Verify Continued Eligibility		X	X	X	X	X	X
Demographics, Medical and Surgical History	X	X					
Physical Examination	X						X
Prior Medications / Concomitant Medications[e]	X		X	X	X	X	X
Pregnancy Test[f]	X						X
Chest X-ray[g]	X						
Vital Signs	X		X	X	X	X	X
ECG	X		X				X
Clinical Laboratory Tests (hematology, chemistry)	X						X
Adjust COPD Medications[h]	X						X

Procedures	Screening Period		Treatment Period				
	Visit 1	Visit 1b[a] (optional)	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6
COPD Worsening and Exacerbations	X		X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X
Inhalation Device Training	X[i]	X	X	X	X	X	
Study Drug Dispensing/Collection	X[j]	X	X				X
Study Drug Administration	X	X	X				
eDiary Training	X[k]	X	X	X	X	X	
Review of eDiary[l]		X	X	X	X	X	X
Review/Record Dose Indicator Reading[m]	X	X	X	X	X	X	X
MDI Weight Assessment[n]	X	X	X	X	X	X	X

Note: Premature Discontinuation Visits will be captured as unscheduled visits.

[a] If the subject's eDiary is <80% compliant, or if the subject's reported count during Visit 1 (Screening) using the Placebo MDI is greater than an absolute difference of 6-actuations from the weight based count, the subject has not met compliance-based entry criteria and will be given the opportunity to meet this compliance requirement. Subjects will have their eDiary reset, be reissued a new Placebo MDI, and be required to return to the clinic in 1 week. If the subject fails to meet these criteria after the second attempt, they will be considered a screen failure.

[b] Scheduling visits: The maximum Screening Period is 14 days, but can be as short as 7 days. Each subject will receive 28 days of study treatment. Subjects who fall outside the visit window will be placed in the appropriate visit window at the next scheduled visit.

[c] Informed consent may be obtained prior to Study Visit 1.

[d] Confirm COPD severity at Visit 1: FEV_1/FVC ratio of <0.70; post-bronchodilator FEV_1 ≥30% and <80% predicted normal value using NHANES III.

[e] At all visits beyond Screening, note time of last dose of short-acting bronchodilator and other COPD medications.

[f] A serum pregnancy test will be performed at Visit 1 (Screening) and Last Visit (Visit 6) unless it is documented in the medical history that the female subject has been irreversibly surgically sterilized (hysterectomy, oophorectomy, or bilateral tubal ligation) or they are at least 2 years post-menopausal. The pregnancy test should be performed prior to any ECG or blood collection for laboratory assessments.

[g] A chest X-ray must be conducted if the most recent chest X-ray or CT scan are more than 6 months old at the time of Visit 1.

[h] At Visit 1 (Screening), stop prohibited COPD medications and change COPD medications as specified in Section 5.4.1 (ie., Sponsor-provided Atrovent HFA). At the end of Visit 6, return subject to pre-study or other appropriate inhaled maintenance COPD medications.

[i] Sites will use Sponsor-provided Placebo MDI to train subjects on the use of MDIs during Screening. Device retraining will be conducted at all study visits, if needed.

[j] Sponsor-provided Atrovent HFA or Ventolin HFA is dispensed only after a subject is determined to be eligible to proceed to Visit 2

[k] Issue and train subjects on eDiary use only after a subject is determined to qualify to proceed to Visit 2. Retraining will be conducted at all study visits, if needed.

[l] Refer to Section 7.1.3 for details of electronic diary review.

[m] Site staff will record the dose indicator reading at each visit. Refer to Section 7.1.1 for details and instructions on recording dose indicator readings.

[n] Refer to Section 7.1.2 for further information on MDI weighing procedures.

8.1 Visit 1 (Screening)

- Obtain informed consent prior to conducting any study procedure
- Register subject in IWRS to obtain subject screening number
- Verify subject meets inclusion/exclusion criteria
- Obtain demographic data, including age, race, smoking history, medical/surgical history (including cardiovascular risk factors and history), and age of onset of COPD
- Obtain medication history, including COPD medications
- Conduct a complete physical examination, including height and weight (general appearance, skin, head, eyes, ears, nose, throat, neck [including thyroid], lymph nodes, chest, heart, abdomen, extremities, and nervous system)
- 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.
- If chest x-ray or CT within 6 months of Visit 1 (Screening) is not available, obtain a new chest x-ray
- Obtain a 12-lead ECG
- Obtain vital signs
- Obtain laboratory samples (hematology, chemistry)
- Stop prohibited COPD medications and change to Sponsor-provided Atrovent HFA for COPD maintenance, and Sponsor-provided Ventolin HFA for rescue therapy.
- Subjects will be provided and trained on eDiary use and instructed how to record study medication and dose indicator information.
- A Sponsor-provided Placebo MDI will be issued to be used during Screening for practice by subject in recording dose indicator information into eDiary.
- Site personnel will dispense Sponsor-provided Placebo MDI and record initial dose indicator reading into the source/eCRF. Site personnel will prime the Placebo MDI by performing four priming shots. The primed Placebo MDI will then be weighed (canister in the MDI without the cap in place) and recorded in the source/eCRF.
- Subjects will be instructed on how to record the dose indicator information in their eDiary and will record the dose indicator reading prior to their first in-clinic dosing.
- Subjects will be administered 2 puffs from the Placebo MDI under site supervision and then record the dosing time, the number of actuations used, and the dose indicator reading following dosing in their eDiary.
- Subjects will be instructed to bring their eDiary, Placebo MDI, Atrovent HFA, and Ventolin HFA to the next scheduled clinic visit.
- Adverse events will be recorded during the Screening Period (time of consent) to Visit 2 (the start of study treatment). **Note:** Adverse events that occur between the time the subject signs the informed consent form for the study and the time when the subject is administered study drug will be summarized as medical history and not as a study adverse event unless the event meets the definition of an SAE.

