Clinical Trial Protocol: PT009001-01

Study Title:	A Randomized, Double-Blind, Chronic Dosing (28 Days), Four-Period, Five-Treatment, Incomplete Block, Multi-Center, Crossover Study to Assess the Efficacy and Safety of PT009, PT008, and PT005 in Subjects With Moderate to Severe COPD
Study Number:	PT009001-01
Study Phase:	IIb
Product Name:	Budesonide and Formoterol Fumarate Inhalation Aerosol; PT009, Budesonide and Formoterol Fumarate Metered Dose Inhaler (BFF MDI) Budesonide Inhalation Aerosol; PT008, Budesonide Metered Dose Inhaler (BD MDI) Formoterol Fumarate Inhalation Aerosol; PT005, Formoterol Fumarate Metered Dose Inhaler (FF MDI)
IND Number:	122166
Indication:	Chronic Obstructive Pulmonary Disease (COPD)
Investigators:	Multi-center
Sponsor:	Pearl Therapeutics, Inc. [redacted]
Sponsor Contact:	[redacted]

	Version Number	Date
Original Protocol	Version 1.0	[redacted]
Amendment 1	Version 2.0	[redacted]

SUMMARY OF CHANGES

Based on points that required clarification/revision, the following changes have been incorporated into to PT009001-00 (Version 1.0). The amended study protocol, PT009001-01 (Version 2.0), includes the following edits:

1. In synopsis, section 3.3, 7.2, and 9.2.3: Respiratory rate, which was listed among other vital sign as a safety endpoint has been **deleted**. Although, respiratory rate is collected as a vital sign, it is not a standard safety endpoint for Pearl.

2. In section 4.1 (***General Guidelines for Treatment Visits 2 through 13***): The duration of washout time for COPD medications prior to clinic visits inadvertently stated the washout period as "within four hours" which was corrected to **"within six hours"**.

3. In section 7.3.1; Pharmacokinetic Plasma Collection and Plasma Sample Storage and Handling, samples shipment address has been corrected from [redacted] to the Central Laboratory.

4. In Table 8.1, Schedule of Events, the following assessments were inserted for accuracy:
    - Per section 7.2.4, clinical laboratory testing will be performed at Visits 5, 8, and 11
    - Per section 8.10, prior/concomitant medications use will be collected at the Follow-Up Period
    - Footer f: "See Section 7.1.1.4" is corrected to "See Section 7.1.1.1"

5. In Table 8.2, Schedule of Events: for clarity, the following changes have been made for accuracy:

    - Per section 7.2.4, clinical laboratory testing has been added at the 30 minutes post- dose timepoint
    - In the table footers, the following text "ECG is not required at Day 15" has been moved from footer "e" to footer "d"

6. In section 8.1 Visit 1a (and Visit 1b), and Section 8.9 Unscheduled Visits/Premature Discontinuation (Early Term) visit; "*peak flow meter*" has been deleted because peak flow meters are not utilized in this study.

7. In section 8.9 Unscheduled Visits/Premature Discontinuation (Early Term) visit, the bolded text has been corrected "*Return subject to pre-study or appropriate maintenance **asthma medications***" to "*Return subject to pre-study or appropriate maintenance **COPD medications***".

8. In Appendix 7; Pharmacokinetic Plasma Collection and Plasma Sample Storage and Handling, the bolded text has been added to clarify the preference for refrigerated centrifugation of samples.

   "*Centrifuge the blood within 30 minutes of collection at >1000 x g (~2500 rpm) for 10 to15 minutes.* ***It is preferred that*** *the rotor chamber of the centrifuge* ***is*** *refrigerated to maintain a temperature of approximately 4^{o}C.*"

   Also, due to the change in Section 7.3.1 (See item #3 above), the shipping address for [redacted] has been deleted and replaced with the following text:

   "*Samples will be shipped frozen to the Central Laboratory. Please see your laboratory manual for instructions*."

SYNOPSIS

Sponsor:

Pearl Therapeutics, Inc. (Pearl)

[redacted]

Name of Finished Product:

Budesonide and Formoterol Fumarate Inhalation Aerosol; PT009, Budesonide and Formoterol Fumarate Metered Dose Inhaler (BFF MDI)

Budesonide Inhalation Aerosol; PT008, Budesonide Metered Dose Inhaler (BD MDI)
Formoterol Fumarate Inhalation Aerosol; PT005, Formoterol Fumarate Metered Dose Inhaler (FF MDI)

Name of Active Ingredient:

Budesonide and Formoterol Fumarate

Budesonide

Formoterol Fumarate

Study Title:

A Randomized, Double-Blind, Chronic Dosing (28 Days), Four-Period, Five-Treatment, Incomplete Block, Multi-Center, Crossover Study to Assess the Efficacy and Safety of PT009, PT008, and PT005 in Subjects With Moderate to Severe COPD

Study Number: PT009001-01

Study Phase: IIb

Study Objective:

The overall objective of this study is to assess the efficacy and safety of treatment with three doses of BFF MDI (320/9.6 µg, 160/9.6 µg, and 80/9.6 µg) ex-actuator twice daily (BID) in comparison to BD MDI 320 µg ex-actuator BID and FF MDI 9.6 µg ex-actuator BID over 28 days in subjects with moderate to severe chronic obstructive pulmonary disease (COPD).

Primary Objective:

Demonstrate that the combination of BD 320 µg and FF 9.6 µg (BFF MDI 320/9.6 µg) provides benefit on lung function compared with BD MDI 320 µg in subjects with moderate to severe COPD.

Secondary Objectives:

- Demonstrate that the combination of BD 320 µg and FF 9.6 µg (BFF MDI 320/9.6 µg) provides benefit on lung function compared with FF MDI 9.6 µg in subjects with moderate to severe COPD.
- Assess the dose response of BD on a fixed-dose background of FF (9.6 µg) using BFF MDI (320/9.6 µg, 160/9.6 µg, and 80/9.6 µg) in subjects with moderate to severe COPD.

Pharmacokinetic Objectives:

- Compare the BD systemic exposure of three doses of BFF MDI to that of BD MDI 320 µg.
- Compare the formoterol systemic exposure of three doses of BFF MDI to that of FF MDI 9.6 µg.

Safety Objective:

- Evaluate the safety and tolerability of BFF MDI, BD MDI, and FF MDI.

Study Design:

This is a Phase IIb, randomized, double-blind, chronic dosing (28 days), four-period, five-treatment, incomplete block, crossover design in subjects with moderate to severe COPD.

This multi-center study will be conducted at approximately 15 sites, contributing approximately 10 subjects per site. Across these sites, it is planned that approximately 160 subjects with moderate to severe COPD will be randomized into one of 12 treatment sequences to provide approximately 130 subjects to complete the study. All treatment sequences will include BFF MDI 320/9.6 µg and FF MDI 9.6 µg and two of the three remaining treatments. The design is balanced for period and first order carryover effects within each block of 12.

Approximately 60 subjects will participate in a pharmacokinetic (PK) sub-study to assess the systemic exposure of BD and formoterol on Day 29 of each treatment period.

The entire study is scheduled to take a maximum of 32 weeks for each individual subject. The study is anticipated to run for approximately 9 months and is not expected to exceed 12 months.

Study Population:

Approximately 160 subjects with moderate to severe COPD will be enrolled to provide approximately 130 subjects to complete the study. Full inclusion and exclusion criteria are listed in Section 5.

Test Product, Dose, and Mode of Administration:

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

Product Name & Dose	Product Strength	Dosage Form	Comments
BFF MDI 320/9.6 µg ex-actuator	160/4.8 µg per actuation	MDI	Taken as 2 inhalations.
BFF MDI 160/9.6 µg ex-actuator	80/4.8 µg µg per actuation	MDI	Taken as 2 inhalations.
BFF MDI 80/9.6 µg ex-actuator	40/4.8 µg µg per actuation	MDI	Taken as 2 inhalations.
BD MDI 320 µg ex-actuator	160 µg per actuation	MDI	Taken as 2 inhalations.
FF MDI 9.6 µg ex-actuator	4.8 µg per actuation	MDI	Taken as 2 inhalations.
Albuterol Sulfate inhalation aerosol [a] 90 µg	US source: Ventolin® HFA Each inhalation contains 108 µg corresponding to 90 µg albuterol base from the mouthpiece	MDI	Taken as needed. Supplies are open-label.
Ipratropium Bromide inhalation aerosol[b] 34 µg ex-actuator	US source: Atrovent® HFA Each inhalation contains 17 µg per actuation	MDI	Taken as 2 inhalations. Supplies are open-label.
Budesonide Inhalation Powder[b] 180 µg	US source: (Pulmicort Flexhaler®) Each inhalation contains 180 µg of budesonide corresponding to 160 µg delivered from the mouthpiece	DPI	Taken as directed. Supplies are open-label.

BD=budesonide; BFF=budesonide and formoterol fumarate; FF=formoterol fumarate; HFA=hydrofluoroalkane; MDI=metered dose inhaler; US=United States

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

a Rescue medication and reversibility testing.

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

Duration of Treatment:

Each subject will receive 28 days of study treatment in each of their assigned treatments for a total of four separate treatment periods. A Washout Period of at least 14 days (and up to 21 days) will occur between each treatment period. The entire study is scheduled to take a maximum of 32 weeks for each individual subject from the time of Screening (Visit 1a).

Efficacy Assessments:

The first day of treatment in each treatment period is Day 1. Each treatment period is planned to contain 28 days between the first and last dose corresponding to a span of 29 calendar days. Therefore, assessments collected on Day 15 (Visits 3, 6, 9, and 12) will occur following 14 days of treatment and assessments collected on Day 29 (Visits 4, 7, 10, and 13) will occur following 28 days of treatment.

Primary Efficacy Endpoint:

- Forced expiratory volume in 1 second (FEV_1) area under the curve from 0 to 12 hours (AUC_{0-12}) on Day 29

Secondary Efficacy Endpoints:

- Change from baseline in morning pre-dose trough FEV_1 over 28 days
- Peak FEV_1 evaluated during chronic dosing utilizing the peak change from baseline on Days 15 and 29
- Peak change from baseline in FEV_1 on Day 1
- Forced vital capacity (FVC) AUC_{0-12} on Day 29
- Transition Dyspnea Index (TDI) focal score on Day 29
- Change from baseline in average daily use of rescue Ventolin HFA over the last week of treatment

Other Efficacy Endpoints:

- Change from baseline in morning pre-dose trough FEV_1 on Days 15 and 29
- Peak change from baseline in FEV_1 on Days 15 and 29
- Change from baseline in 12-hour post-dose trough FEV_1 on Day 29
- FEV_1 AUC_{0-2} on Day 1
- FEV_1 AUC_{0-2}, FEV_1 AUC_{0-6}, and FEV_1 AUC_{6-12} on Day 29
- Change from baseline in FEV_1 by post-dose timepoints on Days 1 and 29
- Change from baseline in morning pre-dose trough FVC on Days 15 and 29 and over 28 days
- Peak change from baseline in FVC on Days 1, 15, and 29 and over 28 days evaluated utilizing the peak change from baseline on Days 15 and 29
- FVC AUC_{0-2} on Day 1
- Change from baseline in FVC by post-dose timepoint on Days 1 and 29
- Change from baseline in 12-hour post-dose trough FVC on Day 29
- Change from baseline in morning pre-dose trough peak expiratory flow rate (PEFR) on Days 15 and 29 and over 28 days
- Peak change from baseline in PEFR on Days 1, 15, and 29 and over 28 days evaluated utilizing Days 15 and 29
- PEFR AUC_{0-2} on Day 1 and PEFR AUC_{0-12} on Day 29
- Change from baseline in PEFR by post-dose timepoint on Days 1 and 29

- Change from baseline in 12-hour post-dose trough PEFR on Day 29
- Change from baseline in average daily use of rescue Ventolin HFA over the treatment period
- Change from baseline in the Breathlessness, Cough, and Sputum Scale (BCSS) total score over the treatment period
- Change from baseline in nighttime awakenings over the treatment period

Pharmacokinetic Assessments:

The PK of BD and formoterol will be assessed from plasma concentrations in a subset of approximately 60 subjects. Timepoints for PK blood sample collection during each of the four periods will be: Day 1 within 30 minutes prior to dosing, and Day 29 within 30 minutes prior to dosing, then 2, 6, 20, and 40 minutes and 1, 2, 4, 8, 10, and 12 hours post-dose.

Pharmacokinetic parameters at all doses will include: maximum plasma concentration (C_{max}); time of maximum plasma concentration; half-life; AUC_{0-12}; AUC_{0-t}; clearance; apparent volume of distribution; and terminal elimination rate constant.

Safety Assessments:

The safety endpoints for this study include adverse events (AEs) and serious adverse events (SAEs), vital signs (blood pressure, heart rate, and temperature), clinical laboratory values (hematology and clinical chemistry), and electrocardiograms (ECGs).

Statistical Methods:

Primary Efficacy Analyses:

FEV_1 AUC_{0-12} is the area under the curve for the change from baseline in FEV_1 calculated using the trapezoidal rule and will be normalized by dividing the AUC by the length of follow-up post-dosing (typically 12 hours). Baseline will be calculated using the average of the pre-dose values from Day 1 of all treatment periods. The primary efficacy analysis will be based on a repeated measures mixed model with covariates of treatment, baseline, period, and the response to Ventolin HFA at Screening (Visits 1a and 1b). The model will not include treatment sequence unless that term is determined to be important ($p<0.10$). Intrasubject correlation will be modeled by including subject as a random effect.

For the primary efficacy objective, the family-wise Type I error will be controlled sequentially by testing the higher dose of BFF MDI compared with BD MDI first before testing the middle and the lower dose compared with BD MDI. For the first secondary objective, sequential dose-ordered testing will also be used for BFF MDI compared with FF MDI. The modified Intent-to-Treat Population will be considered primary, and the Intent-to-Treat Population will be considered supportive.

The secondary endpoints and the other endpoints will be analyzed in a similar fashion. The model for analyses that use multiple values within each period will include treatment day (15 or 29) as an unordered categorical covariate. The interaction of treatment with treatment day will also be included.

Pharmacokinetic Analyses:

The PK sub-analyses parameters will be estimated using a non-compartmental model. Area under the curve and C_{max} parameters will be compared between treatments using log-transformed values and repeated measures analysis to estimate geometric mean ratios.

Safety Analyses:

Safety analyses will be based on descriptive statistics for ECGs, vital signs, and laboratory measurements, and on frequencies of AEs and SAEs.

Sample Size Determination:

Power calculations were based on the properties of the primary endpoint, FEV_1 $AUC_{0-12,}$ on Day 29. Estimates of within-subject standard deviation (SD) of FEV_1 AUC_{0-12} were obtained from previous Pearl studies. A composite within-subject SD of 130 mL is assumed and a total SD of 184 mL. It is further assumed that approximately 20% of subjects will dropout, and a two-sided alpha level of 0.05 will be used. Under these assumptions, 160 randomized subjects will provide approximately 99% power to demonstrate a difference of 100 mL for each dose of BFF MDI compared with BD MDI 320 µg. The power to demonstrate a difference of 50 mL for BFF MDI 320/9.6 µg compared with FF MDI is approximately 90%. For the lower strengths of BFF MDI, the power to demonstrate a difference of 50 mL compared with FF MDI is approximately 54%.

Date of Original Approved Protocol: [redacted]

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

LIST OF APPENDICES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

λ_z	Terminal Elimination Rate Constant
AE	Adverse Event
AR(1)	Autoregressive Order 1
ATS	American Thoracic Society
AUC	Area Under the Curve
AUC_{0-2}	Area Under the Curve From 0 to 2 Hours
AUC_{0-6}	Area Under the Curve From 0 to 6 Hours
AUC_{0-12}	Area Under the Curve From 0 to 12 Hours
AUC_{6-12}	Area Under the Curve From 6 to 12 Hours
AUC_{0-t}	Area Under the Curve from 0 to Time of the Last Measurable Concentration
BCSS	Breathlessness, Cough, and Sputum Scale
BD	Budesonide
BDI	Baseline Dyspnea Index
BFF	Budesonide and Formoterol Fumarate
BID	*Bis In Die*, Twice Daily
BMP	Basic Metabolic Panel
BP	Blood Pressure
BPM	Beats Per Minute
BTPS	Body Temperature and Pressure Saturated
CBC	Complete Blood Count
CFR	Code of Federal Regulations
CI	Confidence Interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration Equation (according to National Kidney Disease Education Program)
CL/F	Clearance
C_{max}	Maximum Plasma Concentration
CMP	Comprehensive Metabolic Panel
CONSORT	CONsolidated Standards of Reporting Trials

COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
CT	Computerized Tomography
DBP	Diastolic Blood Pressure
DPI	Dry Powder Inhaler
ECG	Electrocardiogram
eg.	*Exempli Gratia*, For Example
ERS	European Respiratory Society
EV	Back Extrapolation Volume
ex-actuator	Dose Delivered from the Actuator (ie., Mouthpiece) of the Metered Dose Inhaler
FDA	Food and Drug Administration
FEV_1	Forced Expiratory Volume in 1 Second
FF	Formoterol Fumarate
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GOLD	Global Initiative for Chronic Obstructive Lung Disease
hCG	Human Chorionic Gonadotropin
HR	Heart Rate
HFA	Hydrofluoroalkane
IB	Investigators Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
ICS	Inhaled Corticosteroid
ID	Identification
ie.	*Id Est*, That Is
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ISMPP	International Society for Medical Publications Professionals

ITT	Intent-to-Treat
IWRS	Interactive Web Response System
L	Liter
LABA	Long-Acting β_2-Agonist
LAMA	Long-Acting Antimuscarinic Agents
MDI	Metered Dose Inhaler
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-Treat
mL	Milliliter
msec (ms)	Millisecond
NHANES III	Third National Health and Nutrition Examination Survey
OTC	Over-the-Counter
PEFR	Peak Expiratory Flow Rate
PIN	Personal Identification Number
PFT	Pulmonary Function Test
PK	Pharmacokinetic
QID	*Quarter In Die*, Four Times Daily
QTcF	QT Corrected Using Fridericia's Formula (QT/[RR $^{1/3}$])
SABA	Short-Acting β_2-Agonist
SAC	Self-administered Computerized
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SD	Standard Deviation
$t_{½}$	Half-Life
TDI	Transition Dyspnea Index
t_{max}	Time of Maximum Plasma Concentration
US	United States
VC	Vital Capacity

Vd/F	Apparent Volume of Distribution

TRADEMARK INFORMATION

Trademarks Not Owned By Pearl Therapeutics, Inc.

Aerolizer®
Anoro™
Aqua®
Arcapta™
Atrovent®
Breo™
Daliresp®
Daxas®
Ellipta™
Foradil®
KoKo Spirometer®
Neohaler™
Oxis®
Pulmicort Flexhaler®
R®
Respules®
Rhinocort®
SAS®
Seebri®
Spiriva®
Symbicort®
Tudorza™
Turbuhaler®
Ventolin®
Ziploc®

1 INTRODUCTION

Pearl Therapeutics, Inc. (Pearl) is developing a combination product, Budesonide and Formoterol Fumarate Inhalation Aerosol (PT009; hereafter referred to as budesonide and formoterol fumarate metered dose inhaler [BFF MDI]), as a long-term twice daily (BID) treatment for subjects with chronic obstructive pulmonary disease (COPD). Pearl is also developing the individual products. Budesonide Inhalation Aerosol (PT008; hereafter referred to as budesonide metered dose inhaler [BD MDI]) is being developed as a BID glucocorticosteroid anti-inflammatory treatment. Formoterol Fumarate Inhalation Aerosol (PT005; hereafter referred to as formoterol fumarate metered dose inhaler [FF MDI]) is being developed as a BID maintenance bronchodilator treatment in subjects with COPD.

1.1 Chronic Obstructive Pulmonary Disease

Chronic obstructive pulmonary disease is a common preventable and treatable disease characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases. Exacerbations and co-morbidities contribute to the overall severity in individual patients. Chronic obstructive pulmonary disease is a leading cause of morbidity and mortality worldwide and results in significant economic and social burden that is both substantial and increasing. Pharmacologic therapy in COPD is used to reduce symptoms, reduce the frequency and severity of exacerbations, and improve health status and exercise tolerance [Global Initiative for Chronic Obstructive Lung Disease (GOLD), 2014].

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

Regular treatment with inhaled corticosteroids (ICS) improves symptoms, lung function, and quality of life and reduces the frequency of exacerbations in subjects with COPD with a forced expiratory volume in 1 second (FEV_1) value of <60% of predicted. Withdrawal from treatment of ICS may lead to exacerbations in some patients. When combined with a long-acting β_2-agonist (LABA), an ICS is more effective than the individual components in improving lung function, quality of life, and reducing exacerbations in subjects with moderate to very severe COPD [GOLD, 2014].

1.2 Formoterol Fumarate

Formoterol fumarate is a potent and selective LABA approved in the United States (US) (eg., Foradil® Aerolizer®) and worldwide (eg., Oxis® Turbuhaler®, Foradil) for use in asthma and COPD. Formoterol fumarate is also approved in the US and worldwide in combination with BD (eg., Symbicort® MDI, Symbicort Turbuhaler) for use in patients with asthma and COPD. When inhaled, FF acts locally in the lung as a bronchodilator. Formoterol fumarate

stimulates β_2-adrenoreceptors in the airways, inducing airway smooth muscle relaxation and reducing or preventing bronchoconstriction.