- Ensure subject has adequate supply of Sponsor-provided rescue Ventolin HFA.
- Schedule Visit 2

8.2 Visit 1b (Optional)

- Review eDiary and dose indicator readings of Placebo MDI
- If the subject's eDiary is <80% compliant, or if the subject's reported count during Visit 1 (Screening) using the Placebo MDI is greater than an absolute difference of 6-actuations from the weight based count, the subject has not met compliance-based entry criteria and will be given the opportunity to meet this compliance requirement. Subjects will have their eDiary reset, be reissued a new Placebo MDI, and be required to return to the clinic in 1 week. If the subject fails to meet these criteria after the second attempt, they will be considered a screen failure.

8.3 Visit 2 (Study Initiation)

- Review subject eDiary entries and retrain if subject has not met eDiary compliance requirement of >80% completion of required assessments
- The site will record the dose indicator reading of the Placebo MDI into the source/eCRF and then weigh and record the MDI weight (canister in the MDI without the cap in place) according to weighing procedures in the User's Manual of the Sponsor-provided scale. **Note**: If the subject's reported count during Visit 1 (Screening period) using the Placebo MDI is greater than an absolute difference of 6-actuations from the weight based count, the subject has not met compliance-based entry criteria and will be given one more opportunity to meet this compliance requirement. See Visit 1b above.
- Collect Sponsor-provided Atrovent HFA and Sponsor-provided Placebo MDI dispensed during the Screening Period
- Review subject's eligibility to continue
- Review all prior medications and ensure adherence to COPD regimen
- Obtain vital signs
- Obtain a 12-lead ECG
- Record COPD exacerbations and adverse events (if any)
- Obtain subject number and treatment assignment information from IWRS
- Site personnel will dispense Sponsor-provided GFF MDI and record initial dose indicator reading of the GFF MDI into the source/eCRF. Site personnel will prime the GFF MDI by performing four priming shots. The primed GFF MDI will then be weighed (canister in the MDI without the cap in place) and weight recorded in the source/eCRF.
- Subjects will be instructed on how to record the dose indicator information in their eDiary and will record the dose indicator reading prior to their first dosing of study medication.

- Subjects will be administered 2 puffs from the GFF MDI under site supervision and then record the dosing time, the number of actuations used, and the dose indicator reading following dosing in their eDiary. Subjects will use this GFF MDI throughout the remainder of the study visits.
- Instruct subjects to bring their eDiary, GFF MDI, and Ventolin HFA to the next scheduled clinic visit
- Ensure subject has adequate supply of Sponsor-provided rescue Ventolin HFA
- Schedule next visit

8.4 Visit 3 (Day 8 of Treatment Period)

- Review subject eDiary entries and retrain if subject has not met eDiary compliance requirement of >80% completion of required assessments
- Review subject's eligibility to continue
- Review all prior medications and ensure adherence to COPD regimen
- Obtain vital signs
- Record COPD exacerbations and adverse events (if any)
- Sites will record dose indicator information in the source/eCRF
- Sites will weigh the GFF MDI (canister in the MDI without the cap in place) and record the weight in the source/eCRF
- Re-instruct subjects on recording dose indicator usage in their eDiary, if needed
- Record any reported actuations of the GFF MDI in the source/eCRF that were not captured in the eDiary
- Instruct subjects to bring their eDiary and GFF MDI to the next scheduled clinic visit
- Instruct subjects to clean their GFF MDI after the evening dosing following Visit 3 and record the number of actuations and dose indicator readings (before and after priming) following MDI cleaning in their eDiary.
- Ensure subject has adequate supply of Sponsor-provided rescue Ventolin HFA
- Schedule next visit

8.5 Visit 4 (Day 15 of Treatment Period)

- Review subject eDiary entries and retrain if subject has not met eDiary compliance requirement of >80% completion of required assessments
- Review subject's eligibility to continue
- Review all prior medications and ensure adherence to COPD regimen
- Obtain vital signs
- Record COPD exacerbations and adverse events (if any)
- Sites will record dose indicator information in the source/eCRF

- Sites will weigh the GFF MDI (canister in the MDI without the cap in place) and record the weight in the source/eCRF
- Re-instruct subjects on recording dose indicator usage in their eDiary, if needed
- Record any reported actuations of the GFF MDI in the source/eCRF that were not captured in the eDiary
- Instruct subjects to bring their eDiary and GFF MDI to the next scheduled clinic visit
- Instruct subjects to clean their GFF MDI after the evening dosing following Visit 4 and record the number of actuations and dose indicator readings (before and after priming) following MDI cleaning in their eDiary.
- Ensure subject has adequate supply of Sponsor-provided rescue Ventolin HFA
- Schedule next visit

8.6 Visit 5 (Day 22)

- Review subject eDiary entries and retrain if subject has not met eDiary compliance requirement of >80% completion of required assessments
- Review subject's eligibility to continue
- Review all prior medications and ensure adherence to COPD regimen
- Obtain vital signs
- Record COPD exacerbations and adverse events (if any)
- Sites will record dose indicator information in the source/eCRF
- Sites will weigh the GFF MDI (canister in the MDI without the cap in place) and record the weight in the source/eCRF
- Re-instruct subjects on recording dose indicator usage in their eDiary, if needed
- Record any reported actuations of the GFF MDI in the source/eCRF that were not captured in the eDiary
- Instruct subjects to bring their eDiary and GFF MDI to the next scheduled clinic visit
- Instruct subjects to clean their GFF MDI after the evening dosing following Visit 5 and record the number of actuations and dose indicator readings (before and after priming) following MDI cleaning in their eDiary.
- Ensure subject has adequate supply of Sponsor-provided rescue Ventolin HFA
- Schedule next visit

8.7 Visit 6 - Final Visit (Day 29)

- Collect eDiary and review for data collection compliance
- Review subject's eligibility to continue
- Conduct a complete physical examination, including height and weight (general appearance, skin, head, eyes, ears, nose, throat, neck [including thyroid], lymph nodes, chest, heart, abdomen, extremities, and nervous system)

- 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
- Confirm the subject took their last dose of study medication as scheduled
- Review all prior medications and ensure adherence to COPD regimen
- Obtain laboratory samples (hematology, chemistry)
- Obtain vital signs
- Record COPD exacerbations and adverse events (if any)
- Obtain a 12-lead ECG
- Sites will record dose indicator information in the source/eCRF
- Sites will weigh the GFF MDI (canister in the MDI without the cap in place) and record the weight in the source/eCRF
- Record any reported actuations of the GFF MDI in the source/eCRF that were not captured in the eDiary
- Collect all study medications including Sponsor-provided GFF MDI, Atrovent HFA, and Ventolin HFA

8.8 Unscheduled Visit/Premature Discontinuation Visit

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

- Collect eDiary
- Weigh the GFF MDI and record the weight and dose indicator reading in the eCRF
- Record adverse events (if any)
- Obtain laboratory samples (hematology, chemistry)
- Collect all study medications including Sponsor-provided GFF MDI and Ventolin HFA
- Return subject to pre-study or appropriate maintenance COPD medications
- Capture reason for discontinuation

8.9 Completion of Study or Early Termination

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 (eg., early termination of the study)
- Subject lost-to-follow-up
- Lack of efficacy
- Major protocol deviation
- Death
- Completion of the study
- Protocol specified criteria, ie., use of prohibited medications (Refer to Section 5.7).

9 PLANNED STATISTICAL METHODS

9.1 Introduction

This study will be conducted as an open-label, single-arm study evaluating GFF MDI with dose indicator in approximately 125 subjects. This study will include a 4-week Treatment Period, preceded by a Screening Period.

The primary objective of this study is to evaluate the accuracy, reliability and functionality of the GFF MDI dose indicator in adult subjects with moderate to very severe COPD treated over a 4-week Treatment Period.

9.2 Protocol Variables

9.2.1 Dose Indicator Endpoints

Dose Indicator Assessments:

The dose indicator assessments will include four measures of the number of actuations utilized for each MDI:

- Subject-reported: the total number of actuations of the MDI as reported by the subject including priming shots
- Indicator reading: the total number of actuations of the MDI obtained by subtracting the dose indicator reading from 130
- Weight-based: the total number of actuation of the MDI estimated by dividing the change in weight of each MDI by the estimated mean shot weight
- Lab-advanced indicator reading: the total number of actuations of the MDI obtained by subtracting the dose indicator reading from 130 and adding the additional actuations of the MDI that had been used as determined by the lab (10 minus the number of actuations needed to advance the indicator or 0 if the reading was already 0).

9.2.1.1 Primary Dose Indicator Endpoint

Percentage of devices where the number of actuations as counted at the end of the study using the dose indicator reading is consistent (± 20 actuations) with the number of actuations reported by the subject.

9.2.1.2 Secondary Dose Indicator Endpoints

- Percentage of devices where the number of actuations as counted at the end of the study using the dose indicator reading is consistent (± 20 actuations) with the number of actuations used as estimated by the change in MDI weight
- Percentage of devices where the number of actuations as counted at the end of the study using the lab-advanced dose indicator reading is consistent (± 20 actuations) with the number of actuations used as reported by the subject

- Percentage of devices where the number of actuations as counted at the end of the study using the lab-advanced dose indicator reading is consistent (± 20 actuations) with the number of actuations used as estimated by the change in MDI weight
- Percentage of devices where the dose indicator reading actuation count is >20 less than the subject-reported actuation count (undercount).
- Number of correct advances (±2 actuations) of the dose indicator based on subject reported use
- Percentage of correct advances (±2 actuations) = 100 x (correct advances/total advances) based on subject reported use
- Number of correct advances (±4 actuations) of the dose indicator based on subject reported use
- Percentage of correct advances (±4 actuations) = 100 x (correct advances/total advances)

9.2.1.3 Other Dose Indicator Endpoints

- Percentage of consistent (± 20 actuations) devices at each visit for:
  - The dose indicator reading compared to the number of actuations reported by the subject
  - The dose indicator reading compared to the number of actuations used as estimated by the change in MDI weight
  - The lab-advanced dose indicator reading compared to the number of actuations reported by the subject
  - The lab-advanced dose indicator reading compared to the number of actuations used as estimated by the change in MDI weight

9.2.2 Safety Endpoints

The safety endpoints for this study include:

- AEs
- 12-Lead ECG
- Clinical laboratory testing
- Vital sign measurements

9.3 Analysis

The Intent-to-Treat (ITT) Population will be considered primary. Analyses conducted with the Per Protocol (PP) Population will be considered supportive.

9.3.1 Dose Indicator Analyses

Dose indicator data analyses will be conducted to assess the consistency of actuation counts derived from multiple sources: the subject eDiary, the case report forms, the change in MDI weight and a laboratory advanced count facilitated by the Pearl Analytical Laboratory. The subject diary tracks the number of actuations based on the subjects' reported dosing. The case-report form provides an estimate of the number of doses remaining in the MDI based on the dose indicator reading, which is designed to advance discretely by 10 units after every 10 actuations of the MDI. The change in MDI weight after subject use estimates the number of actuations based on the average shot weight per actuation. After subject MDIs are returned, the Pearl Analytical Laboratory will also count the number of actuations needed to advance the MDI to the next reading, in order for the total number of actuations to be counted more precisely.

9.3.1.1 Primary Analysis

The primary assessment of dose indicator accuracy for each device will be based on a comparison of the number of actuations used according to the dose indicator (as inferred from the eCRF) with the number of actuations reported by the subject using the eDiary. The 2 counts will be considered to be in agreement when the dose indicator count is within ±20 actuations of the diary count. The overall number and percentage of devices with agreement between the 2 counts will be calculated and summarized.

9.3.1.2 Secondary Analyses

The number of actuations used according to the dose indicator (as inferred from the eCRF) will also be compared to the number of actuations estimated by the change in MDI weight.