In patients with COPD, FF is typically administered as an orally inhaled dose of 12 µg BID with doses up to 24 µg BID approved in some countries. Although FF is classified as a LABA, it has a rapid onset of action similar to short-acting β_2-agonists (SABAs). Formoterol fumarate is highly potent, displays high intrinsic activity, and can result in greater than 80% relaxation even under induced tone [Anderson, 1993]. Studies in subjects with COPD have demonstrated that the onset of action with FF is faster than with anticholinergic agents or salmeterol and similar to that of SABAs, such as albuterol, and that the duration of action is ≥12 hours [Berger, 2008]. Five large, placebo-controlled clinical studies of up to 12 months in duration in nearly 2500 patients demonstrated that FF is effective and well tolerated in patients with COPD [Dahl, 2001; Rossi, 2002; Aalbers, 2002; Campbell, 2005; Campbell, 2007].

1.3 Budesonide

Budesonide is a well-established corticosteroid approved worldwide in both intranasal and inhaled formulations. Inhaled BD formulations currently approved in the US include Rhinocort® Nasal Inhaler, Rhinocort Aqua® Nasal Spray, Pulmicort® Turbuhale, Symbicort Inhalation Aerosol (Symbicort MDI), and Pulmicort Respules®.

Inflammation is a component in the pathogenesis of COPD. The predominant inflammatory cells in COPD include neutrophils, CD8+ T-lymphocytes, and macrophages. The effects of ICS on pulmonary and systemic inflammation in patients with COPD are controversial and their role in the management of stable COPD is limited to specific indications. Regular treatment with ICS has been shown to improve symptoms, lung function and quality of life, and reduce the frequency of exacerbations in COPD patients with a FEV_1 value <60% of predicted. The GOLD guidelines acknowledge that combination therapy with an ICS and LABA is more effective than the individual components in improving lung function and health status and reducing exacerbations in patients with moderate to very severe COPD [GOLD, 2014].

1.4 Pearl Therapeutics' BFF MDI

Pearl has licensed and developed a particle engineering technology that utilizes porous particles for pulmonary drug delivery via MDIs. This technology is based on spray-dried porous particles comprised of distearoylphophatidylcholine and calcium chloride that are co-suspended with crystalline active drug substances and formulated into suspension-based hydrofluoroalkane (HFA) MDIs. In vitro and in vivo testing suggest that the Pearl formulations will provide highly efficient, reproducible administration of therapeutics from MDIs in a wide dosing range [Hirst, 2002; Dellamary, 2000]. Pearl is developing a broad range of MDI-based inhalation products using its porous particle technology platform.

1.5 Study Rationale

BFF MDI is a novel fixed-dose double combination MDI product formulated with BD and FF for use in patients with COPD. As described in the GOLD COPD guidelines, in some patients the addition of an ICS to a LABA improves lung function, health-related quality of life, and may further reduce exacerbations. Pearl has planned this study to evaluate the safety and efficacy of treatment with three doses of BFF MDI (320/9.6, 160/9.6, and 80/9.6 μg ex-actuator, BID) compared with BD MDI (320 μg ex-actuator, BID) and FF MDI (9.6 μg ex-actuator, BID) over 28 days in subjects with moderate to severe COPD. To this end, it is anticipated this study will demonstrate that a combination BD and FF will have a benefit on lung function compared with the actions of either study drug acting alone. The dose effect of BD MDI 320, 160, and 80 μg on a fixed-dose background of FF 9.6 μg will also be demonstrated.

2 STUDY OBJECTIVES

The overall objective of this study is to assess the efficacy and safety of treatment with three doses of BFF MDI (320/9.6 µg, 160/9.6 µg, and 80/9.6 µg) ex-actuator BID in comparison to BD MDI 320 µg ex-actuator BID and FF MDI 9.6 µg ex-actuator BID over 28 days in subjects with moderate to severe COPD.

2.1 Primary Objective

The primary objective of this study is to demonstrate that the combination of BD 320 µg and FF 9.6 µg (BFF MDI 320/9.6 µg) provides benefit on lung function compared with BD MDI 320 µg in subjects with moderate to severe COPD.

2.2 Secondary Objectives

The secondary objectives of this study are to:

- Demonstrate that the combination of BD 320 µg and FF 9.6 µg (BFF MDI 320/9.6 µg) provides benefit on lung function compared with FF MDI 9.6 µg in subjects with moderate to severe COPD.

- Assess the dose response of BD on a fixed-dose background of FF (9.6 µg) using BFF MDI (320/9.6 µg, 160/9.6 µg, and 80/9.6 µg) in subjects with moderate to severe COPD.

2.3 Other Objectives

2.3.1 Pharmacokinetic Objectives

The pharmacokinetic (PK) objectives of this study are to:

- Compare the BD systemic exposure of three doses of BFF MDI to that of BD MDI 320 µg.
- Compare the formoterol systemic exposure of three doses of BFF MDI to that of FF MDI 9.6 µg.

2.3.2 Safety Objective

The safety objective of this study is to evaluate the safety and tolerability of BFF MDI, BD MDI, and FF MDI.

3 STUDY ENDPOINTS

3.1 Efficacy Endpoints

The first day of treatment in each treatment period is Day 1. Each treatment period is planned to contain 28 days between the first and last dose corresponding to a span of 29 calendar days. Therefore, assessments collected on Day 15 (Visits 3, 6, 9, and 12) will occur following 14 days of treatment and assessments collected on Day 29 (Visits 4, 7. 10, and 13) will occur following 28 days of treatment.

3.1.1 Primary Efficacy Endpoint

- FEV_1 area under the curve from 0 to 12 hours (AUC_{0-12}) on Day 29

3.1.2 Secondary Efficacy Endpoints

- Change from baseline in morning pre-dose trough FEV_1 over 28 days
- Peak FEV_1 evaluated during chronic dosing utilizing the peak change from baseline on Days 15 and 29
- Peak change from baseline in FEV_1 on Day 1
- FVC AUC_{0-12} on Day 29
- TDI focal score on Day 29
- Change from baseline in average daily use of rescue Ventolin HFA over the last week of treatment

3.1.3 Other Efficacy Endpoints

- Change from baseline in morning pre-dose trough FEV_1 on Days 15 and 29
- Peak change from baseline in FEV_1 on Days 15 and 29
- Change from baseline in 12-hour post-dose trough FEV_1 on Day 29
- FEV_1 AUC_{0-2} on Day 1
- FEV_1 AUC_{0-2}, FEV_1 AUC_{0-6}, and FEV_1 AUC_{6-12} on Day 29
- Change from baseline in FEV_1 by post-dose timepoints on Days 1 and 29
- Change from baseline in morning pre-dose trough FVC on Days 15 and 29 and over 28 days
- Peak change from baseline in FVC on Days 1, 15, and 29 and over 28 days evaluated utilizing the peak change from baseline on Days 15 and 29
- FVC AUC_{0-2} on Day 1
- Change from baseline in FVC by post-dose timepoint on Days 1 and 29
- Change from baseline in 12-hour post-dose trough FVC on Day 29

- Change from baseline in morning pre-dose trough peak expiratory flow rate (PEFR) on Days 15 and 29 and over 28 days
- Peak change from baseline in PEFR on Days 1, 15, and 29 and over 28 days evaluated utilizing Days 15 and 29
- PEFR AUC_{0-2} on Day 1 and PEFR AUC_{0-12} on Day 29
- Change from baseline in PEFR by post-dose timepoint on Days 1 and 29
- Change from baseline in 12-hour post-dose trough PEFR on Day 29
- Change from baseline in average daily use of rescue Ventolin HFA over the treatment period
- Change from baseline in the Breathlessness, Cough, and Sputum Scale (BCSS) total score over the treatment period
- Change from baseline in nighttime awakenings over the treatment period

3.2 Pharmacokinetic Endpoints (For PK Sub-Study Subjects Only)

The PK of BD and formoterol will be assessed from plasma concentrations in a subset of approximately 60 subjects. Timepoints for PK blood sample collection during each of the four periods will be: Day 1 within 30 minutes prior to dosing, and Day 29 within 30 minutes prior to dosing then 2, 6, 20, and 40 minutes and 1, 2, 4, 8, 10, and 12 hours post-dose.

Pharmacokinetic parameters at all doses will include:

- Maximum plasma concentration (C_{max})
- Time of maximum plasma concentration (t_{max})
- Half-life ($t_{½}$)
- AUC_{0-12}
- Area under the curve from 0 to the time of the last measureable data (AUC_{0-t})
- Clearance (CL/F)
- Apparent volume of distribution (Vd/F)
- Terminal elimination rate constant (λ_z)

3.3 Safety Endpoints

The safety endpoints for this study include adverse events (AEs) and serious adverse events (SAEs), vital signs (blood pressure [BP], heart rate [HR], , and temperature), clinical laboratory values (hematology and clinical chemistry), and electrocardiograms (ECGs).

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

This is a randomized, double-blind, chronic dosing (28 days), four-period, five-treatment, incomplete block, multi-center, crossover study to assess the efficacy and safety of BFF MDI 320/9.6, 180/9.6, and 80/9.6 µg ex-actuator BID, BD MDI 320 µg ex-actuator BID, and FF MDI 9.6 µg ex-actuator BID in subjects with moderate to severe COPD.

This multi-center study will be conducted at approximately 15 sites, contributing approximately 10 subjects per site. Across these sites, it is planned that approximately 160 subjects with moderate to severe COPD will be randomized into one of 12 treatment sequences to provide approximately 130 subjects to complete the study. All treatment sequences will include BFF MDI 320/9.6 µg and FF MDI 9.6 µg and two of the three remaining treatments. The study design is balanced for period and first order carryover effects within each block of 12 (see Appendix 8).

Approximately 60 subjects will participate in a PK sub-study to assess the systemic exposure of BD and formoterol on Day 29 of each treatment period.

The entire study is scheduled to take a maximum of 32 weeks for each individual subject. The study is anticipated to run for approximately 9 months and is not expected to exceed 12 months.

Prior to or at the Screening Visit (Visit 1a), all subjects are to sign an Informed Consent Form (ICF) prior to the conduct of any Screening assessments. The Investigator or designee will obtain a medical history, physical examination, and any required documentation in order to determine eligibility for participation (inclusion/exclusion criteria). Reversibility of FEV_1 following four puffs of Ventolin HFA (see Section 7.1.1.3) will be assessed at Screening to characterize the subject population but will not be used to determine eligibility to participate in the study. Subjects who are not using a prohibited medication and meet all other entry criteria will return to the clinic within 28 days after Screening for Visit 2 (Randomization Visit).

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

Subjects who meet all entry criteria but are using certain prohibited COPD medications (eg., oral β_2 agonists, LABAs, corticosteroid/LABA combination products, ICS/LABA, LABA/long-acting muscarinic agents (LAMA), ICS as a single agent, phosphodiesterase inhibitors [eg., theophylline, roflumilast], cromoglycate or nedocromil inhalers, leukotriene antagonists [eg., zafirlukast, montelukast, zileuton], or tiotropium) will discontinue these medications for the duration of the study and be switched to Sponsor-provided Atrovent

HFA, administered four times daily (QID), and Sponsor-provided Ventolin HFA, as needed. Subjects taking an ICS or ICS/LABA for maintenance treatment at Screening (Visit 1a) will be switched to Sponsor-provided Pulmicort Flexhaler BID for use during the washout period, which will be discontinued at the time of randomization (see Section 5.5).

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

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

At Visit 2 (Randomization Visit; Day 1 of Treatment Period 1), subjects will return to the clinic before 10:00 am. Site personnel will confirm that subjects meet the compliance requirement of ≥70% subject completion of eDiary assessments in the last 7 days preceding the Randomization Visit prior to being randomized. Subjects who continue to meet entry inclusion/exclusion criteria and remain eligible for participation in the study will be randomized into one of the pre-defined treatment sequences. Before sites dispense the first dose and prior to any study procedures being performed, site staff must confirm the subject met all protocol specific requirements and ensure adequate washout (6 hours or longer) of short-acting bronchodilators.

During Visit 2 (Randomization Visit; Day 1 of Treatment Period 1), subjects will be dispensed Treatment Period 1 study drug according to their assigned treatment sequence and will administer their first dose in the clinic under site personnel supervision. Subjects will be randomized into one of 12 treatment sequences in order to receive four treatments (all possible treatment sequences to which a subject can be randomized are shown in Appendix 8). Each sequence will include BFF MDI 320/9.6 µg and FF MDI 9.6 µg and two of the three remaining treatments (BFF MDI 160/9.6 µg, BFF MDI 80/9.6 µg, and BD MDI 320 µg) included in this study. The subject, clinical site personnel, and Pearl will be blinded to the treatment dose assigned to a subject; it will not be possible to differentiate between the treatments since they will be identical in all aspects.

Randomization will be centralized through the use of an Interactive Web Response System (IWRS). The BFF MDI, BD MDI, and FF MDI will be administered BID. Each of the four treatments will be administered for 28 days with a Washout Period of at least 14 days (up to 21 days) in between treatments.

Subjects will be required to remain at the clinic until completion of all protocol-defined assessments up to and including the 2-hour post-dose timepoint on Day 1 (see Table 8-2). Following the assessments on Day 1, subjects will be discharged from the clinic and will continue to administer Treatment Period 1 study drug at home until Visit 3 (Day 15 of Treatment Period 1). Subjects will utilize an eDiary in which they will be asked to maintain a daily record of their study drug dosing, rescue medication use, and COPD symptoms.

At Visit 3 (Day 15 of Treatment Period 1), subjects will return to the clinic before 10:00 am. Site personnel must review eDiary data, collect blinded study drug dispensed during the prior visit, and then administer a dose of the newly dispensed study drug at the clinic under site supervision. Subjects will be discharged following the assessments on Day 15 and will continue to administer the Treatment Period 1 study drug at home until the Day 29 Visit.

At Visit 4 (Day 29 of Treatment Period 1), subjects will return to the clinic before 10:00 am for administration of the final dose of Treatment Period 1 study drug under site personnel supervision. Site personnel must review eDiary data prior to dosing study drug in the clinic and will return the eDiary to the subject. Following all protocol-defined assessments, up to and including the 12-hour post-dose assessments on Day 29 (see Table 8-3), subjects will be discharged from the clinic and will undergo a study drug Washout Period of at least 14 days (but no more than 21 days duration), on Sponsor-provided Atrovent HFA MDI, administered QID, and may use Sponsor-provided Ventolin HFA, as needed, prior to initiating the next treatment in their assigned treatment sequence. Subjects treated with Pulmicort Flexhaler during Screening will be administered Sponsor-provided Pulmicort Flexhaler at a dose of 360 µg BID for use during the washout period.

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

Visit 5 (Day 1 of Treatment Period 2): Subjects will return their Sponsor-provided Atrovent HFA, Ventolin HFA, and Pulmicort Flexhaler (if applicable). Subject eDiaries will be reviewed and returned to the subjects. Subjects will be dispensed Treatment Period 2 study drug according to their assigned treatment sequence and will administer their first dose in the clinic under site personnel supervision. Subjects will undergo all protocol-defined assessments up to and including the 2-hour post-dose assessments (see Table 8-2), be discharged, and continue BID administration at home until Visit 6.

Visit 6 (Day 15 of Treatment Period 2): Subject eDiaries will be reviewed and returned to the subjects. Site personnel will collect blinded study drug dispensed during the prior visit, and then administer a dose of the newly dispensed study drug at the clinic under site supervision. Subjects will undergo all protocol-defined assessments up to and including the 2-hour post-dose assessments (see Table 8-2), be discharged, and continue BID administration at home until Visit 7.

Visit 7 (Day 29 of Treatment Period 2): Subject eDiaries will be reviewed and returned to the subjects. Subjects will administer their final dose of Treatment Period 2 study drug in the clinic under site personnel supervision. Subjects will undergo all protocol-defined assessments up to and including the 12-hour post-dose assessments (see Table 8-3) and a Washout Period of at least 14 days (but no more than 21 days duration) on Sponsor-provided Atrovent HFA MDI, administered QID, and Sponsor-provided Ventolin HFA, as needed prior to initiating their next assigned treatment sequence. Subjects treated with Pulmicort Flexhaler during Screening will be administered Sponsor-provided Pulmicort Flexhaler at a dose of 360 µg BID for use during the washout period.

Visit 8 (Day 1 of Treatment Period 3): Subjects will return their Sponsor-provided Atrovent HFA, Ventolin HFA, and Pulmicort Flexhaler (if applicable). Subject eDiaries will be reviewed and returned to the subjects. Subjects will be dispensed Treatment Period 3 study drug according to their assigned treatment sequence and will administer their first dose in the clinic under site personnel supervision. Subjects will undergo all protocol-defined assessments up to and including the 2-hour post-dose assessments (see Table 8-2), be discharged, and continue BID administration at home until Visit 9.

Visit 9 (Day 15 of Treatment Period 3): Subject eDiaries will be reviewed and returned to the subjects. Site personnel will collect blinded study drug dispensed during the prior visit, and then administer a dose of the newly dispensed study drug at the clinic under site supervision. Subjects will undergo all protocol-defined assessments up to and including the 2-hour post-dose assessments (see Table 8-2), be discharged, and continue BID administration at home until Visit 10.

Visit 10 (Day 29 of Treatment Period 3): Subject eDiaries will be reviewed and returned to the subjects. Subjects will administer their final dose of Treatment Period 3 study drug in the clinic under site personnel supervision. Subjects will undergo all protocol-defined assessments up to and including the 12-hour post-dose assessments (see Table 8-3), and undergo washout for at least 14 days (up to 21 days) on Sponsor-provided Atrovent HFA MDI, administered QID, and Sponsor-provided Ventolin HFA, as needed. Subjects treated with Pulmicort Flexhaler during Screening will be administered Sponsor-provided Pulmicort Flexhaler at a dose of 360 µg BID for use during the washout period.

Visit 11 (Day 1 of Treatment Period 4): Subjects will return their Sponsor-provided Atrovent HFA, Ventolin HFA, and Pulmicort Flexhaler (if applicable). Subject eDiaries will be reviewed and returned to the subjects. Subjects will be dispensed Treatment Period 4 study drug according to their assigned treatment sequence and will administer their first dose in the clinic under site personnel supervision. Subjects will undergo all protocol-defined assessments up to and including the 2-hour post-dose assessments (see Table 8-2), be discharged, and continue BID administration at home until Visit 12.

Visit 12 (Day 15 of Treatment Period 4): Subject eDiaries will be reviewed and returned to the subjects. Site personnel will collect blinded study drug dispensed during the prior visit, and then administer a dose of the newly dispensed study drug at the clinic under site supervision. Subjects will undergo all protocol-defined assessments up to and including the 2-hour post-dose assessments (see Table 8-2), be discharged, and continue BID administration at home until Visit 13.

Visit 13 (Day 29 of Treatment Period 4): Subject eDiaries will be reviewed and collected at the end of the in-clinic visit and retained at the site. Subjects will administer their final dose of Treatment Period 4 study drug in-clinic under site personnel supervision. Subjects will undergo all protocol-defined assessments up to and including the 12-hour post-dose assessments (see Table 8-3). Subjects will return to appropriate COPD maintenance medications.

Visit 13 will serve as the final clinic visit. Subjects will complete all post-study assessments, including a final physical examination and recording of any AEs, and will then be discharged from the study. A telephone follow-up will be performed within 7 to 14 days following Visit 13.

Starting at screening (Visit 1a/b) and for the duration of the study including treatment and washout periods, subjects will receive an eDiary in which they will be asked to maintain a daily record of their study drug dosing, rescue medication use, and collection of COPD symptoms (including BCSS).

General Guidance for Treatment Visits 2 through 13 (in clinic):

- At the start of each treatment visit, prior to any study procedures being performed, site personnel must confirm the subject withheld all COPD medications, including study drug, rescue medications (eg., Ventolin HFA), for at least 6 hours, by confirming the last time of dosing for all COPD medication(s).
  - **Note**: Subjects who inadvertently took COPD medication(s) within six hours of the start of study procedures must be rescheduled as soon as is practical, but within the specified visit window.
  - **Note:** Before the in-clinic dose is administered, the site must confirm the subject met all other protocol-specified requirements (eg., FEV_1 baseline criteria; see Section 7.1.1.1). Subjects will remain in the clinic until 30 minutes post-dose for observation (safety).
- Subjects must not ingest xanthine-containing foods and beverages for at least 6 hours prior to each study visit and for the duration of each study visit (see Section 5.6).
- Subjects will be required to refrain from smoking, including electronic cigarettes, for at least 4 hours prior to each study visit and throughout the duration of each study visit**. Note:** nicotine gums and patches are allowed.
- To ensure standardization of dosing times, it is recommended that sites encourage subjects to maintain a dosing schedule at home consistent with their in-clinic dosing time.
  - Subjects will be required to take their study drug BID in the morning between 06:00 and 10:00 am (breakfast time) and in the evening between 06:00 and 10:00 pm (dinner time).
- In order to minimize diurnal variance, sites should make every effort to assess subjects at the same time throughout the study and to discuss the importance of dosing in a timely manner every 12 hours.
  - Subjects should be scheduled to return to the clinic at approximately the same time for all treatment visits (±2 hours) but not past 10:00 am and will be required to remain at the clinic until completion of all protocol-defined assessments.
  - Sites should make every effort to ensure that the in-clinic dosing time is before 10:00 am and within 12±2 hours of the prior at-home evening dosing time.