The weight-based number of actuations will be calculated as follows:

$$1000 \cdot (W_{BEG} - W_{END})/MSW$$

where: W_{BEG} = the MDI weight in grams at the beginning of use (after priming)

W_{END} = the MDI weight in grams at the end of use

MSW = the mean shot weight in milligrams from the release data

For the total weight-based count at the end of the study, an additional 4 actuations will be added to account for the 4 initial priming shots fired before the initial weighing of the MDI.

The dose indicator count will be compared to the weight-based actuation count. Agreement will be achieved when the dose indicator count is within ±20 actuations of the weight-based count. The overall number and percentage of devices with agreement will be calculated and summarized for each comparison.

As a subset to the primary analysis, the number and percentage of devices for which the dose indicator undercounts the number of actuations by more the 20 counts as compared to the subject-reported count will also be tabulated.

Similar comparisons will be performed for the lab-advanced count. The lab-advanced actuation count will be calculated as:

$$140 - (A + B)$$

where: A = the position of the dose indicator upon receipt

B = the number of actuations required to advance the dose indicator to the next decrement

Descriptive statistics (N, mean, standard deviation, median, minimum, maximum) will be tabulated for each of the actuation count variables (subject-reported recordings, actual dose indicator recordings, weight-based recordings and lab-advanced) and for each of the pairwise differences among the actuation count variables relative to the dose indicator. Scatterplots of the pairwise agreement among actuation count variables relative to the dose indicator will also be presented.

Correct advances (+/- 2 actuations): The number of actuations since the previous advance of the dose indicator will be summarized. If the number is from 8 to 12 inclusive, then the advance of the indicator will be deemed correct.

The percentage of correct advances (+/- 2 actuations) = 100 x (correct advances/total advances).

Correct advances (+/- 4 actuations): The number of actuations since the previous advance of the dose indicator will be summarized. If the number is from 6 to 14 inclusive, then the advance of the indicator will be deemed correct.

The percentage of correct advances (+/- 4 actuations) = 100 x (correct advances/total advances).

9.3.2 Safety Analysis

9.3.2.1 Adverse Events

Adverse events will be summarized by the number and percentage of subjects experiencing an event. They will be tabulated at the level of the Medical Dictionary for Regulatory Activities (MedDRA) preferred term (PT), and the MedDRA System Organ Class (SOC). The version of MedDRA current at the time of database lock will be used for final analysis of the data. Tabulations will be broken down by severity and by relationship to study drug. Serious AEs and AEs leading to withdrawal will also be summarized and listed.

9.3.3 Clinical Laboratory Measurements

Summary statistics (mean, median, standard deviation [SD], and range) of change from baseline values will be tabulated for each assessment time. For clinical laboratory measurements, baseline values will be defined by the last value prior to dosing on Day 1.

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

Potentially clinically significant changes from 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. Similarly, potentially clinically significant blood glucose values (>11.1 mmol/L) will also be listed and tabulated.

9.3.4 Vital Signs

Summary statistics (mean, median, standard deviation and range) for absolute values and change from baseline values will be tabulated for each assessment time. For vital signs, baseline values will be defined as the average of the values prior to dosing on Day 1. PCS values for vital signs will be defined in the SAP and the percentage of subjects with PCS values will be summarized.

9.3.5 Electrocardiograms

Summary statistics (mean, median, standard deviation and range) for raw values and change from baseline values in heart rate, PR Interval, QRS Axis, QRS Interval, QT Interval and QTcF interval will be calculated, where baseline is defined as the average of the pre-dose measurements taken prior to dosing on Day 1. The QTcF is defined as ($QT/[RR^{1/3}]$). Heart rate (bpm) is estimated as 60,000/RR. These assessments will be tabulated for each assessment time. PCS values for ECG parameters will be defined in the SAP, and the percentage and number of subjects with PCS ECG values will be tabulated.

9.4 Experimental Design

This is an open-label, chronic-dosing (4 weeks), multi-center study of GFF MDI to evaluate the accuracy, reliability and functionality of GFF MDI dose indicator in adult subjects with moderate to very severe COPD treated. Study treatment is given in addition to permitted COPD background therapy. There will be a Screening visit where informed consent is obtained. Current COPD medications are reviewed and, if necessary, arrangements are made to adjust prohibited COPD therapy to allowable COPD therapy.

9.5 Sample Size

The sample size of approximately 125 enrolled subjects was chosen to ensure adequate patient experience using the GFF MDI dose indicator and to provide a satisfactory estimate

of the percent of devices with agreement between the dose indicator and subject-reported counts. The sample size is consistent with industry trials of similar design and objectives.

9.6 Analysis Plan

All analyses will be specified in a detailed SAP that will be accompanied by table and data listing shells with mock graphical representations. The analysis plan will be approved by signature before database lock.

9.7 Study Populations

The following analysis populations are defined in this study:

- The **Intent-To-Treat (ITT) Population** is defined as all subjects who are enrolled into the treatment period and use at least 10 actuations of GFF MDI as recorded in the eDiary.
- The **Per-Protocol (PP) Population** is a subset of the ITT Population defined as all subjects that complete all visits with ≥80% compliance of completing the eDiary without major protocol deviations that could affect the assessment of the dose indicator.
- The **Safety Population** is defined as all subjects who are enrolled into the treatment period and receive at least one dose of GFF MDI. (Note that a subject who used a study treatment, but took less than one full dose of treatment will qualify for this population).

Analyses will be performed as follows:

Demographics will be summarized for the ITT, PP, Safety, and Non-enrolled Populations. Extent of exposure will be summarized for the Safety Population. The Safety Population will be used to summarize safety. Dose indicator analyses will be performed for the ITT and PP Populations, with the ITT Population being considered the primary population for these analyses.