- Sites are encouraged to call the subject on the day before a scheduled visit to remind the subject of the following:
  - To take their last dose the evening before (12±2 hours) prior to the scheduled visit.
  - To bring their study drugs with them to the clinic, to withhold all COPD medications (including ICS, where applicable) for at least 6 hours prior to pulmonary function tests (PFTs).
  - Refrain from ingesting xanthine-containing foods and beverages for at least 6 hours prior to each study visit and for the duration of each study visit.
  - Refrain from smoking for at least 4 hours prior to the study visit and throughout the duration of each study visit
- The in-clinic dosing time will be recorded as the time of administration of the second puff of study drug.
- Site personnel will instruct subjects not to take any COPD medications, without site personnel permission, during a visit until all study procedures have been completed and the subject is discharged. Site personnel should take every precaution to prevent use of non-study COPD medications during test day. Site personnel may request the subject to surrender all non-study COPD medications prior to the start of the visit before performing any study procedures and return the medications to the subject at the end of the visit when all study procedures are completed.
- If a subject is experiencing severe symptoms and requires Ventolin HFA for relief of COPD symptoms at any time during a test day, site personnel must note the time and justification for use in the subject's chart and all subsequent spirometry and PEFR assessments should be stopped. However, safety assessments should be continued at the discretion of the Investigator or designee.
- Every effort must be made to ensure that subjects return to the clinic on Day 15 following the initiation of each treatment period. To accommodate scheduling conflicts at Day 15 (Visits 3, 6, 9, and 12) a window of ±2 days from Day 1 is permitted (ie., Day 15 procedures must be done between Day 13 and Day 17, inclusive).
- Similarly, every effort must be made to ensure that subjects return to the clinic on Day 29 following the initiation of each treatment arm. To accommodate scheduling conflicts, a window of 29±2 days is permitted (ie., Day 29 procedures must be done within a minimum of 27 days and a maximum of 31 days from Day 1).

During each treatment period (between Visits 2 and 4, Visits 5 and 7, Visits 8 and 10, and Visits 11 and 13), subjects will be administered study drug and advised to use Sponsor-provided Ventolin HFA on an as needed basis for relief of COPD symptoms.

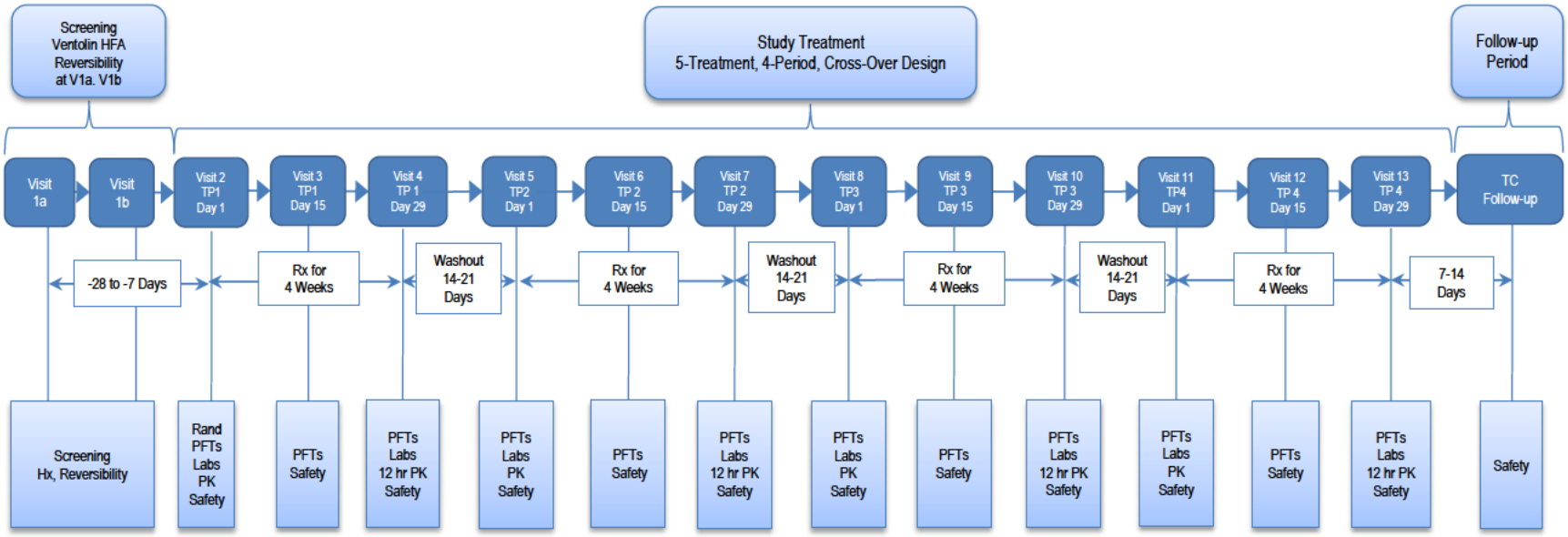
During the Washout Period, when subjects are not taking study drug (between Visits 4 and 5, Visits 7 and 8, and Visits 10 and 11), subjects will use the Sponsor-provided Atrovent HFA MDI, administered QID, and Sponsor-provided Ventolin HFA, as needed. Subjects treated

with Pulmicort Flexhaler during Screening will be administered Sponsor-provided Pulmicort Flexhaler at a dose of 360 µg BID for use during the washout period.

Protocol-adjusted ICS therapy defined at Screening, if any, should be continued and remain stable for the duration of the study (see Section 5.5).

A flow diagram of the study design is displayed in Figure 4-1.

Figure 4-1 Study Design



Hx = Medical History; PFT = Pulmonary Function Test; PK = Pharmacokinetics; Rand = Randomization; Rx = Treatment; TC= telephone call; TP = Treatment Period

5 STUDY POPULATION SELECTION AND WITHDRAWAL CRITERIA

5.1 Study Population

Approximately 160 subjects with moderate to severe COPD will be enrolled to provide approximately 130 subjects to complete the study. Subjects who withdraw from the study after receiving at least one treatment will not be replaced. Subjects who are re-evaluated will maintain one Screening number throughout the study.

5.2 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 1a
3. A female is eligible to enter and participate in the study if she is of:
    a. Non-childbearing potential (ie., physiologically incapable of becoming pregnant, including any female who is 2 years post-menopausal); or
    b. Childbearing potential, has a negative serum pregnancy test at Visit 1a, and agrees to one of the following acceptable contraceptive methods used consistently and correctly as outlined below (ie., in accordance with the approved product label and the instructions of the physician for the duration of the study – from Visit 1a [Screening] until 14 days after Visit 13):
        i. Complete abstinence from intercourse or
        ii. 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
        iii. Injectable progestogen administered for at least 1 month prior to study drug administration; or
        iv. Oral contraceptive (combined or progestogen only) administered for at least one monthly cycle prior to study drug administration; or
        v. Double barrier method: condom or occlusive cap (diaphragm or cervical/vault caps) plus spermicidal agent (foam/gel/film/cream/suppository); or
        vi. An intrauterine device, inserted by a qualified physician, with published data showing that the highest expected failure rate is less than 1% per year; or
        vii. Estrogenic vaginal ring; or
        viii. Percutaneous contraceptive patches.

4. COPD Diagnosis: Subjects with an established clinical history of COPD as defined by the American Thoracic Society (ATS)/European Respiratory Society (ERS) [Celli, 2004] characterized by:
   - Airflow limitation that is not fully reversible. Progressive airflow limitation associated with an abnormal inflammatory response of the lungs to noxious particles or gases, primarily caused by cigarette smoking.
5. Tobacco Use: Current or former smokers with a history of at least 10 pack-years of cigarette smoking.
   (Number of pack-years=[number of cigarettes per day / 20] x number of years smoked [eg., 20 cigarettes per day for 10 years, or 10 cigarettes per day for 20 years represent 10 pack-years]).
6. Severity of Disease: Subjects with an established clinical history of COPD and severity defined as:
   - At Screening (Visit 1a/b), FEV_1/FVC ratio of <0.70.
   - At Randomization (Visit 2), pre-bronchodilator FEV_1/FVC ratio of <0.70.
   - At Screening (Visit 1a/b), post-bronchodilator FEV_1 must be <80% predicted normal value, calculated using NHANES III (Third National Health and Nutrition Examination Survey) reference equations, and the measured FEV_1 must also be ≥30% of predicted normal value.
   - At Visit 2, the average of the -60 minutes and -30 minutes pre-dose FEV_1 assessments must be <80% predicted normal value calculated using NHANES III reference equations.
7. Subject is willing and, in the opinion of the Investigator, able to adjust current COPD therapy as required by the protocol.
8. Screening clinical laboratory tests must be acceptable to the Investigator.
9. Screening ECG must be acceptable to the Investigator.
10. Chest x-ray or computerized tomography (CT) scan within 6 months prior to Visit 1a must be acceptable to the Investigator. Subjects who have a chest x-ray (or CT scan) that reveals clinically significant abnormalities not believed to be due to the presence of COPD should not be included. A chest x-ray must be conducted if the most recent chest x-ray or CT scan is more than 6 months old at the time of Visit 1a.
11. Compliance: Subjects must be willing to remain at the study center as required per protocol to complete all visit assessments.

5.3 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 or women of childbearing potential who are not using an acceptable method of contraception.

3. Respiratory
    a) Asthma: Subjects who have a primary diagnosis of asthma (**Note:** Subjects with a prior history of asthma are eligible if COPD is currently their primary diagnosis).
    b) Alpha-1 Antitrypsin Deficiency: Subjects who have alpha-1 antitrypsin deficiency as the cause of COPD.
    c) Other Respiratory Disorders: Subjects who have other active pulmonary disease such as active tuberculosis, lung cancer, bronchiectasis, sarcoidosis, lung fibrosis, primary pulmonary hypertension, interstitial lung disease, and uncontrolled sleep apnea (ie., in the opinion of the Investigator severity of the disorder would impact the conduct of the study).
    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 one year of Visit 1a (Screening).
    e) Hospitalization: Subjects who have been hospitalized due to poorly controlled COPD within 3 months prior to Visit 1a (Screening) or during the Screening Period (Visit 1a up to Visit 2).
    f) Poorly Controlled COPD: Subjects who have poorly controlled COPD, defined as acute worsening of COPD that requires treatment with oral corticosteroids or antibiotics within 6 weeks prior to Visit 1a (Screening) or during the Screening Period (Visit 1a up to Visit 2). **Note:** Subjects who are steroid dependent and maintained on an equivalent of 5 mg prednisone per day or 10 mg every other day for at least 3 months prior to Visit 1a are eligible for enrollment providing the dose of oral steroids remains stable during the Screening Period (Visit 1a up to Visit 2).
    g) Lower Respiratory Tract Infection: Subjects who had lower respiratory tract infections that required antibiotics within 6 weeks prior to Visit 1a (Screening) or during the Screening Period (Visit 1a up to Visit 2).
    h) Spirometry Performance:
        a. Acceptability: Subjects who cannot perform acceptable spirometry, ie., meet ATS/ERS acceptability criteria (see Appendix 2).
        b. Repeatability: Subjects who cannot perform technically acceptable spirometry with at least three acceptable flow-volume curves meeting ATS repeatability criteria for FEV_1 during the pre-bronchodilator assessment at Visit 1a/1b **or** at the post-bronchodilator assessment at Visit 1a/1b.
        c. Baseline Stability: Subjects who cannot meet protocol-specified baseline stability criteria. FEV_1 baseline stability is defined as the average of the -60 minutes and -30 minutes pre-dose FEV_1 assessments at Visits 5, 8, and 11 (Day 1 of each treatment period), being within ±20% or 200 mL of the mean of the pre-bronchodilator FEV_1 assessments obtained at Visit 2.

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

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

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

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

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

4. Cardiac disease

a) Subjects who have unstable ischemic heart disease, left ventricular failure, or documented myocardial infarction within 12 months of 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 (New York Heart Association Class III/IV)

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

1. Clinically significant conduction abnormalities (eg., left bundle branch block, Wolff-Parkinson-White syndrome or evidence of second degree [Mobitz Type II] or third degree atrioventricular 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 β-blocker, calcium channel blocker, digoxin or ablation therapy) for at least 6 months is allowed for inclusion. In such subjects, atrial fibrillation must be present at pre-randomization visits, with a resting ventricular rate <100/min. At Visit 1a (Screening), the atrial fibrillation must be confirmed by central reading.
3. A mean corrected QT interval using Fridericia's correction factor (QTcF) value at Screening >450 ms for males and >470 ms for females or an ECG that is not suitable for QT measurements (eg., poorly defined termination of the T wave) at Visit 1a that remains elevated on repeat testing post Visit 1a but prior to Visit 2.

4. Ventricular rate <45 beats per minute (bpm)
5. Pathological Q waves of one 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.

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

5. Neurological
   - Subjects with seizures requiring anticonvulsants within 12 months prior to Visit 1a (Screening). **Note:** Subjects treated with anticonvulsant medication for 12 months or more with no seizure events are eligible.
   - Subjects taking selective serotonin reuptake inhibitors or serotonin-norepinephrine reuptake inhibitors whose dose has not been stable for at least 4 weeks prior to Visit 1a or is altered at any point during the Screening Period (Visit 1a up 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 or full resection of the prostate within 6 months prior to Visit 1a are excluded from the study.
   b) Subjects with bladder neck obstruction or urinary retention that is clinically significant in the opinion of the Investigator.
   c) Subjects with a calculated creatinine clearance ≤50 mL/minute using Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula [Levey, 2009] at Visit 1a and on repeat testing prior to Visit 2.
   Note: Subjects with overactive bladder syndrome treated with oral anticholinergics that have been on treatment for at least one month are allowed in the study.
7. Endocrine
   a) Subjects who in the opinion of the Investigator have uncontrolled hypo- or hyperthyroidism, hypokalemia, or hyperadrenergic state.
   b) Subjects who in the opinion of the Investigator have uncontrolled Type I or II diabetes.
8. Liver: Subjects with abnormal liver function tests defined as aspartate aminotransferase, alanine aminotransferase, or total bilirubin ≥1.5 times upper limit of normal at Visit 1a and on repeat testing prior to Visit 2.
9. Cancer: Subjects who had cancer that has not been in complete remission for at least 5 years (excluding squamous cell and basal cell carcinoma that has been resected for cure).

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 β-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.
13. Medication prior to spirometry: Subjects who are medically unable to withhold their short-acting bronchodilators for the 6-hour period required prior to spirometry testing at each study visit will be excluded.
14. Prohibited Medications: Subjects who, in the opinion of the Investigator, would be unable to abstain from protocol-defined prohibited medications during the Screening Period (Visit 1a up to Visit 2) and treatment phases of this study (see Section 5.5).
15. Vaccinations: Subjects who received a live attenuated vaccination within 30 days prior to Visit 1a (Screening) or during the Screening Period (Visit 1a up to Visit 2). **Note:** Inactivated influenza vaccination, pneumococcal vaccination or any other inactivated vaccine is acceptable provided it is not administered within 48 hours prior to Visit 1a (Screening) or Visit 2.
16. Non-compliance: Subjects unable to comply with study procedures including non-compliance with eDiary completion (ie., <70% subject completion of eDiary assessments in the last 7 days preceding Visit 2).
17. Affiliations with Investigator site: Study Investigators, sub-Investigators, study coordinators, employees of a participating Investigator or immediate family members of the aforementioned are excluded from participation in this study.
18. Questionable validity of consent: Subjects with a history of psychiatric disease, intellectual deficiency, poor motivation, substance abuse (including drug and alcohol), or other conditions that will limit the validity of informed consent to participate in the study.
19. Subjects using prohibited medications (see Section 5.5).
20. Investigational Drugs or Devices: Treatment with investigational study drug or device in another clinical study within the last 30 days or five half-lives prior to Visit 1a (Screening), whichever is longer. **Note:** Subject participation in observational studies (ie., studies that do not require change to medication or an additional intervention) is not exclusionary.
21. Hand-to-Breath Coordination: Subjects who require 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 study.

5.4 Subject Identification

All subjects who undergo Screening will be assigned a unique Screening identification number at the Screening Visit (Visit 1a). Only subjects continuing to meet entry

inclusion/exclusion criteria at Visit 2 will be assigned a unique subject randomization number.

5.5 Prior, Concomitant, and Prohibited Medications

All prescription and over-the-counter (OTC) medications taken by the subject during 30 days before Screening (Visit 1a) will be recorded on the Concomitant Medications Case Report Form (CRF) page. Any additions, deletions, or changes in the dose of these medications while in the study should be entered on the CRF. Any current ongoing medications, including OTC drugs and herbal supplements, will be allowed provided they are not prohibited by the protocol (see Section 5.5.1) and are approved by the Investigator. Subjects who develop an illness of any type are instructed to contact the Investigator.

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

5.5.1 Prohibited Chronic Obstructive Pulmonary Disease Medications

The following medications used for the treatment of COPD are not permitted during this study. These medications must be discontinued at Screening (Visit 1a) and are not permitted during the Screening Period. The minimum Washout Period between Visit 1a and Visit 2 is shown in Table 5-1.

Table 5-1 COPD Medications: Required Washout Period Prior to Visit 2

Class of Medication	Minimum Washout Period Prior to Visit 2
Long-acting anticholinergics	Tiotropium Bromide (Spiriva®): 14 days; Aclidinium Bromide (Tudorza™): 2 days
Short-acting anticholinergics	6 hours
LABA/LAMA	3 days (Anoro™)
Fixed-combinations of LABA/ICS [a]	7 days (Breo™ 5 days [b]); at Visit 1 (Screening) the ICS component will be switched to Sponsor-provided Pulmicort Flexhaler 360 µg
Fixed-combinations of SABAs and short-acting anticholinergics	6 hours
LABA [a]	48 hours (Indacaterol [Arcapta™]: 15 days)
SABAs (including study rescue Ventolin HFA)	6 hours
Phosphodiesterase-4 inhibitor (Daliresp®/Daxas®) [c]	6 days
Theophylline (total daily dose >400 mg/day) [d]	7 days

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

a. Please note that the washout periods for the LABA/ICS fluticasone furoate and vilanterol inhalation

Table 5-1 COPD Medications: Required Washout Period Prior to Visit 2

Class of Medication	Minimum Washout Period Prior to Visit 2

powder (Breo™ Ellipta™) and for the LABA indacaterol inhalation powder (Arcapta™ Neohaler™) are 5 days and 15 days, respectively.

b. Subject to their approval in the respective countries.

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

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

Subjects that have received depot corticosteroids, including intra-articular or intraocular corticosteroids, require a 3-month washout prior to Screening. Subjects that have received oral, intravenous, or intramuscular corticosteroids for any reason require a 6-week Washout Period prior to Screening. Any subject that requires systemic corticosteroids during the Screening Period (between Visits 1a and 2) will be screen failed.

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 1a are eligible providing the dose of oral steroids remains stable during the Screening Period (between Visits 1a and 2).
- During the Treatment Period (between Visits 2 and 13), subjects may be treated with corticosteroids if required.

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 taking the above listed COPD medications at Screening (Visit 1a) will discontinue these medications for the duration of the study and be switched to Sponsor-provided Atrovent HFA MDI administered QID, Sponsor-provided Ventolin HFA to be administered as needed for control of COPD symptoms during the Screening Period.
- Subjects receiving a maintenance dose of an ICS as part of a fixed-dose combination therapy containing fluticasone and salmeterol, mometasone and formoterol, BD and formoterol or fluticasone and formoterol must have been on the ICS component for at least 4 weeks prior to Screening and maintained on a stable dose for at least 4 weeks prior to Screening. These subjects will be switched to Sponsor-provided Pulmicort Flexhaler 360 µg BID during Screening, which will be discontinued at the time of randomization. These subjects will also receive Sponsor-provided Atrovent HFA MDI, administered QID, and Sponsor-provided Ventolin HFA, as needed, for control of COPD symptoms during the Screening Period through the day prior to Visit 2.

- Subjects receiving a maintenance dose of an ICS that is not administered as a fixed-dose combination together with a LABA for at least 4 weeks prior to Screening will be switched to Sponsor-provided Pulmicort Flexhaler 360 µg BID during Screening, and will be permitted to continue the ICS through the day prior to Visit 2.
- All subjects treated with either a LABA (salmeterol, formoterol, indacaterol, vilanterol) or currently marketed LAMA (tiotropium, aclidinium, glycopyrronium bromide [eg., Seebri®]) administered alone or in combination will have these medications discontinued and replaced with Sponsor-provided Atrovent HFA MDI administered QID and Sponsor-provided Ventolin HFA administered as needed for control of COPD symptoms during the Screening Period.

Note: During the Screening Period (between Visits 1a and 2) and Washout Periods (between Visits 4 and 5, Visits 7 and 8, and Visits 10 and 11), Sponsor-provided Atrovent HFA MDI is to be used as maintenance medication administered QID, and Sponsor-provided Ventolin HFA is to be used as rescue medication administered as needed; however, both medications must be withheld for at least 6 hours before each study visit.

Note: During study treatment (ie., between Visits 2 and 4, Visits 5 and 7, Visits 8 and 10, and Visits 11 and 13), subjects will receive study drug and are allowed Sponsor-provided Ventolin HFA to be used as needed for relief of COPD symptoms. No other inhaled COPD medications are permitted.

The following respiratory medications are not permitted during this study (Table 5-2).

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

Class of Medication	Minimum Washout Period Prior to Visit 2
Leukotriene antagonists (eg., zafirlukast, montelukast, and zilueton)	3 days
Cromoglycate	7 days
Nedocromil	7 days
Ketotifen [a]	7 days

a Ketotifen eye drops are allowed.

5.5.2 Other Prohibited Medications

The following medications should be used under the stated conditions during this study (Table 5-3). Each concomitant drug must be individually assessed against all exclusion criteria. If in doubt, the Investigator should contact the Pearl Medical Monitor before randomizing a subject or allowing a new medication to be started.

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

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

Abbreviations: COPD=chronic obstructive pulmonary disease

Subjects who require the following medications are prohibited from this study (Table 5-4). Subjects who recently discontinued use of these medications may be considered for study enrollment providing they have met the minimum washout period prior to Screening (Visit 1a). The medications listed in Table 5-4 are prohibited from use during the study. If a subject requires the use of any of the listed medications, they should be discontinued from the study.

Table 5-4 Prohibited Medications

Prohibited Medications	Minimum Cessation Period Prior to Screening (Visit 1a)
Any drug with potential to significantly prolong the QT interval	14 days or 5 half-lives, whichever is longer
Other investigational drugs	30 days or 5 half-lives whichever is longer
Non-selective β-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 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

Table 5-4 Prohibited Medications

Prohibited Medications	Minimum Cessation Period Prior to Screening (Visit 1a)
Systemic calcineurin inhibitors, systemic antifungal agents, protease inhibitors, and cimetidine	30 days
Systemic anticholinergics [b]	7 days

Note: Benzodiazepines are not exclusionary.

a Antipsychotic agents used for other indications may be allowed after consultation with the Pearl Medical Monitor of the study.

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.

5.6 Other Restrictions, Illicit Drugs or Drugs of Abuse

Illicit drugs or drugs of abuse will not be allowed from the start of Screening (Visit 1a) to the end of Visit 13 or to whenever the subject discontinues the study. If any illicit drugs or drugs of abuse are used by the subject during the study, the dates of use and the amount will be documented. Medical marijuana is not an exclusionary drug if used for medical purposes, and there is no change in the dose or frequency of consumption. Inhaled medical marijuana must be withheld for at least 4 hours prior to each study visit and throughout the duration of each study visit.

Subjects are not allowed to consume grapefruits or grapefruit juice throughout the study.

Subjects must not ingest xanthine-containing foods and beverages for at least 6 hours prior to each study visit and for the duration of each study visit. Examples of such products include coffee, tea, chocolate, and cola. Decaffeinated beverages are acceptable.

Subjects will be required to refrain from **smoking** for at least 4 hours prior to each study visit and throughout the duration of each study visit. Electronic cigarettes and inhaled medical marijuana will be treated the same way as smoking is considered in the protocol. Study participants may utilize various nicotine replacement treatments such as chewing gum and patches as needed, in accordance with recommendations from the Investigator during the entire study visit.

5.7 Reasons and Procedures for Early Termination

Subjects may be withdrawn from the study at any time at their own request, upon request of the Investigator, or by Pearl at any time or for any reason.

If a subject is lost to follow-up (ie., fails to return for study visits) reasonable efforts must be made to contact the subject and complete study termination procedures.

All subjects who discontinue the study because of AEs will be followed up at suitable intervals in order to evaluate the course of the AE and to ensure the reversibility or stabilization of the abnormality.

All subjects who prematurely discontinue the study after being randomized, regardless of the cause, should undergo only the assessments outlined in Section 8.8 on the date of discontinuation.

A subject will be discontinued if any of the following parameter changes are noted on two consecutive assessments conducted approximately 15 minutes apart or at the discretion of the Investigator:

- QTcF prolongation increase of >60 msec from test day baseline (QTc interval obtained from test day baseline ECGs corrected using Fridericia's correction formula) and QTcF >500 msec at any time after taking study drug.
- Heart rate increase of >40 bpm from test day baseline (before taking study drug) and >120 bpm at any time within the 12-hour interval after taking study drug.
- Systolic BP increase of >40 mmHg from test day baseline (before taking study drug) and SBP >180 mmHg at any time within the 12-hour interval after taking study drug.
- Paradoxical bronchospasm, defined as a reduction in FEV_1 of >20% from baseline (ie., the mean FEV_1 values obtained 60 and 30 minutes prior to study drug administration) occurring within 30 minutes post-dosing with associated symptoms of wheezing, shortness of breath, or cough.

If a subject experiences a significant decline in pre-dose FEV_1 at any visit (ie., pre-dose FEV_1 declines ≥ 30% from the pre-dose value obtained at Randomization [Visit 2]), the Investigator or designee will need to determine whether the subject is having a COPD exacerbation and will also make a determination as to the suitability of continuing the subject in the specific treatment period.

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

A COPD exacerbation will be defined as a change in the subject's baseline dyspnea, cough, and/or sputum (increase in volume or change in color towards purulence) that lasts ≥3 days, is beyond normal day-to-day variations, is acute in onset, and may warrant a change in regular medication. The severity of COPD exacerbations will be classified as follows:

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

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 [redacted] 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 Description

Investigational materials will be provided by Pearl as summarized in Table 6-1. Treatments will be blinded in terms of dose administered within the three Pearl devices (BFF MDI, BD MDI, and FF MDI); these products are identical in form and function and indistinguishable from each other.

Table 6-1 Product Descriptions

Product Name & Dose	Product Strength	Dosage Form	Fill Count	Comments
BFF MDI 320/9.6 µg ex-actuator	160/4.8 µg per actuation	MDI	1 MDI 120 actuations	Taken as 2 inhalations.
BFF MDI 160/9.6 µg ex-actuator	80/4.8 µg µg per actuation	MDI	1 MDI 120 actuations	Taken as 2 inhalations.
BFF MDI 80/9.6 µg ex-actuator	40/4.8 µg µg per actuation	MDI	1 MDI 120 actuations	Taken as 2 inhalations.
BD MDI 320 µg ex-actuator	160 µg per actuation	MDI	1 MDI 120 actuations	Taken as 2 inhalations.
FF MDI 9.6 µg ex-actuator	4.8 µg per actuation	MDI	1 MDI 120 actuations	Taken as 2 inhalations.
Albuterol Sulfate inhalation aerosol [a] 90 µg	US source: Ventolin® HFA Each inhalation contains 108 µg corresponding to 90 µg albuterol base from the mouthpiece	MDI	1 MDI 60 or 200 actuations	Taken as needed. Supplies are open-label.
Ipratropium Bromide inhalation aerosol[b] 34 µg ex-actuator	US source: Atrovent® HFA Each inhalation contains 17 µg per actuation	MDI	1 MDI 200 actuations	Taken as 2 inhalations. Supplies are open-label.
Budesonide Inhalation Powder[b] 180 µg	US source: (Pulmicort Flexhaler®) Each inhalation contains 180 µg of budesonide corresponding to 160 µg delivered from the mouthpiece	DPI	1 DPI 120 actuations	Taken as directed. Supplies are open-label

BD=budesonide; BFF=budesonide and formoterol fumarate; FF=formoterol fumarate; HFA=hydrofluoroalkane; MDI=metered dose inhaler; US=United States

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

a Rescue medication and reversibility testing.

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

For open-label Atrovent HFA (ipratropium bromide, 34 µg), bulk commercial MDIs will be provided. Manufacturer's instructions for study drug administration are provided in Appendix 4).

For open-label Ventolin HFA (albuterol sulfate inhalation aerosol 90 µg) bulk commercial MDIs with dose counters will be provided. Manufacturer's instructions for study drug administration are provided in Appendix 6).

For open-label Pulmicort Flexhaler (budesonide inhalation powder 180 µg), commercial dry powder inhalers (DPIs) will be provided. Manufacturer's instructions for study drug administration are provided in Appendix 5)

6.3 Primary Packaging and Labeling

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

BFF MDI, BD MDI, and FF MDI will be supplied as blinded study drug. Atrovent HFA, Ventolin HFA, and Pulmicort Flexhaler supplies will be supplied as open-label.

Blinded Supplies: Each MDI will be labeled with a single label. The foil pouch will be labeled with a single label and the carton will be labeled with a two-part label.

Open-label Supplies: Open-label Pulmicort Flexhaler will be provided as individually labeled DPIs. Atrovent and Ventolin HFA will be provided as individually labeled MDIs. Each inhaler will contain a single investigational label. The final labeling configuration of each open-label product will be determined by the labeling constraints of each product.

Study drug labels will include both single and two-part labels 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 Labeling

Investigational drug supplies, and open-label Atrovent HFA, Ventolin HFA, and Pulmicort Flexhaler supplies will be provided in boxes/cartons as outlined in Table 6-2. Box configuration is subject to change as a result of packaging constraints.

Table 6-2 Description of Boxes

Drug Supplies	Box Contents
Blinded	1 MDI
Atrovent HFA	1 MDI
Ventolin HFA	1 MDI
Pulmicort Flexhaler	1DPI

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

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

6.5 Unblinding Procedures

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

6.6 Storage Requirements

Blinded supplies: Store blinded study supplies as indicated on the package label.

Ventolin HFA supplies: Store Ventolin HFA supplies as indicated on the package label.

Atrovent HFA supplies: Store Atrovent HFA supplies as indicated on the package label.

Pulmicort Flexhaler supplies: Store Pulmicort Flexhaler supplies as indicated on the package label.

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

6.7 Instructions for Preparation of Treatments for Administration and Dispensing

BFF, BD, and FF MDIs

Individual BFF, BD, and FF MDIs will be packaged in a foil pouch and contained in an individual visit treatment box/carton. Both the visit treatment box and the foil overwrap 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 box/carton is labeled with a two-part label. Write the subject number and treatment visit number on each of the two-part labels. The 'tear-off' part of the label is to be placed on the IWRS confirmation report.

All MDIs must be primed before the first use. Priming involves releasing a certain number of sprays (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 it is ready to use.

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

To prime the inhaler, gently shake the inhaler for 5-10 seconds and then spray once into the air away from yourself and others. Wait approximately 30 seconds and repeat the process three more times.

Each dose will consist of two puffs from the MDI. Subjects will be dispensed the MDI and instructed to continue taking study drug BID, two puffs in the morning and two puffs in the evening approximately 12 hours apart, until subject returns to the clinic. The MDI should be stored at room temperature by the subject, avoiding temperature extremes and storage in direct sunlight. See Appendix 3 for instructions on the administration of BFF, BD, and FF MDIs.

Atrovent HFA MDI (ipratropium bromide)

Individual Atrovent HFA MDIs will be 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 box/carton is labeled with a two-part label. Write the subject number and treatment visit number on each of the two-part labels. The 'tear-off' part of the label is to be placed on the IWRS confirmation report.

Atrovent HFA is a solution aerosol that does not require shaking. However, as with any other MDI, some coordination is required between actuating the canister and inhaling the medication. Atrovent HFA should be primed per manufacturer's instructions prior to

dispensing to subject (ie., "prime" or actuate Atrovent HFA before using for the first time by releasing two test sprays into the air away from the face). In cases where the inhaler has not been used for more than 3 days, prime the inhaler again by releasing two test sprays into the air away from the face. Subjects should avoid spraying Atrovent HFA into their eyes.

As needed, subjects will be dispensed the MDI for COPD maintenance therapy during Screening (Visit 1a up to Visit 2) and Washout Periods (between Visits 4 and 5, Visits 7 and 8, Visits 10 and 11) per the manufacturer's instruction, two puffs with each administration QID, approximately 6 hours apart. The MDI should be stored at room temperature by the subject, avoiding temperature extremes and storage in direct sunlight. See Appendix 4 for the manufacturer's instructions on the administration of Atrovent HFA.

Ventolin HFA (albuterol sulfate inhalation aerosol)

Individual open-label Ventolin HFA labeled with a component ID number for IWRS assignment and tracking will be provided by Pearl. Sites will use IWRS to dispense Ventolin HFA to subjects. See Appendix 6 for the manufacturer's instructions on the administration of Ventolin HFA. Study personnel will record number on the dose counter at the time of dispensing (following priming) and upon return.

Pulmicort Flexhaler (budesonide inhalation powder)

Individual open-label Pulmicort Flexhaler DPIs labeled with a component ID number for IWRS assignment and tracking will be provided by Pearl. Sites will use IWRS to dispense Pulmicort Flexhaler to subjects during screening and Washout Periods. See Appendix 5 for the manufacturer's instructions on the administration of Pulmicort Flexhaler.

6.8 Drug Accountability/Return of Clinical Supplies

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

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

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

The Investigator or designated assistant should not open individual clinical supply containers until all pre-dose assessments have been completed and the subject is eligible to be randomized/continue with the study. Deviations from this process must be escalated to Pearl or designee for evaluation.

For each subject, all used study drug materials will be collected and consolidated [for example placed in a plastic bag (eg., Ziploc® or similar type bag) and labeled with the subject number]. Used subject supplies will be kept at room temperature in a secure and locked location until returned to Pearl or designee. **Note:** Used study drug will be stored separately from unused study drug.

7 STUDY PROCEDURES

A time and events schedule is provided in Table 8-1. Detailed schedules for pre- and post-dose procedures to be performed on Day 1 and Day 15 (Visits 2, 3, 5, 6, 8, 9, 11, and 12) and on Day 29 (Visits 4, 7, 10, and 13) of each treatment period are provided in Table 8-2 and Table 8-3, respectively.

All assessments during Visits 2 through 13 are recommended to be conducted in the following order: vital signs, ECGs, clinical laboratory assessments, and spirometry.

7.1 Efficacy Assessments

7.1.1 Pulmonary Function Tests (Spirometry)

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

A spirometry assessment will be conducted pre- and post-bronchodilator at Visit 1a. **Note:** Subjects who do not meet spirometry criteria at Visit 1a may, at the discretion of the investigator or designee, repeat evaluation of spirometry criteria at Visit 1b

At Visits 2 through Visit 13, spirometry assessments will be conducted 60 minutes and 30 minutes prior to study drug administration. The average of these two assessments will be used to establish test day baseline FEV_1, FVC, and PEFR.

At Visits 2, 3, 5, 6, 8, 9, 11, and 12 (Day 1 and Day 15) of each treatment period, following study drug administration, spirometry will be obtained at 15 and 30 minutes, and 1 and 2 hours post-dosing of study drug.

At Visits 4, 7, 10, and 13 (Day 29) of each treatment period, following study drug administration, spirometry will be obtained at 15 and 30 minutes, and 1, 2, 4, 6, 8, 10, 11.5, and 12 hours post-dosing of study drug.

At Visits 5, 8 and 11 (Day 1 of Treatment Periods 2, 3 and 4, respectively), subjects must meet the Baseline Stability Criteria (see Section 7.1.1.1) prior to dosing.

7.1.1.1 FEV_1 Baseline Stability Criteria

It is important to ensure that the baseline FEV_1 is stable and reflective of the subject's COPD severity prior to being randomized into the study. As such, the baseline FEV_1 at Visits 5, 8, and 11 must be within ±20% or 200 mL of the pre-dose FEV_1 obtained at the Randomization Visit (Visit 2). At Visits 5, 8, and 11, if the pre-dose FEV_1 average is outside of the ±20% or 200 mL range, but the 30-minute pre-dose assessment is within ±22% or 220 mL, then another assessment may be conducted 30 minutes later. If the last two assessments meet the baseline stability requirements (ie., within ±20% or 200 mL), the initial 60-minute pre-dose assessment will not be used and the last two assessments will be used to establish the

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

7.1.1.2 Rescue Criteria for Randomized Subjects

Rescue criteria will be evaluated at Visits 3, 6, 9, and 12 (Day 15 of each Treatment Period), and during any unscheduled visits occurring during any Treatment Period. Subjects meeting rescue criteria will be advanced to the Washout Period and given Sponsor-provided Atrovent HFA, Ventolin HFA, and Pulmicort Flexhaler, as appropriate.

Rescue criteria are met if the average of the -60 min and -30 min FEV_1 are ≥ 30% below the average of the -60 min and -30 min FEV_1 values from Visit 2 and, in the opinion of the Investigator or designee, it is in the best interest of the subject to discontinue therapy. At these visits, if the pre-dose FEV_1 average is ≥ 30% below the average of Visit 2 baseline FEV_1, but the -30 min assessment is within 30%, then another assessment may be conducted 30 minutes later (at the Investigator or designee's discretion). If the last two assessments meet the rescue criteria requirements (i.e., ≥ 30%), the initial 60 minute pre-dose assessment will not be used and the last two assessments will be used to establish whether the subject meets rescue criteria.

In lieu of FEV_1 criteria, if a Rescue Period is required based on worsening of COPD symptoms (e.g. cough, wheeze, nighttime awakenings, increased use of Ventolin HFA, etc.), and, in the opinion of the Investigator or designee, it is in the best interest of the subject to discontinue therapy, the subject may to be transitioned to a Washout Period. The Investigator or designee should make every effort to collect trough PFTs prior to transitioning the subject to a Washout Period.

If a subject is advanced to a Washout Period and that period is completed, subjects may continue in the study to the next Treatment Period provided the FEV_1 baseline stability criteria are met (see Section 7.1.1.1).

If the Rescue Criteria are met during the fourth and final Treatment Period, then the procedures for discontinuation should be followed and the subject will be considered to have successfully completed the treatment portion of the study.

7.1.1.3 Characterization of Reversibility Criteria

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

- Perform pre-bronchodilator PFTs prior to administration of Ventolin HFA (albuterol)
- Administer 4 puffs of Ventolin HFA (albuterol)

- Perform post-bronchodilator PFT within 30-60 minutes after the administration of Ventolin HFA.

7.1.1.4 Standardization of Spirometry Collections

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

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

The volume accuracy of the spirometer is to be checked daily using a 3-L syringe across 3 flow ranges, eg., at <2 L/sec, 4 to 6 L/sec, and >8 L/sec with temperature and barometric pressure correction. The calibration syringe must meet ATS specifications and must not be used beyond the expiry date. Required accuracy is ±3%, ie., 3.09 L to 2.91 L (ATS/ERS). The results will be printed and maintained in a calibration log, which will be monitored for compliance during the monitoring visits (refer to Appendix 2, Spirometry Assessment Criteria).

Refer to Section 7.1.1.1 for specific FEV_1 criteria that prompt subjects to be discontinued from the study.

7.1.1.5 Subject eDiary Data Collection

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

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

Subjects will be issued and trained on eDiary use at the Screening Visit (Visit 1) and will be instructed to collect eDiary data during the Screening Period (between Visits 1 and 2).

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

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

Starting at screening (Visit 1a/b) and for the duration of the study including treatment and washout periods, subjects will receive an eDiary in which they will be asked to maintain a daily record of their study drug dosing, rescue medication use, and collection of COPD symptoms (including BCSS).

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

At Visits 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, and 13, site personnel must review eDiary data prior to dosing study drug in the clinic (see Table 8-1).

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

7.1.1.6 Breathlessness, Cough, and Sputum Scale

The BCSS was developed by [redacted] [Leidy, 2003]. The BCSS will be uploaded to the eDiary and, as directed, subjects will self-administer the survey each evening (irrespective of subject's location [ie., at home or at the study site]) from Visit 2 through Visit 13; each subject-response will be recorded in the eDiary.

Sample questions are provided below:

How much difficulty did you have breathing today?

0 _ None: unaware of any difficulty

1 _ Mild: noticeable during strenuous activity (eg., running)

2 _ Moderate: noticeable during light activity (eg., bed making)

3 _ Marked: noticeable when washing or dressing

4 _ Severe: almost constant, present even when resting

How was your cough today?

0 _ None: unaware of coughing

1 _ Rare: cough now and then

2 _ Occasional: less than hourly

3 _ Frequent: one or more times an hour

4 _ Almost constant: never free of cough or need to cough

How much trouble was your sputum today?

0 _ None: unaware of any difficulty

1 _ Mild: rarely caused problem

2 _ Moderate: noticeable as a problem

3 _ Marked: caused a great deal of inconvenience

4 _ Severe: an almost constant problem

7.1.2 Rescue Ventolin HFA Use

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

7.1.3 Medication Compliance

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

7.1.4 Baseline and Transition Dyspnea Indices

Dyspnea is the primary symptom of COPD and its relief is an important goal of therapy. In the evaluation of pharmacotherapy for COPD, several instruments are available to provide a discriminative and evaluative assessment of dyspnea. Among these are the BDI and TDI dyspnea indices, which assess breathlessness in domains related to functional impairment, magnitude of task, and magnitude of effort. The reliability and validity of the BDI have been reported [Mahler, 1984]. The validity of the BDI/TDI based on its association with other

related measures has also been demonstrated [Witek, 2003]. The BDI/TDI questionnaire should always be completed before any other assessments are made to avoid influencing the responses. The self-administered computerized (SAC) version will be used. The SAC includes the same questions as the paper version but also includes an initial practice question related to tiredness, which is not included in the overall score. The paper version of the questionnaire can be found in Appendix 9 and is provided for illustrative purposes only. The appropriate language version of the questionnaires will be used. The BDI score ranges from 0 (very severe impairment) to 4 (no impairment) for each domain and are summed to determine the BDI focal score (0 to 12) (ie., the lower the score, the worse the severity of dyspnea).