9.8 Statistical Software

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

10 ADMINISTRATIVE CONSIDERATIONS

10.1 Regulatory Authority Approval

Pearl Therapeutics 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 Institutional Review Board or Independent Ethics Committee Approval

The study will be conducted in accordance with Good Clinical Practice (GCP). These standards respect the following guidelines:

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

The Investigator (or Pearl Therapeutics, where applicable) is responsible for ensuring that this protocol, the site's informed consent form (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 institutional review board (IRB) and/or independent ethics committee (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 Therapeutics 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 Therapeutics promptly.

10.3 Subject Information and Consent

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

The Investigator will be responsible for obtaining written informed consent from potential subjects prior to any study-specific screening and entry into the study. A copy of the signed ICF will be provided to the subject. The original will be retained by the Investigator.

10.4 Laboratory Accreditation

Any laboratory facility intended to be used for analysis of clinical laboratory samples required by this protocol must provide evidence of adequate licensure or accreditation according to the prevailing regulations in that state and/or country. Reference values and/or normal ranges for the test results must be provided to Pearl Therapeutics. Pearl Therapeutics must be notified promptly in writing of any changes occurring in reference values during the course of the study.

10.5 Confidentiality

10.5.1 Confidentiality of Data

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

10.5.2 Confidentiality of Subject/Patient Records

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

10.6 Quality Control and Assurance

Pearl Therapeutics is responsible for implementing and maintaining quality control and quality assurance systems with written standard operating procedures (SOPs) to ensure that

trials are conducted and data are generated, documented, and reported in compliance with the protocol, accepted standards of GCP guidelines, and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the clinical study.

10.7 Data Management

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

10.8 Study Monitoring

In accordance with applicable regulations, GCP, and Pearl Therapeutics procedures, clinical monitors will contact the site prior to subject enrollment to review the protocol and data collection procedures with site staff. In addition, the monitor will periodically contact the site, including conducting on-site visits. The extent, nature, and frequency of on-site visits will be based on such considerations as the study objective and/or endpoints, the purpose of the study, study design complexity, and enrollment rate.

During these contacts, the monitor will:

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

This will be done in order to verify that the:

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

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

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

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

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

10.9 Retention of Data

Documents that individually and collectively permit evaluation of the conduct of the study and the quality of the data produced must be maintained for review by Pearl Therapeutics' quality assurance auditors and by all applicable regulatory authorities. The period of time these documents must be maintained is governed by applicable regulations.
Pearl Therapeutics or its designee will inform the Investigator when these documents may be destroyed. Pearl Therapeutics or its designee must be notified in writing *at least 6 months* prior to the intended date of disposal of any study record related to this protocol to allow Pearl Therapeutics to make alternate storage arrangements.

10.10 Financial Disclosure

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

10.11 Investigator's Final Report

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

10.12 Publication Policy

Pearl Therapeutics intends to publish the results of all of the clinical studies that it sponsors in compliance with the Declaration of Helsinki (http://www.wma.net/en/10home/index.html). Consistent with the recommendations of the editors of several leading medical journals, the International Committee of Medical Journal Editors (ICMJE), authorship of publications resulting from Pearl Therapeutics-sponsored studies should fairly recognize the activities of those that have made a significant contribution to the study. Thus, it is anticipated that authorship will reflect the contribution made by Pearl Therapeutics personnel, the Investigators and others involved, such as statisticians.

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

1. **Responsibility:** Each principal Investigator is responsible for the accuracy and completeness of all data from their site. Pearl Therapeutics (or its representatives) is

responsible for the accuracy of the data entered into the study databases and for the accuracy of the analyses conducted.

2. **Authorship and Publication Committee:** Pearl Therapeutics, in collaboration with the Investigators, will establish the appropriate authorship and responsibility for drafting study documents in accordance with the principles of the ICMJE. It is anticipated that a publication committee will be formed to assume oversight of these activities. All manuscripts will be reviewed and agreed upon before submission for publication by all authors.
3. **Sponsor Review of External Manuscripts:** Consistent with the previous bullet point, drafts of any and all publications or presentations that may arise from this study must be submitted at least 30 days prior to submission for publication or presentation to Pearl Therapeutics for review, approval, and to ensure consistency with the policy in this protocol. Pearl Therapeutics will have the right to request appropriate modification to correct facts and to represent its opinions, or the opinions of the publication committee, if these differ with the proposed publication.
4. **Confidentiality:** Investigators will conduct all interactions with Pearl Therapeutics and with third parties consistent with the executed confidentiality agreements. While publication, by intention, presents the critical scientific data in a public forum, some information (such as future plans, results of nonclinical studies, or chemical formulae) may still need to remain confidential.
5. **Medical Journal Review:** Consistent with the intention of Pearl Therapeutics to publish the study in a fair and accurate manner, Pearl Therapeutics supports diligence in the publication review process of medical journals. Accordingly, upon request, all pertinent study data and information will be made available as supplemental information for journal editors and reviewers to evaluate and audit, eg., protocol and amendments, data tabulations, etc. The journal and reviewers will need to make arrangements to maintain the confidentiality of such supplemental information, where relevant, and Pearl Therapeutics will make suitable arrangements to ensure that the identity of journal reviewers is kept confidential. Records will be maintained of reviewers and the respective documents and datasets that were reviewed by each of them.
6. **Reporting of Clinical Trials Results:** To provide transparency in the conduct and reporting of randomized clinical trials, Pearl reports clinical findings based on the guidance of The CONSORT (CONsolidated Standards of Reporting Trials) Statement [CONSORT, 2010] and a 25-item checklist which is intended to improve the reporting of a randomized controlled trial, and to facilitate reader understanding of the trial design, conduct, analysis and interpretation, and to support their ability to assess the validity of its results.

7. Internet Clinical Trial Listing: In addition, also consistent with the recommendations of the ICMJE, Pearl Therapeutics will make available appropriate information regarding the study via the internet. This will include registration and listing of the study on www.clinicaltrials.gov, the US National Institutes of Health listing of clinical trials, and other clinical trial listings as appropriate. Per Astra Zeneca policy, Pearl Therapeutics posts clinical study protocols for public viewing when a manuscript is published in a medical journal. Prior to being made public, the protocol is reviewed by Astra Zeneca Intellectual Property.