The TDI domains are: Change in Functional Impairment, Change in Magnitude of Task, and Change in Magnitude of Effort. The TDI score ranges from -3 (major deterioration) to +3 (major improvement) for each domain. The sum of all domains yields the TDI focal score (-9 to +9) (ie., the lower the score, the more deterioration in severity of dyspnea). The subject should complete the questionnaires in a quiet area and be allowed to ask questions; however, site staff should take care not to influence the subject's responses. The subject will be instructed to provide the truest and for them best response. The questionnaire will be checked for completeness and collected before the subject leaves the center. At later visits, subjects are not allowed to review their previous responses.

The BDI will be completed at Visit 2 (Day 1 of Treatment Period 1). The TDI will be completed on Day 29 of each treatment period (Visits 4, 7, 10, and 13).

The BDI/TDI will be completed prior to study drug administration.

7.2 Safety Assessments

The safety assessments include AEs and SAEs, vital signs (BP, HR, and temperature), clinical laboratory values (hematology and clinical chemistry), and ECGs.

7.2.1 Medical/Surgical History and Physical Examination

Medical history will be taken at Screening (Visits 1a) (and Visit 1b, if applicable) and updated at the Randomization Visit (Visit 2). History of COPD exacerbation within 12 months of Screening will also be collected. A complete physical examination will be performed at Screening (Visit 1a) and the final clinic visit on Day 29 of Treatment Period 4 (Visit 13). A complete physical examination will include the following: general appearance, skin, head, eyes, ears, nose, throat, neck (including thyroid), lymph nodes, chest, heart, abdomen, extremities, and nervous system. Weight, assessed in ordinary indoor clothing with shoes removed, will be recorded at Screening (Visit 1a) and Visit 13. Height will be recorded at Screening (Visit 1a) only.

7.2.2 Vital Sign Measurements

Heart rate, systolic and diastolic blood pressure (DBP/SBP), and temperature ('vital signs') will be assessed at each visit; assessments may be obtained in either the supine or seated position. Vital signs to be assessed as follows:

- A single set of vitals will be obtained at Screening (Visit 1a), and at the Premature Discontinuation Visit (if applicable)
- At Visits 2 through 13, pre-dose vitals will be conducted at 60 and 30 minutes prior to study drug administration
- At Visits 2, 3, 5, 6, 8, 9, 11, and 12 (Days 1 and 15) of each treatment period, post-dose vitals will be conducted at 15 and 30 minutes, and 1 and 2 hours after study drug administration,
- At Visits 4, 7, 10, and 13 (Day 29) of each treatment period, post-dose vitals will be conducted at 15 and 30 minutes, and 1, 2, 4, 6, 8, 10, 11.5, and 12 hours after study drug administration,
- Temperature will be obtained at Screening (Visit 1a), and at pre-dose at all visits and will not be repeated post-dose at subsequent timepoints unless clinically indicated.

Refer to Section 5.7 for specific criteria for HR and SBP/DBP readings that could result in subjects to be discontinued from the study.

7.2.3 12-Lead Electrocardiogram

An ECG will be obtained at Screening (Visit 1a) and Premature Discontinuation Visit (if applicable).

At Visits 2, 5, 8, and 11 (Day 1), ECGs will be will be obtained at pre-dose 60 and 30 minutes prior to study drug administration and post-dose at 15 and 30 minutes, and 1 and 2 hours after study drug administration.

At Visits 4, 7, 10, and 13 (Day 29) of each treatment period, ECGs will be obtained will be conducted at pre-dose 60 and 30 minutes prior to study drug administration and post-dose at 15 and 30 minutes, and 1, 2, 4, and 12 hours after study drug administration.

If there is a >30 ms difference in QTcF observed between the two baseline (pre-dose) ECGs at a visit, then the Investigator or designee will make a determination as to the suitability of the subject to proceed. If the subject does proceed in the study, a third baseline ECG is to be obtained prior to dosing.

Additional ECGs will be obtained if the subject's HR is <60 bpm and is >20 bpm below test day baseline or is >100 bpm and is >20 bpm above the test day baseline value (where baseline is defined as the mean of the HR assessments obtained 60 and 30 minutes prior to study drug administration on the same test day).

7.2.3.1 Standardization of ECG Data Collection

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

The ECG parameters that will be assessed include HR, RR interval, PR interval, QRS axis, QRS interval, and QT/QTcF interval.

QT intervals and calculated QTcF intervals will be reviewed and checked for gross inaccuracies by the Investigator or designated ECG reviewer. If the calculated QTcF intervals are >500 msec, and have increased by 60 msec or more over baseline value, the Investigator or designee will make a determination on the suitability of continuing the subject in the study. Refer to Section 5.7 for specific criteria for QTcF that prompt discontinuation of affected subjects from the study. If QTcF interval prolongation exceeding these limits is verified during treatment, the subject's medical background should be examined closely for risk factors that may have contributed to the event, including genotyping for hereditary long QT syndromes, if appropriate.

Any sign of arrhythmia should be noted. During treatment, any indication of Torsade de Pointes, a polymorphic ventricular tachyarrhythmia that appears on the ECG as continuous twisting of the vector of the QRS complex around the isoelectric baseline, must be recorded as an AE and reported to the Pearl Medical Monitor.

The decision to continue the treatment of any subject with prolonged QT or QTcF interval must be discussed and agreed upon by the Investigator or designee and the Pearl Medical Monitor. All such subjects, including subjects with cardiac arrhythmias, should be monitored closely. If appropriate, ECG monitoring should be performed until the QT and QTcF interval and waveform morphology have returned to normal. If the prolongation or abnormal rhythm persists, the Pearl Medical Monitor must be contacted.

7.2.4 Clinical Laboratory Tests

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

At the Screening Visit (Visit 1a) and at Visits 2, 4, 5, 7, 8, 10, 11 and 13 (Days 1 and 29), and Premature Discontinuation Visit (if applicable), hematology (complete blood count

[CBC]) and chemistry (comprehensive metabolic panel [CMP]) will be obtained within 60 minutes prior to dosing.

At Visits 2, 4, 5, 7, 8, 10, 11 and 13 (Days 1 and 29), a basic metabolic panel (BMP) with focus on potassium and glucose parameters will be obtained at 30 minutes and 2 hours post-dose on all subjects (see Table 8-2 and Table 8-3).

In women of childbearing potential, serum pregnancy testing will be performed at Screening (Visit 1a) and at the final clinic visit (Visit 13), and urine human chorionic gonadotropin (hCG) testing occurring prior to the start of each treatment period (Visits 2, 5, 8, and 11).

The following clinical laboratory parameters will be assessed:

Hematology	
Hemoglobin	Mean corpuscular hemoglobin
Hematocrit	Mean corpuscular hemoglobin concentration
White Blood Cell count with differential	Mean corpuscular volume
Red Blood Cell count	
Platelet Count	
Clinical Chemistry	
Liver Enzyme and Other Function Tests	**Other Clinical Chemistry**
Alanine aminotransferase	Albumin
Aspartate aminotransferase	Blood urea nitrogen [a]
Alkaline phosphatase	Calcium[a]
Bilirubin, total	Chloride[a]
Gamma-glutamyl transferase	Cholesterol
	Bicarbonate
	Creatinine[a]
	Glucose[a]
	Magnesium
	Potassium[a]
	Phosphate
	Protein, total
	Sodium[a]
	Triglycerides
Other Tests:	
Pregnancy test (women of childbearing potential only): serum hCG at Screening and Final Visit only and urine hCG at Visits 2, 5, 8, and 11.	
Creatinine clearance will be estimated by the CKD-EPI published formula.	

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

a Parameters included in the Basic Metabolic Panel.

7.3 Pharmacokinetic Assessments (PK Sub-Study Subjects Only)

7.3.1 Pharmacokinetic Plasma Collection and Plasma Sample Handling

Approximately 10 mL of whole blood will be collected by direct venipuncture or may be obtained from an indwelling intravenous cannula (per site standard operating procedure [SOP] after review by the Pearl Medical Monitor or designee) using a vacuum collection tube (for example Vacutainer plasma collection tube) containing ethylenediaminetetraacetic acid tripotassium according to the Schedule of Events (Table 8-1). After processing, the plasma from each sample is to be harvested, equally divided into two aliquots, and transferred into cryotubes appropriate for plasma. Aliquots are to be frozen at less than or equal to -20 C. Refer to Appendix 7 for details regarding plasma collection, storage and handling.

Samples are to be shipped frozen to the Central Laboratory for storage.. Plasma levels of BD and/or formoterol will be determined using a validated high performance liquid chromatography tandem mass spectrometry method. Refer to Appendix 7 for sample shipping details.

7.3.2 Adverse Events Assessments

7.3.2.1 Performing Adverse Event Assessments

The Investigator is responsible for promptly documenting and reporting all AEs observed during the study in the subject's CRF and on the AE Reporting Form. In addition, certain AEs (as described in Section 7.3.2.7) are classified as "serious" and must be reported no later than 24 hours after the Investigator recognizes/classifies the event as an SAE to Pearl or its designee.

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

7.3.2.2 Adverse Event Definitions

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

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

Adverse events include, but are not limited to:

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

An AE does not include:

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

7.3.2.3 Pre-Randomization Adverse Events

Adverse events that occur between the time subject signs the ICF for the study and the time when the subject is randomized will be summarized as medical history and not as a treatment emergent AE unless the event meets the definition of an SAE as defined below in Section 7.3.2.7.

7.3.2.4 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.

7.3.2.5 Relationship

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

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

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

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

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

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

Criteria for a "clinically significant" laboratory abnormality are:

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

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

7.3.2.7 Serious Adverse Events

DEFINITION

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

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

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

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

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

REPORTING SERIOUS ADVERSE EVENTS

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

Post-study SAEs following the last dose of study drug must be reported to Pearl as described in Section 7.3.2.10.

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.

7.3.2.8 Supplemental Investigation of Serious Adverse Events

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

7.3.2.9 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 Follow-up/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 CRF or reported to Pearl if the CRFs 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.

7.3.2.10 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, it must be reported to Pearl, whether or not the event is attributable to study drug. All SAEs must be reported to Pearl no later than 24 hours after the Investigator recognizes/classifies the event as a SAE.

7.3.2.11 IRB/IEC Notification of Serious Adverse Events

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

7.3.2.12 Health Authority Safety Reports

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

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

7.3.3 Adverse Events of Interest

Paradoxical bronchospasm may occur following inhalation from an MDI.

Monitoring for paradoxical bronchospasm will occur at each visit during the Treatment Period (Visits 2 through 13) at 15 and 30 minutes post-dose. In this study, paradoxical bronchospasm is defined as a reduction in FEV_1 of >20% from baseline (ie., the mean FEV_1 values obtained 60 and 30 minutes prior to study drug administration) occurring within 30 minutes post-dosing with associated symptoms of wheezing, shortness of breath, or cough All AEs and SAEs will be recorded as appropriate.

7.3.4 Overdose

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

Investigators Brochures (IBs) for BD MDI, FF MDI, BFF MDI, and the approved product labeling for Ventolin HFA, Atrovent HFA, and Pulmicort Flexhaler, as appropriate.

7.3.5 Pregnancy

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

7.3.6 Pharmacokinetic Evaluations

A subset of sites will be identified and designated for PK sample collection. The PK assessments will be obtained in a subset of approximately 60 subjects. Sampling will be performed: on Day 1 within 30 minutes prior to dosing, and on Day 29 30 minutes prior to dosing, then 2, 6, 20, and 40 minutes and 1, 2, 4, 8, 10, and 12 hours post-dose.

7.4 Termination of the Study

The study may be terminated prematurely with sufficient notice in advance by the Investigator for any reason as per the terms of the contract with Pearl. The reason should be communicated in writing to Pearl.

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

The study will be placed on hold and a safety board convened in the event of:

1. 3 or more deaths deemed to be cardiac or respiratory in origin; or
2. 4 or more deaths from any cause during the study.

Stopping criteria based on deaths were based on estimates of rates of mortality taken from the integrated data from umeclidinium and vilanterol program (PADAC 2013). These criteria imply a 0.5% chance of placing the study on hold if there is no true increase in mortality.

8 STUDY ACTIVITIES

A time and events schedule is provided in Table 8-1. Detailed schedules for pre- and post-dose procedures to be performed on Day 1 (Visits 2, 5, 8, and 11) and Day 15 (Visits 3, 6, 9, and 12) are provided in Table 8-2 and on Day 29 (Visits 4, 7, 10, and 13) are provided and Table 8-3.

Table 8-1 Schedule of Events

Procedures	Screening[a]		Treatment Period 1[a]			Treatment Period 2[a]			Treatment Period 3[a]			Treatment Period 4[a]			Follow-Up Period[a]
	Visit 1a	Visit 1b (as needed)	Rand. Visit 2 Day 1	Visit 3 Day 15	Visit 4 Day 29	Visit 5 Day 1	Visit 6 Day 15	Visit 7 Day 29	Visit 8 Day 1	Visit 9 Day 15	Visit 10 Day 29	Visit 11 Day 1	Visit 12 Day 15	Visit 13 Day 29	Telephone Follow-up
Treatment Day[a]	**Up to -28**	**Up to -27**	**1[a]**	**15±2[a]**	**29±2[a]**	**1[a]**	**15±2[a]**	**29±2[a]**	**1[a]**	**15±2[a]**	**29±2[a]**	**1[a]**	**15±2[a]**	**29±2[a]**	**7-14[a]**
Informed Consent	X														
Eligibility Criteria	X	X	X												
Chest x-ray[b]	X														
Verify Cont. Eligibility				X	X	X	X	X	X	X	X	X	X	X	
Ventolin HFA Reversibility[c]	X	X													
Demographics, Medical, Surgical History	X														
Prior/Concomitant Medications[e]	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Spirometry[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Physical Examination[g]	X													X	
Vital Signs[h]	X		X	X	X	X	X	X	X	X	X	X	X	X	
12-Lead ECG[i]	X		X		X	X		X	X		X	X		X	
Pregnancy Test[j]	X		X			X			X			X		X	
Clinical Laboratory Testing[k]	X		X		X	X		X	X		X	X		X	
PK Sampling[l]			X		X	X		X	X		X	X		X	
Adverse Events	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Inhalation Device Training[m]	X														
Distribute Sponsor-provided inhalers for washout period[d]	X[d]				X			X			X				
Study Drug Administration[n]			X	X	X	X	X	X	X	X	X	X	X	X	

Table 8-1 Schedule of Events

Procedures	Screening[a]		Treatment Period 1[a]			Treatment Period 2[a]			Treatment Period 3[a]			Treatment Period 4[a]			Follow-Up Period[a]
	Visit 1a	Visit 1b (as needed)	Rand. Visit 2 Day 1	Visit 3 Day 15	Visit 4 Day 29	Visit 5 Day 1	Visit 6 Day 15	Visit 7 Day 29	Visit 8 Day 1	Visit 9 Day 15	Visit 10 Day 29	Visit 11 Day 1	Visit 12 Day 15	Visit 13 Day 29	Telephone Follow-up
Treatment Day[a]	**Up to -28**	**Up to -27**	**1[a]**	**15±2[a]**	**29±2[a]**	**1[a]**	**15±2[a]**	**29±2[a]**	**1[a]**	**15±2[a]**	**29±2[a]**	**1[a]**	**15±2[a]**	**29±2[a]**	**7-14[a]**
Return of Sponsor-provided inhalers for washout period			X			X			X			X			
Dispense Subject eDiary[o]	X		X												
Review Subject eDiary[o]			X	X	X	X	X	X	X	X	X	X	X	X	
Study Drug Dispensing/ Collection	X[p]		X	X	X	X	X	X	X	X	X	X	X	X	
Paradoxical Bronchospasm[q]			X	X	X	X	X	X	X	X	X	X	X	X	
BDI/TDI[r]			X		X			X			X			X	
Return to Maintenance COPD Medications[s]														X	

BDI=Baseline Dyspnea Index; COPD=chronic obstructive pulmonary disease; ECG=electrocardiogram; HFA=hydrofluoroalkane; PEFR=peak expiratory flow rate; PK=pharmacokinetic; QID=four times daily; Rand=Randomization; TDI=Transition Dyspnea Index

a Visit windows during each treatment period are relative to Day 1 of that treatment period. Washout Periods occur between Visits 4 and 5, Visits 7 and 8, and Visits 10 and 11 and are 14 to 21 days. Visit 1b must occur before Visit 2.

b A chest x-ray must be conducted within the screening period if the most recent chest x-ray or CT scan is more than 6 months old at the time of Visit 1a.

c See instructions for reversibility assessment in Section 7.1.1.3.

d At Screening and post randomization (during wash-out periods), change COPD medications as specified to Sponsor-provided therapies Atrovent HFA, Ventolin HFA, and Pulmicort Flexhaler (if applicable) see Section 5.5

e See listing of prohibited and concomitant medication in Section 5.5. At all visits beyond Screening, note time of last dose of short-acting bronchodilator and other COPD medications (if <6 hours, visit should be rescheduled).

f See Section 7.1.1.41 for guidance related to spirometry assessments and criteria.

g Weight, assessed in ordinary indoor clothing with shoes removed at Visit 1a (Screening) and Visit 13. Height will be recorded at Visit 1a (Screening) only. (See Section 7.2.1).

Table 8-1 Schedule of Events

Procedures	Screening[a]		Treatment Period 1[a]			Treatment Period 2[a]			Treatment Period 3[a]			Treatment Period 4[a]			Follow-Up Period[a]
	Visit 1a	Visit 1b (as needed)	Rand. Visit 2 Day 1	Visit 3 Day 15	Visit 4 Day 29	Visit 5 Day 1	Visit 6 Day 15	Visit 7 Day 29	Visit 8 Day 1	Visit 9 Day 15	Visit 10 Day 29	Visit 11 Day 1	Visit 12 Day 15	Visit 13 Day 29	Telephone Follow-up
Treatment Day[a]	Up to -28	Up to -27	1[a]	15±2[a]	29±2[a]	1[a]	15±2[a]	29±2[a]	1[a]	15±2[a]	29±2[a]	1[a]	15±2[a]	29±2[a]	7-14[a]

h See Section 7.2.2 for guidance on vital signs collection.

i See Section 7 2 3 for guidance on ECG assessment.

j See Section 7.2.4 for guidance on the administration of pregnancy test (women of childbearing potential only).

k See Section 7.2.4 for guidance on clinical laboratory testing.

l On Day 1 PK sampling will be performed 30 minutes pre-dose. On Day 29, PK sampling will be performed 30 minute pre-dose, and at 2, 6, 20, and 40 minutes and 1, 2, 4, 8, 10, and 12 hours post-dose.

m Sites may use sponsor provided Atrovent HFA or Ventolin HFA to train subjects on the use of MDIs.

n At the start of each treatment visit, subjects must withhold all COPD medications, including study drug and rescue medications (Ventolin HFA) for at least 6 hours prior to start of test day procedures. At Visits 3, 6, 9 and 12 (Day 15 of each treatment period), site personnel will collect blinded study drug dispensed during the prior visit and then administer a dose of the newly dispensed study drug at the clinic under site supervision.

o See Section 7.1.1.5 for guidance on subject eDiary use.

p Sponsor-provided Atrovent HFA, Ventolin HFA, and Pulmicort Flexhaler (if applicable) is dispensed only after a subject is determined to be eligible to proceed to Visit 2 (ie., only if a subject meets COPD definition following spirometry assessments at Screening).

q See Section 7.3.3 for definition of paradoxical bronchospasm.

r See Section 7.1.4 for guidance on the BDI/TDI.

s At the end of the Visit 13, return subject to pre-study or other appropriate inhaled maintenance COPD medications.