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Appendix 1 Instructions for Use of GFF and Placebo MDI

Before using GFF MDI and Placebo MDI

1. Take the inhaler out of the foil pouch. Safely throw away the pouch and the drying packet that comes inside the pouch. Check the indicator at the top of the canister; the indicator should read as shown in Figure 1.

Figure 1. Indicator at Top of Canister

2. Take the cap off the inhaler and 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.
3. The inhaler should be stored at room temperature.

How to prime GFF MDI and Placebo MDI

1. The inhaler must be primed before the first use. Priming involves releasing a certain number of sprays (4) into the air before the first use of the inhaler. Shaking and priming the inhaler fills a chamber inside the canister with the correct dose and mix of medication so that the inhaler is ready to use.
2. Take the cap off the mouthpiece of the actuator.
3. To prime the inhaler, gently shake the inhaler for 5-10 seconds and then spray once into the air away from yourself and others.
4. Wait approximately 5-10 seconds and repeat the process three more times.

How to take a dose from GFF MDI and Placebo MDI

Steps 3-6 below should be done one after the other.

1. Take the cap off the mouthpiece of the actuator.
2. Hold the inhaler with the mouthpiece down.
3. Shake the canister for 5-10 seconds.
4. Breathe out fully through mouth, expelling as much air from the lungs as possible.
5. Tilt head back slightly, place the mouthpiece into mouth, and close lips around it. To allow the medication to enter the lungs, keep tongue flat on the floor of your mouth. Keep the mouthpiece at the bottom and the dose indicator at the top.

6. While breathing in deeply and slowly, press down on the center of the dose indicator with finger. Fully depress the canister until it stops moving in the actuator while delivering the dose. **Note**: It is normal to hear a soft click from the indicator as it counts down during use.
7. Hold breath as long as possible, up to 10 seconds, and then breathe normally.
8. Repeat steps 3 to 7, with gentle shaking for 5-10 seconds before the second spray.
9. Put the cap back on the mouthpiece after every time the inhaler is used, and make sure it is firmly seated in place.

How to clean GFF MDI and Placebo MDI

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

Wash the actuator once a week for the first three weeks as directed below.

1. Take the canister out of the actuator, and take the cap off the mouthpiece.
2. Wash the actuator through the top of the actuator with warm running water for 30 seconds (Figure 2).

Figure 2. Wash Actuator through Top of Actuator

3. Then wash the actuator again through the mouthpiece (Figure 3).

Figure 3. Wash Actuator through Mouthpiece

4. 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 visible build-up, repeat steps 2 and 3.
5. Let the actuator air dry completely, such as overnight.
6. When the actuator is dry, put the canister in the actuator, making sure the canister is fully and firmly fitted into the actuator. Shake the inhaler gently for 5-10 seconds and spray it 2 times into the air away from your face, shaking gently 5-10 seconds before each spray. Put the cap back on the mouthpiece.

If the actuator becomes blocked

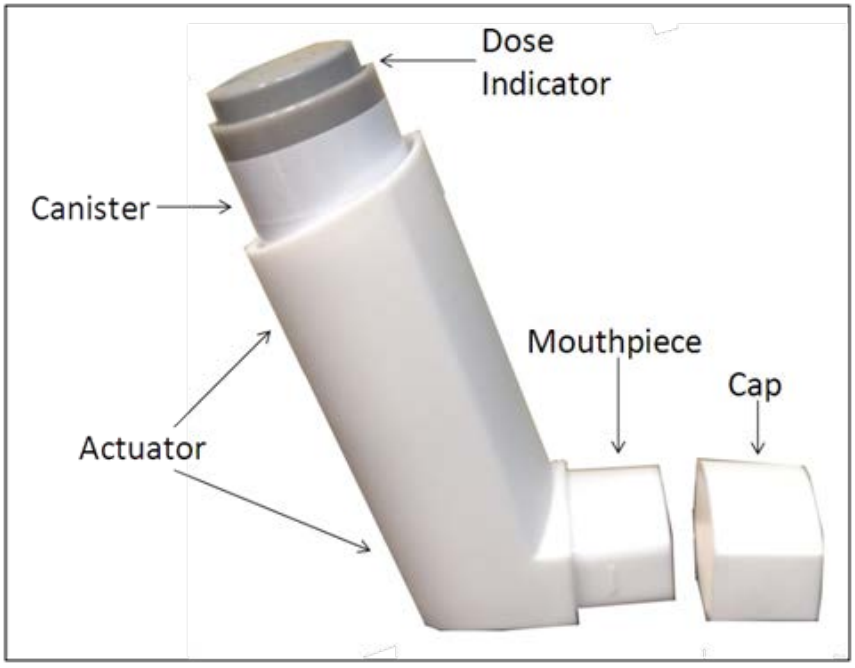
Blockage from medicine build-up is more likely to happen if the actuator is not routinely cleaned and the actuator is not air-dried completely. If the actuator gets blocked so that little or no medicine comes out of the mouthpiece, wash the actuator as described in cleaning steps 1-6.

If the inhaler is needed before the actuator is completely dry, shake as much water off the actuator as possible. Put the canister in the actuator and make sure it fits firmly. Shake the inhaler gently for 5-10 seconds and spray it 2 times into the air away from your face, shaking gently 5-10 seconds before each spray. Then take the dose as prescribed and described above. Then clean and air-dry it completely.

How to read the inhaler dose indicator

The inhaler is fitted with a dose indicator which shows how much medicine is left during use. The dose indicator display will move after every tenth puff. The dose indicator pointer will start to point to the red area when there are 20 puffs remaining. This means that the inhaler needs to be replaced soon.

Figure 5. Metered Dose Inhaler Parts



Appendix 2 Instructions for Use of Atrovent HFA Inhalation Aerosol Device

Inhaler Description

ATROVENT HFA Inhalation Aerosol (Figure 1) consists of a metal canister containing the medicine and a mouthpiece that releases the medicine from the canister. The mouthpiece includes a clear colorless sleeve, a white plastic portion and a green protective dust cap.

The inhaler comes with a dose indicator you can see through a small window on the plastic mouthpiece (See Figure 1). A new inhaler first shows "200" in the dose indicator window. The dose indicator will show the approximate number of actuations (sprays) of medicine remaining in the inhaler. As you use the inhaler, the dose indicator will typically rotate during every 5 to 7 actuations (sprays) towards the next decreasing number (See Figure 2).

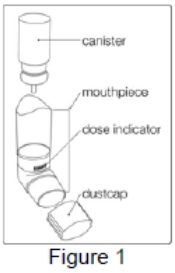


Figure 1

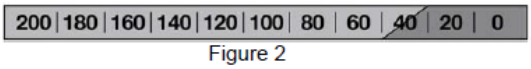


Figure 2

Instructions for Use:

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 canister is to be used only with the ATROVENT HFA mouthpiece.**
   - **Do not use the ATROVENT HFA mouthpiece with other inhaled medicines.**
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 inhaler upright (See Figure 3), between your thumb and first 2 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.** If sprayed into the eyes, ATROVENT HFA can cause blurry vision and other vision abnormalities, eye pain or discomfort, dilated pupils, or narrow-angle glaucoma or worsening of this condition. If any combination of these symptoms develops, you should consult your physician immediately.

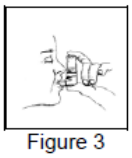


Figure 3

4. **Breathe in (inhale) slowly through your mouth and at the same time spray the ATROVENT HFA into your mouth.**
   - To spray ATROVENT HFA firmly press the canister against the mouthpiece 1 time (See Figure 4). Keep breathing in deeply.


Figure 4

5. **Hold your breath for ten seconds and then take the mouthpiece out of your mouth and breathe out slowly (See Figure 5).**


Figure 5

6. **Wait at least 15 seconds and repeat steps 3 to 5 again.**
7. **Replace the green protective dust cap after use.**
8. **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 **Mouthpiece Cleaning Instructions**).

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 6). Do not use anything other than water to wash the mouthpiece.

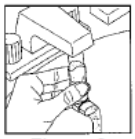


Figure 6

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 little or no medicine comes out of the mouthpiece, wash the mouthpiece as described in Steps A to E under the "**Mouthpiece Cleaning Instructions**".

9. **When to get a new ATROVENT HFA inhaler.**

There are approximately 40 actuations (sprays) left when the dose indicator displays "40," where the background changes from green to red (See Figure 7a). This is when you need to refill your prescription or ask your doctor if you need another prescription for ATROVENT HFA inhalation aerosol.

The background color will be all red when the indicator approaches 20. The indicator will stop moving at "0". Discard the inhaler once the dose indicator displays "0" (See Figure 7b). Even though the canister may not be empty, you cannot be sure of the amount of medicine in each actuation (spray) once the dose indicator displays "0".

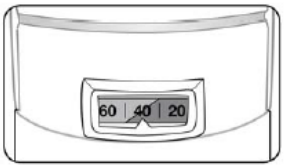


Figure 7a

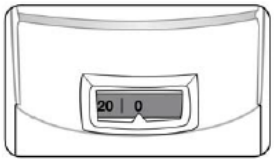


Figure 7b

Appendix 3 Instructions for Use of Ventolin HFA Inhaler

The Parts of Your VENTOLIN HFA Inhaler

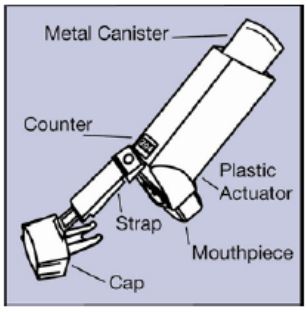


Figure A

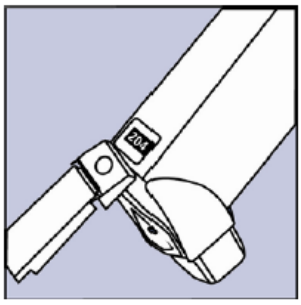


Figure B

There are 2 main parts of your VENTOLIN HFA inhaler:

- the blue plastic actuator that sprays the medicine into your mouth. See Figure A.
- the metal canister that holds the medicine. See Figure A.

The actuator has a protective cap that covers the mouthpiece. The strap on the cap will stay attached to the actuator.

Do not use this actuator with a canister of medicine from any other inhaler.

Do not use this canister of medicine with an actuator from any other inhaler.

The canister has a counter that shows you how many sprays of medicine you have left. The number shows through a window in the back of the actuator. The counter starts at either 204 or 64, depending on which size inhaler you have. See Figure B.

Priming your VENTOLIN HFA inhaler:

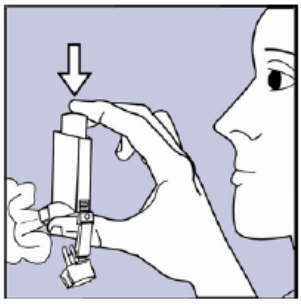


Figure C

Your VENTOLIN HFA inhaler must be primed before you use it for the first time, when it has not been used for more than 14 days in a row, or if it has been dropped. Do not prime your VENTOLIN HFA every day.

- Remove your VENTOLIN HFA inhaler from its packaging.
- Throw away the pouch and the drying packet that comes inside the pouch.
- Remove the protective cap from the mouthpiece.
- Shake the inhaler well, and spray it into the air away from your face. See Figure C.