Table 8-2 Visit Procedures on Day 1 and Day 15 of Each Treatment Period (Visits 2, 3, 5, 6, 8, 9, 11, and 12)

Clinical Variable[a]	Pre-dosing		Post-dosing			
	-1 hour	-30 minutes	15 minutes	30 minutes	1 hour	2 hours
BDI[b]	X					
Vital Signs[c]	X	X	X	X	X	X
12-Lead ECG[d]	X[d]	X[d]	X	X	X	X
Clinical Laboratory Testing[e]	X			X		X
Spirometry (FEV_1, FVC, PEFR)[f]	X[f]	X[f]	X	X	X	X
Pharmacokinetic Assessment[g]		X				
Paradoxical Bronchospasm[h]			X	X		
Dispense/Review Subject eDiary[i]		X				
Collect/Dispense Drug Supplies[j]		X				

BDI=Baseline Dyspnea Index; BMP=Basic Metabolic Panel; ECG=electrocardiogram; FEV_1=Forced Expiratory Volume in 1 second; FVC=Forced Vital Capacity; PEFR=peak expiratory flow rate; PFT=pulmonary function test; QTcF=QT Corrected Using Fridericia's Formula; TP=Treatment Period

a Safety assessments (vital signs and ECG) should be started approximately 5 to 10 minutes ahead of the specified timepoint for spirometry assessment to ensure that spirometry for FEV_1, FVC, and PEFR determination will be conducted as close to the specified timepoints as possible (ie., FEV_1, FVC, and PEFR assessments need to be conducted within ±15 minutes of specified time prior to study drug administration; ±5 minutes of specified timepoint for the first 60 minutes post study drug administration; ±15 minutes of specified timepoint for assessments obtained thereafter).

b The BDI administered at Visit 2 (Randomization Visit) must be completed by the subject prior to any other visit procedures. The BDI is not a timed assessment; therefore, sites should plan to perform this activity so as not to interfere with collection of timed assessments such as spirometry.

c Temperature will be obtained at pre-dose at all visits; no further temperature assessments required unless clinically indicated.

d Two baseline ECGs should be conducted, one between 60 to 120 minutes and another between 30 to 60 minutes prior to dosing. If >30 ms difference in QTcF is observed between the two baseline ECGs then the Investigator will make a determination as to the suitability of the subject to proceed. If the subject does proceed in the study, a third baseline ECG is to be obtained prior to dosing. ECG is not required at Day 15.

e All specified clinical laboratory parameters will be obtained within 60 minutes prior to study drug administration on Day 1 of Treatment Period 1(Visit 2). At Visit 2, a BMP with focus on potassium and glucose parameters will be obtained at 30 minutes and 2 hours post-dose on all subjects.

f The baseline FEV_1 at Visit 3 must be within ±20% or 200 mL of the baseline FEV_1 obtained at the Randomization Visit (Visit 2). On initial assessment if the subject fails to meet the reproducibility criteria, but the 30-minute pre-dose assessment is within 20% of the baseline FEV_1 obtained at

Table 8-2 Visit Procedures on Day 1 and Day 15 of Each Treatment Period (Visits 2, 3, 5, 6, 8, 9, 11, and 12)

Clinical Variable[a]	Pre-dosing		Post-dosing			
	-1 hour	-30 minutes	15 minutes	30 minutes	1 hour	2 hours

Randomization, another assessment may be conducted 30 minutes later. If the last two assessments meet the baseline stability requirements, the initial 60-minute pre-dose assessment will not be used and the last two assessments will be used to establish the eligibility criteria. If the test day FEV_1 is not within ±20% or 200 mL, the visit may be rescheduled (for a maximum of three attempts) at the Investigator's discretion (eg., within 1 week), or the subject discontinued.

g Pharmacokinetic sampling will be performed at -30 minutes pre-dose on Day 1 only.

h Please refer to Section 7.3.3 for definition of paradoxical bronchospasm.

i Subject eDiaries are only dispensed at Visit 2. See Section 7.1.1.5 for guidance on subject eDiary use.

j See Section 6.7 for instructions for preparation of treatments for administration and dispensing. At Visits 3, 6, 9 and 12 (Day 15 of each treatment period) site personnel will collect blinded study drug dispensed during the prior visit and then administer a dose of the newly dispensed study drug at the clinic under site supervision.

Note: Where data collection timepoints are concurrent, variables are recommended to be collected in the following order: Vital signs, ECG, clinical laboratory assessments, and spirometry.

Table 8-3 Visit Procedures on Day 29 of Each Treatment Period (Visits 4, 7, 10, and 13)

Clinical Variable[a]	Pre-dosing		Post-dosing													
	-1 hr	-30 min	2 min	6 min	15 min	20 min	30 min	40 min	1 hr	2 hr	4 hr	6 hr	8 hr	10 hr	11.5 hr	12 hr
TDI[b]	X															
Vital Signs[c]	X	X			X		X		X	X	X	X	X	X	X	X
12-Lead ECG[d]	X[d]	X[d]			X		X		X	X	X					X
Clinical Laboratory Testing[e]	X						X			X						
Spirometry (FEV_1, FVC, PEFR)	X	X			X		X		X	X	X	X	X	X	X	X
Pharmacokinetic Assessment[f]		X	X	X		X		X	X	X	X		X	X		X
Paradoxical Bronchospasm[g]					X		X									
Collect/Review Subject eDiary[h]	X															
Collect/Dispense Drug Supplies[i]							X									

BMP=Basic Metabolic Panel; CMP=Comprehensive Metabolic Panel; ECG=electrocardiogram; FEV_1=Forced Expiratory Volume in 1 second; FVC=Forced Vital Capacity; hr=hour; min=minute; PEFR=peak expiratory flow rate; PFT=pulmonary function test; QTcF=QT Corrected Using Fridericia's Formula ; TDI=Transition Dyspnea Index; TP=Treatment Period

a Safety assessments (vital signs and ECG) should be started approximately 5 to 10 minutes ahead of the specified timepoint for spirometry assessment to ensure that spirometry for FEV_1, FVC and PEFR determination will be conducted as close to the specified timepoints as possible (ie., FEV_1, FVC and PEFR assessments need to be conducted within ±15 minutes of specified time prior to study drug administration; ±5 minutes of specified timepoint for the first 60 minutes post study drug administration; ±15 minutes of specified timepoint for assessments obtained thereafter).

b The TDI administered on Day 29 of each treatment period must be completed by the subject prior to any other visit procedures. The TDI is not a timed assessment; therefore, sites should plan to perform these activities so as not to interfere with collection of timed assessments such as spirometry.

Table 8-3 Visit Procedures on Day 29 of Each Treatment Period (Visits 4, 7, 10, and 13)

Clinical Variable[a]	Pre-dosing			Post-dosing											
	-1 hr	-30 min	2 min	6 min	15 min	20 min	30 min	40 min	1 hr	2 hr	4 hr	6 hr	8 hr	10 hr	11.5 hr	12 hr

c Temperature will be obtained at pre-dose at all visits; no further temperature assessments required unless clinically indicated.
d Two baseline ECGs should be conducted, one between 60 to 120 minutes and another between 30 to 60 minutes prior to dosing. If >30 msec difference in QTcF observed between the two baseline ECGs then the Investigator will make a determination as to the suitability of the subject to proceed. If the subject does proceed in the study, a third baseline ECG is to be obtained prior to dosing.
e All specified clinical laboratory parameters will be obtained within 60 minutes prior to study drug administration. A BMP will be obtained at 30 minutes and 2 hours post-dosing on all subjects, respectively.
f Pharmacokinetic sampling will be performed at -30 minutes pre-dose and at 2, 6, 20, and 40 minutes, and 1, 2, 4, 8, 10, and 12 hours post-dose.
g Please refer to Section 7.3.3 for definition of paradoxical bronchospasm.
h Subject eDiaries will be collected at Visit 13 only. See Section 7.1.1.5 for guidance on subject eDiary use.
i Used and unused study drug will be collected on Day 29 of each treatment period.
j See Section 6.7 for instructions for preparation of treatments for administration and dispensing.

Note: Where data collection timepoints are concurrent, variables are recommended to be collected in the following order: Vital signs, ECG, clinical laboratory assessments, and spirometry.

8.1 Screening Visit 1a (and Visit 1b) (Up to Day -28 and Day -27, respectively)

- Obtain informed consent
- Register subject in IWRS to obtain subject Screening number
- Obtain demographic data, including age, race, smoking history, medical/surgical history including glaucoma, and age of onset of COPD
- Obtain history of COPD exacerbation within 12 months of the Screening Visit
- Verify that subject meets inclusion/exclusion criteria
- Obtain medication history, including COPD medications
- Conduct a serum pregnancy test for all female subjects unless it is documented in the medical history that the subject has been irreversibly surgically sterilized (hysterectomy, oophorectomy or bilateral tubal ligation) or they are at least 2 years post-menopausal
- Conduct a complete physical examination (general appearance, skin, head, eyes, ears, nose, throat, neck [including thyroid], lymph nodes, chest, heart, abdomen, extremities, and nervous system)
- Obtain height, weight, and vital signs
- Obtain a 12-lead ECG
- Conduct baseline spirometry assessments (FEV_1, FVC, and PEFR)
- Conduct inhalation device training
- Conduct reversibility testing to four puffs of Ventolin HFA (see Section 7.1.1.3)
- Obtain laboratory samples (hematology and chemistry)
- If a chest x-ray or CT scan within six months of Visit 1a (Screening) is not available, obtain a new chest x-ray
- Stop prohibited COPD medications and change concurrent COPD medications as specified in protocol (see Section 5.5). **Note:** Subjects taking an ICS or ICS/LABA for maintenance treatment at Screening will be switched to Sponsor-provided Pulmicort Flexhaler for use during this period, which will be discontinued at the time of randomization.
- Adverse events must be recorded during the Screening period that is from the time of informed consent to the start of study treatment (Visit 2). Adverse events that occur between the time subject signs the ICF for the study and the time the subject is randomized will be summarized as medical history and not as an AE unless the event meets the definition of an SAE as defined in Section 7.3.2.7).

- Dispense subject eDiary, and provide instructions on use of eDiary completion
- Arrange date of Visit 1b or Visit 2 as appropriate
    - Visit 1b is to be used only for repeat spirometry entry criteria, all other repeat assessments, if needed, will be captured as an unscheduled visit.

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

- Review subject eDiary. Screen fail subject if he/she has not met the eDiary compliance requirement (see Section 7.1.1.5)
- Determine the last dosing of short-acting bronchodilator and other COPD medications (if <6 hours, Visit 2 must be rescheduled)
- Have the subjects complete BDI questionnaire before any other study procedures are performed
- Review inclusion/exclusion criteria to confirm subject eligibility
- Review concomitant medications to ensure adherence to COPD regimen
- Record AEs (if any)
- Collection of Sponsor-provided Atrovent HFA, Ventolin HFA, or Pulmicort Flexhaler (if applicable)
- Complete all pre-dose assessments, including vital signs, ECGs, clinical laboratory testing, urine pregnancy testing (if appropriate), and spirometry (Table 8-2)
- Perform pre-dose PK sampling (subjects participating in PK collection only) (see Table 8-2)
- Obtain subject treatment assignment information from IWRS
    - At 15-30 minutes prior to dosing, it is recommended that the seal around the study day treatment box is to be opened and the instructions for administration of study drug followed. Refer to Section 6.7 for detailed instructions for preparation of treatments for administration. These instructions are to be adhered to and are relevant to all study treatment visits.
- Subject will administer first dose of newly assigned study drug at the clinic
- The subject is to be considered randomized after receiving a randomization number from the IWRS
- Perform all post-dosing assessments (see Table 8-2)
- Schedule Visit 3 and ensure subject has adequate supply of study drug and rescue Ventolin HFA

8.3 Visit 3 (Day 15 of Treatment Period 1)

- Review subject eDiary. Retrain subject if subject has not met eDiary compliance requirement (see Section 7.1.1.5)
- Determine the last dosing of short-acting bronchodilator and other COPD medications (if <6 hours, visit must be rescheduled)
- Review concomitant medications to ensure adherence to COPD regimen
- Record AEs (if any)
- Collect blinded study drug dispensed during the prior visit
- Complete all pre-dose assessments, including vital signs, clinical laboratory testing, urine pregnancy testing (if appropriate), and spirometry (Table 8-2)
- Review subject's eligibility to continue
- Obtain new MDI assignment from IWRS
    - Refer to Section 6.7 for detailed instructions for preparation of treatment for administration, including priming the MDI prior to subject use
- Subject will administer a dose of the newly dispensed study drug at the clinic under site supervision
- Perform all post-dosing assessments (see Table 8-2)
- Schedule Visit 4 and ensure subject has adequate supply of study drug and rescue Ventolin HFA

8.4 Visit 4 (Day 29 of Treatment Period 1)

- Review subject eDiary. Retrain subject if subject has not met eDiary compliance requirement (see Section 7.1.1.5)
- Determine the last dosing of short-acting bronchodilator and other COPD medications (if <6 hours, visit must be rescheduled)
- Obtain TDI
- Review concomitant medications to ensure adherence to COPD regimen
- Record AEs (if any)
- Confirm subject's eligibility to continue

- Complete all pre-dose assessments, including vital signs, ECGs, clinical laboratory testing, urine pregnancy testing (if appropriate), and spirometry (see Table 8-3)
- Perform pre-dose PK sampling (subjects participating in PK collection only) (see Table 8-2)
- Subjects will administer final dose in-clinic from the MDI dispensed at the previous visit (Day 15 of the treatment period)
- Perform all post-dosing assessments, including PK sampling (subjects participating in PK collection only) (see Table 8-3)
- Collect previously dispensed study drug
- Schedule next Visit (following a Washout Period of at least 14 days but no longer than 21 days) and ensure subject has adequate supply of COPD medication, including Sponsor-provided Atrovent HFA, Ventolin HFA, or Pulmicort Flexhaler (if applicable). **Note:** Subjects that were treated with an ICS during Screening must resume their previous dosing regimen of the ICS prescribed at Screening.

8.5 Visit 5, 8, and 11 (Day 1 of Treatment Periods 2, 3, and 4, respectively)

- Review subject eDiary. Retrain subject if subject has not met eDiary compliance requirement (see Section 7.1.1.5)
- Determine the last dosing of short-acting bronchodilator and other COPD medications (if <6 hours, visit must be rescheduled)
- Review inclusion/exclusion criteria to confirm subject eligibility
- Review concomitant medications to ensure adherence to COPD regimen
- Record AEs (if any)
- Collection of Sponsor-provided Atrovent HFA, Ventolin HFA, or Pulmicort Flexhaler (if applicable)
- Complete all pre-dose assessments, including vital signs, ECGs, clinical laboratory testing, urine pregnancy testing (if appropriate), and spirometry (see Table 8-3)
- Perform pre-dose PK sampling (subjects participating in PK collection only) (see Table 8-2)
- Obtain subject treatment assignment information from IWRS
    - At 15-30 minutes prior to dosing, it is recommended that the seal around the study day treatment box is to be opened and the instructions for administration of study drug followed. Refer to Section 6.7 for detailed instructions for preparation of

treatments for administration. These instructions are to be adhered to and are relevant to all study treatment visits.

- Subject will administer first dose of newly assigned study drug at the clinic
- Perform all post-dosing assessments (see Table 8-2)
- Schedule Visit 6 and ensure subject has adequate supply of study drug and rescue Ventolin HFA

8.6 Visit 6, 9, and 12 (Day 15 of Treatment Periods 2, 3, and 4, respectively)

- Review subject eDiary. Retrain subject if subject has not met eDiary compliance requirement (see Section 7.1.1.5)
- Determine the last dosing of short-acting bronchodilator and other COPD medications (if <6 hours, visit must be rescheduled)
- Review concomitant medications to ensure adherence to COPD regimen
- Record AEs (if any)
- Collect blinded study drug dispensed during the prior visit
- Complete all pre-dose assessments, including vital signs, clinical laboratory testing, urine pregnancy testing (if appropriate), and spirometry (see Table 8-3)
- Review subject's eligibility to continue
- Obtain new MDI assignment from IWRS
    - Refer to Section 6.7 for detailed instructions for preparation of treatment for administration, including priming the MDI prior to subject use
- Subject will administer a dose of the newly dispensed study drug at the clinic under site supervision
- Perform all post-dosing assessments (see Table 8-2)
- Schedule Visit 7 and ensure subject has adequate supply of study drug and rescue Ventolin HFA

8.7 Visit 7, 10 and 13 (Day 29 of Treatment Periods 2, 3, and 4, respectively)

- Review subject eDiary. Retrain subject if subject has not met eDiary compliance requirement (see Section 7.1.1.5)

- Determine the last dosing of short-acting bronchodilator and other COPD medications (if <6 hours, visit must be rescheduled)
- Obtain TDI
- Review concomitant medications to ensure adherence to COPD regimen
- Record AEs (if any)
- Confirm subject's eligibility to continue
- Complete all pre-dose assessments, including vital signs, ECGs, clinical laboratory testing, urine pregnancy testing if appropriate, and spirometry (see Table 8-3)
- Perform pre-dose PK sampling (subjects participating in PK collection only) (see Table 8-2)
- Subjects will administer final dose in-clinic from the MDI dispensed at the previous visit (Day 15 of the treatment period)
- Perform all post-dosing assessments, including PK sampling (subjects participating in PK collection only) (see Table 8-3)
- Collect previously dispensed study drug
- **At Visits 7 and 10 only**: Schedule next Visit (following a Washout Period of at least 14 days but no longer than 21 days) and ensure subject has adequate supply of COPD medication, including Sponsor-provided Atrovent HFA, Ventolin HFA, or Pulmicort Flexhaler (if applicable). **Note:** Subjects that were treated with an ICS during Screening must resume their previous dosing regimen of the ICS prescribed at Screening.
- **At Visit 13 only**: Complete final visit procedures, including serum pregnancy (if appropriate), and physical exam. Schedule a final telephone follow-up at least 7 days but no longer than 14 days from Visit 13. At completion of all Visit 13 assessments, return subject to pre-study or appropriate inhaled maintenance COPD medications. Subject eDiaries will be reviewed and collected at the end of the in-clinic visit and retained at the site.

8.8 Management of Randomized Subjects Who Meet Rescue Criteria

- If rescue criteria are met at a scheduled visit at Day 15 of each Treatment Period, and during any unscheduled visits occurring during any Treatment Period (see Section 7.1.1.2), the Investigator at their discretion, may complete the remaining scheduled visit procedures (i.e. clinical laboratory testing, vital signs, etc.) and transition the subject to the washout period as follows:
  - Obtain from IWRS washout medication [e.g. Atrovent HFA, Ventolin HFA and Pulmicort Flexhaler (if appropriate)] for use during the Rescue Period. Subjects will

be instructed to bring their washout medication to the next visit, and continue to complete their and their eDiary at home during the Washout Period.
- Schedule the next visit (Day 1 of the next Treatment Period) within 14–21 days from the day the Washout Period was initiated.
- After the Washout Period, subjects may continue in the study to the next Treatment Period provided the Baseline Stability Criteria are met (See Section 7.1.1.1).

- Except during Treatment Period 4, if an unscheduled visit is required to manage worsening of COPD symptoms, and in the opinion of the Investigator, the subject may be transitioned to the Washout Period, the procedures outlined in Section 5.5. Day 29 may be conducted at the Investigator's discretion during the unscheduled visit, prior to the Washout Period transition described below.
  - Obtain from IWRS washout medication [e.g. Atrovent HFA, Ventolin HFA and Pulmicort Flexhaler (if appropriate)] for use during the Washout Period. Subjects will be instructed to bring their washout medication to the next visit, and continue to complete their eDiary at home during the Washout Period.
  - Schedule the next visit (Day 1 of the next Treatment Period) within 14–21 days from day the Washout Period was initiated.
  - After the Washout Period, subjects may continue in the study to the next Treatment Period provided the Baseline Stability Criteria are met (See Section 7.1.1.1).
- If the Rescue is required during the fourth and final Treatment Period, then the procedures for discontinuation should be followed and the subject will be considered to have successfully completed the treatment portion of the study.

8.9 Unscheduled Visits/Premature Discontinuation (Early Termination) Visits

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

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

☐ Review eDiary data and peak flow values.

☐ Record adverse events (if any).

☐ Review concomitant medications

☐ Conduct a physical examination, including vital signs.

☐ Perform ECG and collect blood samples for hematology and chemistry.

☐ Collect a blood sample for pregnancy test for women of child bearing potential.

☐ Collect subject eDiary.

- ☐ Collect all study drug.
- ☐ Inform subject about reporting all SAEs up to 14 days following the last dose of study drug.
- ☐ Return subject to pre-study or appropriate maintenance COPD medications.
- ☐ Capture the subject discontinuation reason.
- ☐ Schedule a follow-up telephone call 7-14 days post last study drug dosing. If the discontinuation visit is performed > 7 days post last study drug dosing a follow-up telephone call will not be required.

8.10 Follow-Up Telephone Call

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

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

8.11 Completion of the Study

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

- ☐ Subject discretion (document reason)
- ☐ Investigator or designee considers it to be in the best interest of the subject
- ☐ Adverse events(s)
- ☐ Administrative reasons (e.g., early termination of the study)
- ☐ Subject lost-to-follow-up
- ☐ Lack of efficacy
- ☐ Major protocol deviation
- ☐ Death
- ☐ Completion of the study
- ☐ Protocol specified discontinuation criteria (See Section 8.9).

Subjects who complete all visits, but did not complete a follow-up telephone call, will be regarded as study completers, and will be included in efficacy and safety analyses.

9 PLANNED STATISTICAL METHODS

9.1 Introduction

This study will be conducted as a four-period, five-treatment, incomplete block crossover design evaluating the following five treatments in approximately 160 subjects:

- BFF MDI 320/9.6 µg BID
- BFF MDI 160/9.6 µg BID
- BFF MDI 80/9.6 µg BID
- BD MDI 320 µg BID
- FF MDI 9.6 µg BID

The primary objective of this study is demonstrate that the combination of BD 320 µg and FF 9.6 µg (BFF MDI 320/9.6 µg) provides benefit on lung function compared with BD MDI 320 µg in subjects with moderate to severe COPD. The secondary objectives of this study are to demonstrate that the combination of BD 320 µg and FF 9.6 µg (BFF MDI 320/9.6 µg) provides benefit on lung function compared with FF MDI 9.6 µg, and to assess the dose response of BD on a fixed-dose background of FF (9.6 µg) using BFF MDI (320/9.6 µg, 160/9.6 µg, and 80/9.6 µg) in subjects with moderate to severe COPD.