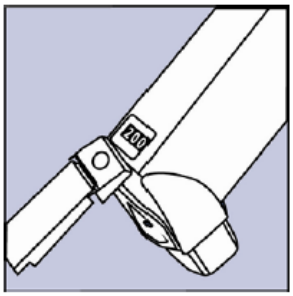


Figure D

- Shake and spray the inhaler like this 3 more times to finish priming it. After you prime the actuator for the first time, the dose counter in the window on the back of the actuator should show the number 200 or 60, depending on which size inhaler you have. See Figure D.

Each time you use your VENTOLIN HFA inhaler:

- Make sure the canister fits firmly in the plastic actuator.
- 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 the cap has not been used to cover the mouthpiece.

Reading the dose counter on your VENTOLIN HFA actuator:

- The dose counter will count down by 1 number each time you spray the inhaler.
- The dose counter stops counting when it reaches **000.** It will continue to show **000**.
- The dose counter cannot be reset, and it is permanently attached to the metal canister. **Never** try to change the numbers for the dose counter or take the counter off the metal canister.
- **Do not** remove the canister from the plastic actuator except during cleaning to prevent accidently spraying a dose of VENTOLIN HFA into the air.

Using your VENTOLIN HFA inhaler:

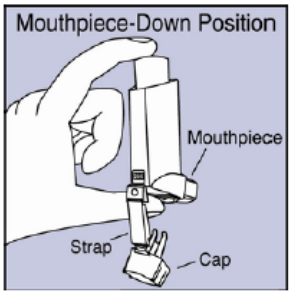


Figure E

Step 1. **Shake the inhaler well** before each spray. Take the cap off the mouthpiece of the actuator.

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

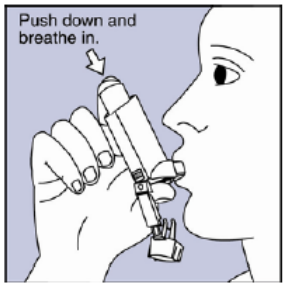


Figure F

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

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

Step 5. 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.

Step 6. **Hold your breath as long as you can**, up to 10 seconds, then breathe normally.

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

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

Cleaning your VENTOLIN HFA actuator:

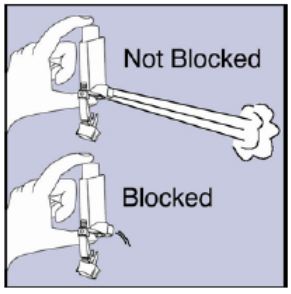


Figure G

It is very important to keep the plastic actuator clean so the medicine will not build-up and block the spray. See Figure G.

- **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 as follows:

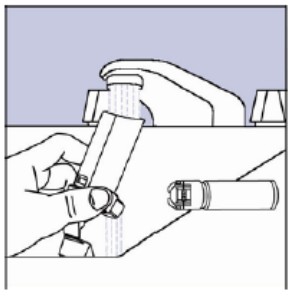


Figure H

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

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

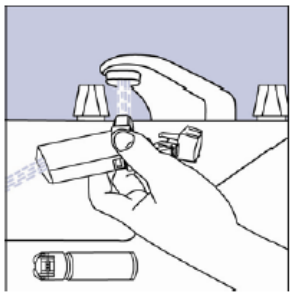


Figure I

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

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

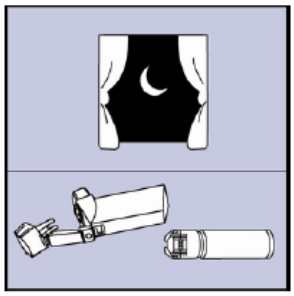


Figure J

Step 12. Let the actuator air-dry completely, such as overnight. See Figure J.

Step 13. 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 number.) Put the cap back on the mouthpiece.

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

- Shake as much water off the actuator as you can.
- Put the 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.
- Take your VENTOLIN HFA dose as prescribed.
- Follow cleaning Steps 8 through 13 above.

Replacing your VENTOLIN HFA inhaler:

- **When the dose counter on the actuator shows the number 020**, you need to refill your prescription or ask your doctor for another prescription for VENTOLIN HFA.
- **Throw the VENTOLIN HFA inhaler away** as soon as the dose counter shows **000**, after the expiration date on the VENTOLIN HFA packaging, or 12 months after you open the foil pouch, whichever comes first. You should not keep using the inhaler after the dose counter shows **000** even though the canister may not be completely empty. You cannot be sure you will receive the right amount of medicine.

Appendix 4 Dose Indicator 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 5 Sponsor Signatory

Study Title: An Open-Label, Multi-Center, Dose Indicator Study of Glycopyrronium and Formoterol Fumarate (GFF) Metered Dose Inhaler (MDI) in Adult Subjects with Moderate to Very Severe Chronic Obstructive Pulmonary Disease (COPD)

Study Number: PT003016-00

Final Date: [redacted]

Signature: [redacted] Date: [redacted]

Name: [redacted]

Title: [redacted]

[redacted] Pearl Therapeutics, Inc.

Appendix 6 Investigator's Agreement and Signature Page

Study Title: An Open-Label, Multi-Center, Dose Indicator Study of Glycopyrronium and Formoterol Fumarate (GFF) Metered Dose Inhaler (MDI) in Adult Subjects with Moderate to Very Severe Chronic Obstructive Pulmonary Disease (COPD)

Study Number: PT003016-00

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.
- Not to implement any changes to the protocol without agreement from the Sponsor and prior review and written approval from the IRB/IEC, except where necessary to eliminate an immediate hazard to the subjects, or for administrative aspects of the study (where permitted by all applicable regulatory requirements).
- That I am aware of, and will comply with good clinical practices (GCP) and all applicable regulatory requirements.
- That I am thoroughly familiar with the appropriate use of the investigational product(s), and other information provided by the Sponsor 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 Therapeutic 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 Therapeutics 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 Therapeutics
- 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 case report forms (CRFs). The CRFs will be provided to the Sponsor in a timely manner at the completion of the study, or as otherwise specified by the Sponsor.
- To allow authorized representatives of Pearl Therapeutics 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: _____

_____