9.2 Protocol Variables

9.2.1 Efficacy Endpoints

The first day of treatment in each treatment period is Day 1. Each treatment period is planned to contain 28 days between the first and last dose corresponding to a span of 29 calendar days. Therefore, assessments collected on Day 15 (Visits 3, 6, 9, and 12) will occur following 14 days of treatment and assessments collected on Day 29 (Visits 4, 7, 10, and 13) will occur following 28 days of treatment.

Since pre-dose values are known to be variable and an isolated timepoint may not accurately reflect the true baseline, the following baseline will be used for statistical analyses unless otherwise specified: the mean of available pre-dose values on the first day of each treatment period, ie., the mean of pre-dose values at Visits 2, 5, 8, and 11, where the mean of the -60 and -30 minute value for each visit day is obtained and then all visit means are averaged. Note that all spirometry and eDiary-based endpoints will utilize changes from baseline and that area under the curve (AUC) assessments will be normalized by dividing the AUC by the length of follow-up post-dosing (typically 12 hours).

9.2.1.1 Primary Efficacy Endpoint

- FEV_1 $AUC_{0\text{-}12}$ on Day 29

9.2.1.2 Secondary Efficacy Endpoints

- Change from baseline in morning pre-dose trough FEV_1 over 28 days
- Peak FEV_1 over 28 days evaluated during chronic dosing utilizing the peak change from baseline on Days 15 and 29
- Peak change from baseline in FEV_1 on Day 1
- FVC AUC_{0-12} on Day 29
- TDI focal score on Day 29
- Change from baseline in average daily use of rescue Ventolin HFA over the last week of treatment

9.2.1.3 Other Efficacy Endpoints

- Change from baseline in morning pre-dose trough FEV_1 on Days 15 and 29
- Peak change from baseline in FEV_1 on Days 15 and 29
- Change from baseline in 12-hour post-dose trough FEV_1 on Day 29
- FEV_1 AUC_{0-2} on Day 1
- FEV_1 AUC_{0-2}, FEV_1 AUC_{0-6}, and FEV_1 AUC_{6-12} on Day 29
- Change from baseline in FEV_1 by post-dose timepoints on Days 1 and 29
- Change from baseline in morning pre-dose trough FVC on Days 15 and 29 and over 28 days
- Peak change from baseline in FVC on Days 1, 15, and 29 and over 28 days evaluated utilizing the peak change from baseline on Days 15 and 29
- FVC AUC_{0-2} on Day 1
- Change from baseline in FVC by post-dose timepoint on Days 1 and 29
- Change from baseline in 12-hour post-dose trough FVC on Day 29
- Change from baseline in morning pre-dose trough peak expiratory flow rate (PEFR) on Days 15 and 29 and over 28 days
- Peak change from baseline in PEFR on Days 1, 15, and 29 and over 28 days evaluated utilizing Days 15 and 29
- PEFR AUC_{0-2} on Day 1 and PEFR AUC_{0-12} on Day 29
- Change from baseline in PEFR by post-dose timepoint on Days 1 and 29
- Change from baseline in 12-hour post-dose trough PEFR on Day 29
- Change from baseline in average daily use of rescue Ventolin HFA over the treatment period
- Change from baseline in the Breathlessness, Cough, and Sputum Scale total score over the treatment period
- Change from baseline in nighttime awakenings over the treatment period

9.2.2 Pharmacokinetic Assessments

The PK of BD and formoterol will be assessed from plasma concentrations in a subset of approximately 60 subjects. Timepoints for PK blood sample collection during each of the four periods will be: Day 1 within 30 minutes prior to dosing; and Day 29 within 30 minutes prior to dosing, then 2, 6, 20, and 40 minutes and 1, 2, 4, 8, 10,and 12 hours post-dose. PK parameters at all doses will include: C_{max}, $t_{max,}$ $t_{½}$, AUC_{0-12}, AUC_{0-t}, CL/F, Vd/F, and λ_z.

9.2.3 Safety Endpoints

The safety endpoints for this study include AEs and SAEs, vital signs (BP, HR, and temperature), clinical laboratory values (hematology and clinical chemistry), and ECGs.

9.3 Analysis

9.3.1 Primary Efficacy Analysis

The primary efficacy analysis will involve comparisons between treatments for the primary endpoint: FEV_1 AUC_{0-12} on Day 29:

1. BFF MDI (all doses) versus BD MDI 320 µg
2. BFF MDI (all doses) versus FF MDI 9.6 µg

The analysis of these comparisons will be sequential. Each comparison will be interpreted inferentially using a significance level of 0.05 if the preceding comparison is significant. The order of comparisons will be based on dose starting (high to low) with the comparisons of BFF MDI to BD MDI 320 µg occurring first, followed by the comparisons of BFF MDI to FF MDI 9.6 µg.

FEV_1 AUC_{0-12} is the area under the curve for the change from baseline in FEV_1 calculated using the trapezoidal rule. All observed data will be used and to aid in interpretation, all AUC values will be normalized by dividing the AUC by the time from the first to the last non-missing value (typically 12 hours).

The analysis of FEV_1 AUC_{0-12} on Day 29 will be based on a repeated measures mixed model with covariates of treatment, baseline FEV_1, period, and the response to Ventolin HFA at Visit 1a. The model will not include treatment sequence unless that term is determined to be important ($p<0.10$). Intrasubject correlation will be modeled by including subject as a random effect. Two-sided 95% confidence intervals (CIs) will be tabulated.

9.3.2 Secondary Efficacy Analysis

9.3.2.1 Morning Pre-dose Trough FEV_1

The change from baseline in morning pre-dose trough FEV_1 over 28 days will be analyzed using a repeated measures mixed model with covariates of treatment, baseline FEV_1, period, day, treatment by day interaction, and the response to Ventolin HFA at Visit 1a. Period,

treatment, and day will be treated as unordered categorical variables. The model will not include treatment sequence unless that term is determined to be important ($p<0.10$). Intrasubject correlation will be modeled by including subject as a random effect.

The change from baseline in morning pre-dose trough FEV_1 on Day 15 and on Day 29 will be analyzed using the same model.

9.3.2.2 Peak Change in FEV_1

Peak change from baseline in FEV_1 on Day 1 is defined as the change at the highest value of FEV_1 post-dose on Day 1. The peak change from baseline in FEV_1 over 12 hours post-dosing will be identified from all non-missing change values up through and including the 12-hour time window, provided that there are at least 2 non-missing values during the first 2 hours post-dose. Peak change in FEV_1 on Day 1 will be analyzed in a similar fashion to FEV_1 AUC_{0-12}. Peak FEV_1 over 28 days evaluated during chronic dosing utilizing the peak change from baseline on Days 15 and 29 will be analyzed using a similar model to trough FEV_1.

9.3.2.3 FVC AUC_{0-12}

FVC AUC_{0-12} following chronic dosing on Day 29 will be calculate similarly to FEV_1 AUC_{0-12} and analyzed in a similar fashion, but using baseline FVC rather than baseline FEV_1 as a covariate.

9.3.2.4 TDI

The TDI focal score on Day 29 will be analyzed in a similar fashion to FEV_1 AUC_{0-12}, but using the BDI rather than baseline FEV_1 as a covariate.

9.3.2.5 Rescue Ventolin HFA Usage

Analyses of rescue Ventolin HFA usage will use the average of the non-missing values recorded in the subject diaries over each week and over the last week of treatment within each period. Baseline for these measures will be obtained using the non-missing values from the last 7 days prior to Randomization.

The change from baseline in rescue Ventolin HFA usage over the last week of treatment will be analyzed in a similar fashion to FEV_1 AUC_{0-12}, but using baseline Ventolin HFA usage rather than baseline FEV_1 as a covariate. An analysis of Ventolin HFA usage over the entire treatment period and for each week of the treatment period will also be performed. For this analysis, the change from baseline in the average of Ventolin HFA usage during each of the four scheduled weeks in each treatment period will be analyzed using a repeated measures mixed model with covariates of treatment, baseline Ventolin HFA usage, period, week, treatment by week interaction, and the response to Ventolin HFA at Visit 1. Period, treatment, and week will be treated as unordered categorical variables. The model will not include treatment sequence unless that term is determined to be important ($p<0.10$).

Intrasubject correlation will be modeled across periods by including subject as a random effect and will be modeled within periods as AR(1).

The change from baseline in Ventolin HFA usage for each week of the treatment period will be analyzed using the same model.

9.3.3 Other Efficacy Analysis

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

9.3.4 Pharmacokinetic Analyses

Non-compartmental parameter estimates will be natural ln-transformed and analyzed using a repeated measures mixed model in which treatment will be a fixed effect and within-subject errors (between visits) are correlated, but between subject errors are independent. Subject will be included as a random effect in order to account for intrasubject correlation. The primary analysis will be the comparisons of BD AUC and C_{max} parameters on Day 29 between BFF MDI doses and BD MDI and formoterol AUC and C_{max} parameters between BFF MDI and FF MDI to evaluate the potential for drug-drug interactions. Doses of BFF MDI will also be compared to evaluate dose proportionality for BD and to compare FF levels.

9.3.5 Safety Analysis

9.3.5.1 Adverse Events

Adverse events during each treatment period will be summarized by the number of subjects experiencing an event. They will be tabulated at the level of the Medical Dictionary for Regulatory Activities (MedDRA) preferred term, and the MedDRA system organ class. The version of MedDRA current at the time the first subject is randomized will be used throughout the study. Tabulations will be broken down by severity, seriousness, AEs leading to discontinuation, and by relationship to study drug. No hypothesis tests will be performed.

9.3.5.2 Paradoxical Bronchospasm

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

9.3.5.3 Clinical Laboratory Measurements

Summary statistics (mean, median, standard deviation [SD], and range) of change from baseline values will be tabulated for each treatment and each assessment time. For clinical

laboratory measurements, baseline will be defined as the last available value prior to Randomization. Potentially clinically significant values will be identified and summarized.

9.3.5.4 Vital Signs

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

9.3.5.5 ECGs

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

9.4 Randomization

Subjects will be randomly assigned to one of 12 treatment sequences using an IWRS. Each sequence will include exactly 4 of the 5 treatment groups included in this study. All subjects will receive BFF 320/9.6 µg and FF MDI 9.6 µg and 2 of the 3 remaining treatments: BFF MDI 160/9.6 µg, BFF MDI 80/9.6 µg, and BD MDI 320 µg.

The 12 treatment sequences are shown below where A is BFF 320/9.6 µg, B is FF MDI 9.6 µg, C is BFF 160/9.6 µg, D is BFF 80/9.6 µg, and E is BD MDI 320 µg:

ABCD	ABDE	ABCE
BDAC	BEAD	BEAC
CADB	DAEB	CAEB
DCBA	EDBA	ECBA

Randomization will be stratified by participation in the PK sub-study (yes or no).

9.5 Experimental Design

The experimental design was chosen to be balanced with respect to period and first order carry-over effects. The design was selected to limit exposure to 90 days of BFF MDI or BD MDI treatment at any dose and to focus on the highest dose.

Type I error will be controlled for the primary endpoint by following a sequential approach. Each comparison will be interpreted inferentially using a significance level of 0.05 if the preceding comparison is significant. The order of comparisons will be high dose to low dose with the comparisons of BFF MDI to BD MDI 320 µg occurring first, followed by the comparisons of BFF MDI to FF MDI 9.6 µg.

Other than the specification of secondary endpoints, no further adjustments for Type I error will be made.

9.6 Sample Size Consideration

Power calculations were based on the properties of the primary endpoint, FEV_1 $AUC_{0-12,}$ on Day 29. Estimates of within-subject SD of FEV_1 AUC_{0-12} were obtained from previous Pearl studies. A composite within-subject SD of 130 mL is assumed and a total SD of 184 mL. It is further assumed that approximately 20% of subjects will dropout, and a two-sided alpha level of 0.05 will be used. Under these assumptions, 160 randomized subjects will provide approximately 99% power to demonstrate a difference of 100 mL for each dose of BFF MDI compared with BD MDI 320 µg. The power to demonstrate a difference of 50 mL for BFF MDI 320/9.6 µg compared with FF MDI is approximately 90%. For the lower strengths of BFF MDI, the power to demonstrate a difference of 50 mL compared with FF MDI is approximately 54%.

9.7 Data Validation and Transformation

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

Changes in spirometry measures from baseline, and from timepoint to timepoint will be examined graphically before data base lock, and before unblinding, as part of data quality management. This will include production of normal probability plots, kernel density estimates, and normal order outlier statistics.

9.8 Analysis Plan

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

9.9 Study Populations

The following analysis populations are defined in this study:

- The **Intent-To-Treat (ITT) Population** is defined as all subjects who are randomized to treatment. Treatment is assigned as randomized regardless of the treatment actually received.

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

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

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

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

Analyses will be performed as follows:

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

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

9.10 Handling of Missing Data

Pre-dose spirometry values will use the average of the non-missing -60 minutes and -30 minutes values. Weekly averages for eDiary-based parameters will use all non-missing values.

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

For the mITT analyses, FEV_1 AUC_{0-12} will be calculated if there are at least two non-missing data-points during the first 2 hours post-dose and there is at least one non-missing value at 4 hours post-dose or later. Peak FEV_1 will be calculated if there are at least two non-missing data-points missing during the first 2 hours post-dose.

9.11 Statistical Software

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

10 ADMINISTRATIVE CONSIDERATIONS

10.1 Regulatory Authority Approval

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

10.2 Ethical Conduct of the Study and IRB or IEC Approval

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

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

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

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

10.3 Subject Information and Consent

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

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

10.4 Confidentiality

10.4.1 Confidentiality of Data

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

10.4.2 Confidentiality of Subject/Patient Records

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

10.5 Quality Control and Assurance

Pearl is responsible for implementing and maintaining quality control and quality assurance systems with written SOP to ensure that studies are conducted and data are generated, documented, and reported in compliance with the protocol, accepted standards of GCP, and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the clinical study.

10.6 Data Management

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

10.7 Study Monitoring

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

During these contacts, the monitor will:

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

This will be done in order to verify that the:

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

The Investigator agrees to allow the monitor direct access to all relevant documents and to allocate his/her time and the time of his/her staff to the monitor to discuss findings and any relevant concerns. Upon completion of the study, the monitor will conduct the following activities in conjunction with the Investigator or site staff, as appropriate:

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

After the final review of the study files, the files should be secured for the appropriate time period as specified in Section 10.8. The Investigator will also permit inspection of the study files by Pearls' Quality Assurance auditors, and authorized representatives of the FDA or other applicable regulatory agencies.

10.8 Retention of Data

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

10.9 Financial Disclosure

The Principal Investigator or sub-Investigators named on the Form FDA 1572 will need to complete a financial disclosure form prior to study initiation, at any time during the study execution if new information needs to be disclosed, and for 1 year after study completion.

Investigators should make the IRB/IEC aware of any financial interests that the Investigator has in the investigational product.

10.10 Investigator's Final Report

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

10.11 Publication Policy

Pearl 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-sponsored studies should fairly recognize the activities of those that have made a significant contribution to the study. In addition, Pearl recognizes and adheres to the precepts of the International Society for Medical Publications Professionals (ISMPP), which provides guidance to the preparation of publications, disclosure of conflicts of interest, and the protection of intellectual property. Thus, it is anticipated that authorship will reflect the contribution made by Pearl 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 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 (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, in collaboration with the Investigators, will establish the appropriate authorship and responsibility for drafting study documents in accordance with the principles of the ICMJE and ISMPP. It is anticipated that a publication committee will be formed to assume oversight of these activities. All manuscripts will be reviewed and agreed upon before submission for publication by all authors.
3. **Sponsor Review of External Manuscripts:** Consistent with the 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 for review, approval, and to ensure consistency with the policy in this protocol. Pearl 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 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 to publish the study in a fair and accurate manner, Pearl 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 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 CONsolidated Standards of Reporting Trials (CONSORT) Statement [Moher, 2010] and a 25-item checklist which is intended to improve the reporting of a randomized controlled trial, 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.

11 REFERENCE LIST

Aalbers R, Ayres J, Backer V, et al. Formoterol in patients with chronic obstructive pulmonary disease: a randomized, controlled 3-month trial. Eur Respir J. 2002;19(5):936-943.

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

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

Campbell M, Eliraz A, Johansson G, et al. Formoterol for maintenance and as-needed treatment of chronic obstructive pulmonary disease. Respir Med. 2005;99(12):1511-1520.

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

Celli B, MacNee W, ATS/ERS Task Force. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. Eur Respir J. 2004; 23(6):932-46.

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

Dellamary LA, Tarara TE, Smith DJ, et al. Hollow porous particles in metered dose inhalers. Pharm Res. 2000;17(2):168-74.

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

Hirst PH, Pitcairn GR, Weers JG, et al. In vivo lung deposition of hollow porous particles from a pressurized metered dose inhaler. Pharm Res. 2002;19(3):258-64.

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

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

Mahler DA, Weinberg DH, Wells CK, Feinstein AR. The measurement of dyspnea. Contents, interobserver agreement, and physiologic correlates of two new clinical indexes. Chest. 1984;85(6):751-58.

Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. Eur Respir J. 2005;26(2):319-338.

Moher D, Hopewell S, Schulz KF, et al. CONSORT 2010 Explanation and Elaboration: updated guidelines for reporting parallel group randomised trials. Int J Surg. 2012;10(1):28-55. doi: 10.1016/j.ijsu.2011.10.001. Epub 2011 Oct 12. Review.

Pulmonary Allergy Drugs Advisory Committee Meeting (PADAC) FDA Briefing Document, NDA 203-975: umeclidinium and vilanterol inhalation powder for the long-term, once-daily maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), Sept 2013.

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

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

Witek TJ, Mahler DA. Minimal important difference of the transition dyspnoea index in a multinational clinical trial. Eur Respir J. 2003;21:267-272.

Appendix 1 Spirometry Performance Recommendations

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

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

FEV_1 AND FVC MANEUVERS

Equipment Requirements

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

Display

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

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

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

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

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

a The correct aspect ratio for flow versus volume display is two units of flow per one unit of volume.

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

Validation

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

Quality Control

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

Key aspects of equipment quality control are summarized in Table A1-1.

Table A1-2 Summary of Equipment Quality Control

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

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

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

Quality Control for Volume-Measuring Devices

The volume accuracy of the spirometer must be checked at least daily, with a single discharge of a 3-L calibrated syringe. Daily calibration checking is highly recommended so that the onset of a problem can be determined within one day, and also to help define day-to-day laboratory variability. More frequent checks may be required in special circumstances, such as: 1) during industrial surveys or other studies in which a large number of subject maneuvers are carried out, the equipment's calibration should be checked more frequently than daily; and 2) when the ambient temperature is changing (eg., field studies), volume accuracy must be checked more frequently than daily and the BTPS correction factor appropriately updated.

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

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

Volume-type spirometer systems must be evaluated for leaks every day. The importance of undertaking this daily test cannot be overstressed. Leaks can be detected by applying a constant positive pressure of ≥3.0 cmH_2O (0.3 kPa) with the spirometer outlet occluded (preferably at or including the mouthpiece). Any observed volume loss of 0.30 mL after one minute indicates a leak and needs to be corrected.

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

Quality Control for Flow-Measuring Devices

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

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

VITAL CAPACITY MANEUVERS

Equipment

For measurements of vital capacity (VC), the spirometer or flow meter must comply with the requirements for FVC (as described previously) and be capable of accumulating volume for ≥30 s. Expiratory maneuvers or, ideally, both inspiratory and expiratory maneuvers should be included in the display of VC maneuver. Regardless of whether the inspiratory or expiratory maneuver is used for deriving measurements, a display of the entire recorded VC maneuver must be provided. The maximal expiratory volume must be assessed to determine

whether the subject has obtained a plateau in the expiratory effort. For display of the slow VC, the time scale may be reduced to 5 mm-s^{-1}.

TECHNICAL CONSIDERATIONS

Minimal recommendations for spirometry systems

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

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

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

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

BTPS correction

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

Appendix 2 Spirometry Assessment Criteria

Acceptable Versus Usable Tests

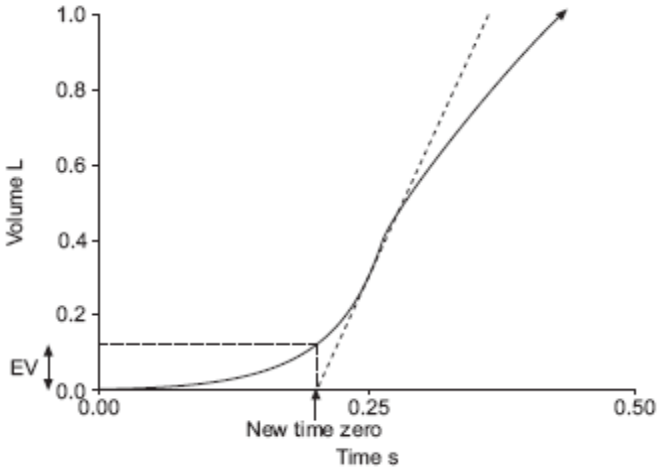
***Acceptable* Tests must meet the following Criteria:**

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

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

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

Figure A2-1 Example of a Usable Spirogram



EV=back extrapolation volume

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

Between-Maneuver Reproducibility Criteria

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

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

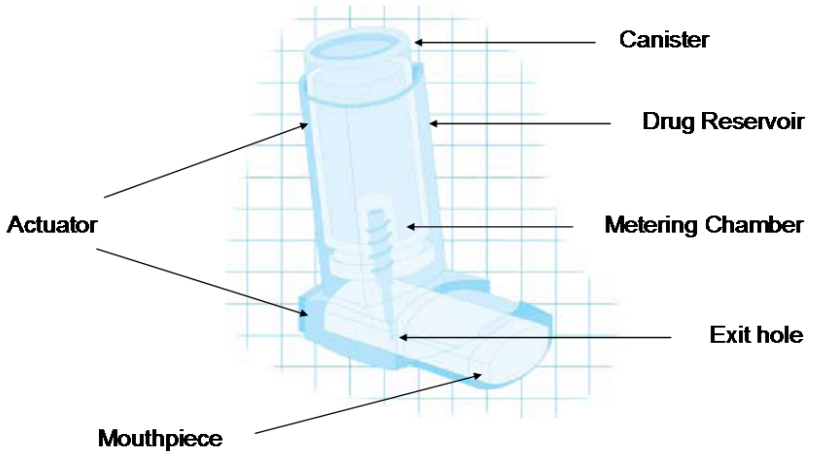
If these criteria are met, the spirometry testing for that timepoint may conclude. The highest FEV_1 and the highest FVC obtained at each testing timepoint (even if from different reproducible tracings), will be collected.

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

Appendix 3 Subject Instructions for Use of BFF MDI, BD MDI, and FF MDI Devices

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

METERED DOSE INHALER SCHEMA



Appendix 4 Instructions for Use of Atrovent HFA Inhalation Aerosol MDI Device

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

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

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

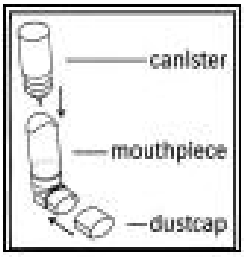


Figure 1

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

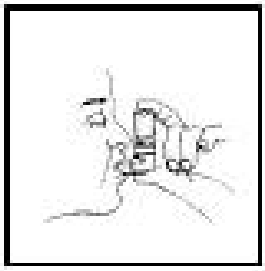


Figure 2

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

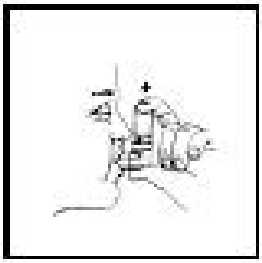


Figure 3

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

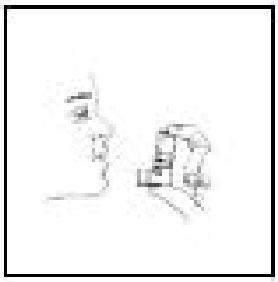


Figure 4

6. Replace the green protective dust cap after use.
7. **Keep the mouthpiece clean**. It is very important to keep the mouthpiece clean. At least once a week, wash the mouthpiece, shake it to remove excess water and let it air dry all the way (see the instructions below).
   - Mouthpiece Cleaning Instructions:
   - **Step A.** Remove and set aside the canister and dust cap from the mouthpiece (see Figure 1).
   - **Step B.** Wash the mouthpiece through the top and bottom with warm running water for at least 30 seconds (see Figure 5). Do not use anything other than water to wash the mouthpiece.

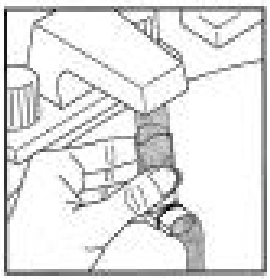


Figure 5

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

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

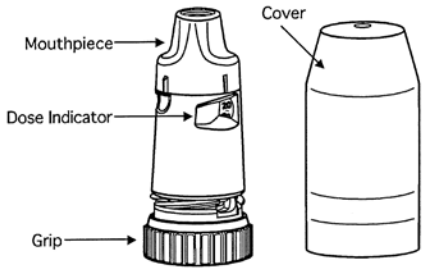
Appendix 5 Instructions for Use of Pulmicort Flexhaler (budesonide inhalation powder)

Patient Instructions for Use

How to use your PULMICORT FLEXHALER

Parts of your PULMICORT FLEXHALER

Fig 1



Priming PULMICORT FLEXHALER:

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

To prime your PULMICORT FLEXHALER, follow the steps below:

1. Hold the inhaler by the brown grip so that the white cover points upward (upright position). With the other hand, turn the white cover and lift it off (see Figure 2).
2. Continue to hold your PULMICORT FLEXHALER upright as shown in Figure 1. Use your other hand to hold the inhaler in the middle. Do not hold the inhaler at the top of the mouthpiece.
3. Twist the brown grip as far as it will go in one direction and then fully back again in the other direction until it stops (it does not matter which way you turn it first). You will hear a "click" during one of the twisting movements (see Figures 3 and 4).
4. Repeat Step 3. Your PULMICORT FLEXHALER is now primed. You are ready to load your first dose.

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

❶ Loading a dose

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

Fig 2

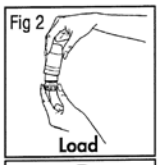


Fig 3

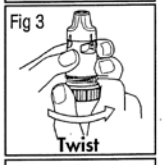


Fig 4

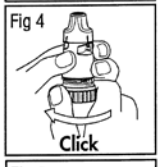
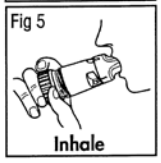


Fig 5



❷ Inhaling a dose

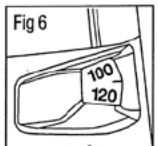
1. Turn your head away from the inhaler and breathe out (exhale). If you accidentally blow into your inhaler after loading a dose, follow the instructions for loading a new dose.
2. Place the mouthpiece in your mouth and close your lips around the mouthpiece. Breathe in (inhale) deeply and forcefully through the inhaler (see Figure 5).

3. You may not sense the presence of any medication entering your lungs when inhaling from PULMICORT FLEXHALER. This lack of sensation does not mean that you did not get the medication. You should not repeat your inhalations even if you did not feel the medication when inhaling.
4. Do not chew or bite on the mouthpiece.
5. Remove the inhaler from your mouth and exhale. **Do not blow or exhale into the mouthpiece.**
6. If more than one dose is prescribed repeat the steps above.
7. When you are finished taking your dose place the white cover back on the inhaler and twist shut.
8. **Rinse your mouth with water after each dose to decrease your risk of getting thrush. Do not swallow the water.**

Reading the Dose Indicator Window

- The label on the box or cover will tell you how many doses are in your PULMICORT FLEXHALER.
- Your PULMICORT FLEXHALER has a dose indicator window just below the mouthpiece. The dose indicator tells you about how many doses are left in the inhaler. Look at the middle of the window to find out about how many doses are left in your inhaler (see Figure 6).

Fig 6



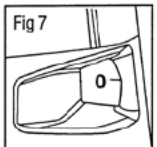
Dose Indicator

- The dose indicator is connected to the turning grip and moves (counts down) every time a dose is loaded. **It is not likely that you will see the dose indicator move with each dose.** You can usually see the indicator move each time you use about 5 doses.
- The dose indicator starts with either the number 60 or 120 when full, depending upon the strength of the inhaler. The indicator is marked in intervals of 10 doses. Markings are either with numbers or dashes (alternating), counting down to "0".

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

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

Fig 7



Empty

- **Do not put your PULMICORT FLEXHALER in water (do not immerse it) to find out if it is empty. Check the dose indicator window to see how many doses are left.**
- Refill your PULMICORT FLEXHALER prescription before your medicine runs out. You will get a new inhaler each time you refill your prescription.

Cleaning your PULMICORT FLEXHALER

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

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

PULMICORT FLEXHALER is a registered trademark of [redacted]

Rev. 07/10 1241504 5/11

[redacted]

Appendix 6 Instructions for Use of Ventolin HFA Inhaler

The Parts of Your VENTOLIN HFA Inhaler

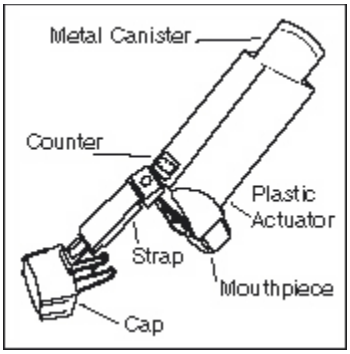


Figure 1

There are two main parts to your VENTOLIN HFA inhaler:

1. The metal canister that holds the medicine and
2. The blue plastic actuator that sprays the medicine from the canister (see Figure 1).
    a. The inhaler also has a cap that covers the mouthpiece of the actuator.
    b. The strap on the cap will stay attached to the actuator.
    c. The canister has a counter to show how many sprays of medicine you have left. The number shows through a window in the back of the actuator.

The counter starts at 204, the number will count down by 1 each time you spray the inhaler. The counter will stop counting at 000.
Never try to change the numbers or take the counter off the metal canister. The counter cannot be reset, and it is permanently attached to the canister.

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

How to Use Your VENTOLIN HFA

Before using your VENTOLIN HFA:

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

Priming your VENTOLIN HFA:

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

Instructions for taking a dose from your VENTOLIN HFA:

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

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

2. Hold the inhaler with the mouthpiece down (see Figure 2). **Breathe out through your mouth** and push as much air from your lungs as you can. Put the mouthpiece in your mouth and close your lips around it.

3. **Push the top of the canister all the way down while you breathe in deeply and slowly through your mouth** (see Figure 3). Right after the spray comes out, take your finger off the canister. After you have breathed in all the way, take the inhaler out of your mouth and close your mouth.

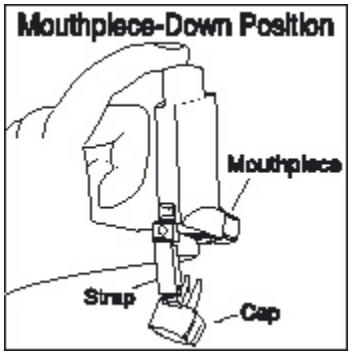


Figure 2

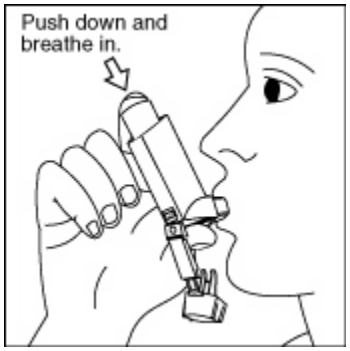


Figure 3

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

5. If your doctor has prescribed more sprays, wait 1 minute and **shake** the inhaler again. Repeat steps 2 through 4.

6. Put the cap back on the mouthpiece after every time you use the inhaler, and make sure it snaps firmly into place.

When to Replace Your VENTOLIN HFA

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

How to Clean Your VENTOLIN HFA

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

Wash the actuator at least once a week.

Cleaning instructions:

1. Take the canister out of the actuator, and take the cap off the mouthpiece. The strap on the cap will stay attached to the actuator.
2. Wash the actuator through the top with warm running water for 30 seconds (see Figure 4). Then wash the actuator again through the mouthpiece (see Figure 5).

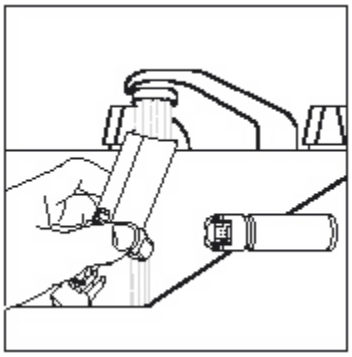


Figure 4

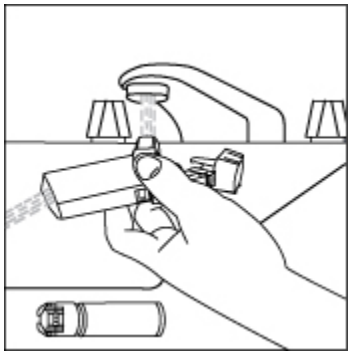


Figure 5

3. Shake off as much water from the actuator as you can. Look into the mouthpiece to make sure any medicine build-up has been completely washed away. If there is any build-up, repeat step 2.
4. Let the actuator air-dry completely, such as overnight (see Figure 6).

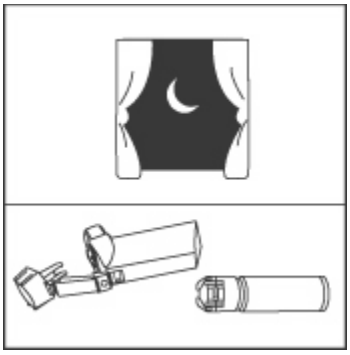


Figure 6

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

If your actuator becomes blocked:

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

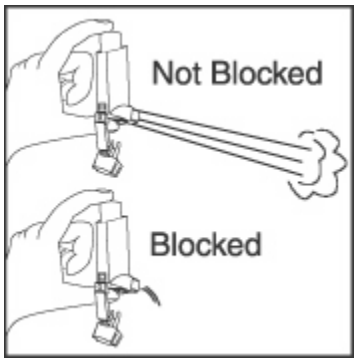


Figure 7

If you need to use your inhaler before the actuator is completely dry, shake as much water off the actuator as you can. Put the canister in the actuator and make sure it fits firmly. Shake the inhaler well and spray it once into the air away from your face. Then take your dose as prescribed. Then clean and air-dry it completely.

Storing Your VENTOLIN HFA

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

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

Appendix 7 Plasma Collection, Storage and Handling (PK Samples)

- Collect approximately 10 mL of blood in a tube containing EDTA tripotassium (4×10^3 M in PBS). Care should be taken to minimize hemolysis during sample collection.
- Place all tubes on wet ice immediately after collection.
- Centrifuge the blood within 30 minutes of collection at >1000 x g (~2500 rpm) for 10-15 minutes. It is preferred that the rotor chamber of the centrifuge is refrigerated to maintain a temperature of approximately 4°C.
- Transfer approximately equal aliquots (Aliquot A and Aliquot B) of plasma into duplicate labeled polypropylene test tubes with a snap or screw cap. Care should be taken to minimize contamination with red blood cells during transfer of plasma.
- Securely cap the labeled tubes. Please ensure the following when labeling the plasma aliquots.
- Sample vials must be clearly and accurately labeled using a solvent resistant ink (do not use ballpoint pen) or using supplied labels.
- The information on the labels should correspond to the information recorded on the PK Sample Log worksheet for each subject.
- The actual date and clock time (24 hour clock) of sample collection should be entered on the PK Sample Log worksheet.
- The plasma samples should then be placed in a freezer capable of maintaining a temperature of at least -20°C as soon as possible after aliquoting for storage. Store Aliquot A samples separate from Aliquot B samples as these will be shipped separately.
- Total time from collection to frozen storage should not exceed 60 minutes.
- Complete the Sample Shipping form and include a copy in each shipment. Ship frozen plasma samples within dry ice using a supplied cooler and labeling according to the procedure provided by the courier service.
- Ship samples only on a Monday, Tuesday or Wednesday or at least three days prior to a holiday via priority overnight delivery.
- Ship Aliquot A samples first.
- Aliquot B samples should be retained frozen until receipt of Aliquot A samples is confirmed and then shipped according to instruction.

Shipping Address:
Samples will be shipped frozen to the Central Laboratory. Please see your laboratory manual for instructions.

Appendix 8 Treatment Sequences

The 12 planned treatment sequences are shown in Table A7-1 where A is BFF 320/9.6 µg, B is FF MDI 9.6 µg, C is BFF 160/9.6 µg, D is BFF 80/9.6 µg, and E is BD MDI 320 µg.

Table A7-1 Planned Treatment Sequences

Sequence	Treatment Period			
	1	2	3	4
ABCD	BFF 320/9.6 µg	FF MDI 9.6 µg	BFF 160/9.6 µg	BFF 80/9.6 µg
BDAC	FF MDI 9.6 µg	BFF 80/9.6 µg	BFF 320/9.6 µg	BFF 160/9.6 µg
CADB	BFF 160/9.6 µg	BFF 320/9.6 µg	BFF 80/9.6 µg	FF MDI 9.6 µg
DCBA	BFF 80/9.6 µg	BFF 160/9.6 µg	FF MDI 9.6 µg	BFF 320/9.6 µg
ABDE	BFF 320/9.6 µg	FF MDI 9.6 µg	BFF 80/9.6 µg	BD MDI 320 µg
BEAD	FF MDI 9.6 µg	BD MDI 320 µg	BFF 320/9.6 µg	BFF 80/9.6 µg
DAEB	BFF 80/9.6 µg	BFF 320/9.6 µg	BD MDI 320 µg	FF MDI 9.6 µg
EDBA	BD MDI 320 µg	BFF 80/9.6 µg	FF MDI 9.6 µg	BFF 320/9.6 µg
ABCE	BFF 320/9.6 µg	FF MDI 9.6 µg	BFF 160/9.6 µg	BD MDI 320 µg
BEAC	FF MDI 9.6 µg	BD MDI 320 µg	BFF 320/9.6 µg	BFF 160/9.6 µg
CAEB	BFF 160/9.6 µg	BFF 320/9.6 µg	BD MDI 320 µg	FF MDI 9.6 µg
ECBA	BD MDI 320 µg	BFF 160/9.6 µg	FF MDI 9.6 µg	BFF 320/9.6 µg

Appendix 9 BDI/TDI Questionnaire

(The samples provided here is for illustrative purposes only)

Baseline/Transition Dyspnea Index (BDI/TDI)

BASELINE DYSPNEA INDEX

Baseline Functional Impairment

_____Grade 4	*No Impairment*	Able to carry out usual activities and occupation without shortness of breath.
_____Grade 3	*Slight Impairment*	Distinct impairment in at least one activity but no activities completely abandoned. Reduction, in activity at work *or* in usual activities, that seems slight or not clearly caused by shortness of breath.
_____Grade 2	*Moderate Impairment*	Subject has changed jobs *and/or* has abandoned at least one usual activity due to shortness of breath.
_____Grade 1	*Severe Impairment*	Subject unable to work or has given up most or all usual activities due to shortness of breath.
_____Grade 0	*Very Severe Impairment*	Unable to work *and* has given up most or all usual activities due to shortness of breath.
_____W	*Amount Uncertain*	Subject is impaired due to shortness of breath, but amount cannot be specified. Details are not sufficient to allow impairment to be categorised.
_____X	*Unknown*	Information unavailable regarding impairment.
_____Y	*Impaired for Reasons Other than Shortness of Breath*	For example, musculoskeletal problem or chest pain.

Usual activities refer to requirements of daily living, maintenance or upkeep of residence, yard work, gardening, shopping, etc.

Baseline Magnitude of Task

_____Grade 4	*Extraordinary*	Becomes short of breath only with extraordinary activity such as carrying very heavy loads on the level, lighter loads uphill, or running. No shortness of breath with ordinary tasks.
_____Grade 3	*Major*	Becomes short of breath only with such major activities as walking up a steep hill, climbing more than three flights of stairs, or carrying a moderate load on the level.
_____Grade 2	*Moderate*	Becomes short of breath with moderate or average tasks such as walking up a gradual hill, climbing fewer than three flights of stairs, or carrying a light load on the level.
_____Grade 1	*Light*	Becomes short of breath with light activities such as walking on the level, washing, or standing.
_____Grade 0	*No Task*	Becomes short of breath at rest, while sitting, or lying down.
_____W	*Amount Uncertain*	Subject's ability to perform tasks is impaired due to shortness of breath, but amount cannot be specified. Details are not sufficient to allow impairment to be categorised.
_____X	*Unknown*	Information unavailable regarding limitation of magnitude of task.
_____Y	*Impaired for Reasons Other than Shortness of Breath*	For example, musculoskeletal problem or chest pain.

Baseline Magnitude of Effort

_____Grade 4	*Extraordinary*	Becomes short of breath only with the greatest imaginable effort. No shortness of breath with ordinary effort.
_____Grade 3	*Major*	Becomes short of breath with effort distinctly submaximal, but of major proportion. Tasks performed without pause unless the task requires extraordinary effort that may be performed with pauses.
_____Grade 2	*Moderate*	Becomes short of breath with moderate effort. Tasks performed with occasional pauses and requiring longer to complete than the average person.
_____Grade 1	*Light*	Becomes short of breath with little effort. Tasks performed with little effort or more difficult tasks performed with frequent pauses and requiring 50-100% longer to complete than the average person might require.
_____Grade 0	*No Effort*	Becomes short of breath at rest, while sitting, or lying down.
_____W	*Amount Uncertain*	Subject's exertional ability is impaired due to shortness of breath, but amount cannot be specified. Details are not sufficient to allow impairment to be categorised.
_____X	*Unknown*	Information unavailable regarding limitation of effort.
_____Y	*Impaired for Reasons Other than Shortness of Breath*	For example, musculoskeletal problems, or chest pain.

TRANSITION DYSPNEA INDEX

Change in Functional Impairment

_____-3	*Major Deterioration*	Formerly working and has had to stop working and has completely abandoned some of usual activities due to shortness of breath.
_____-2	*Moderate Deterioration*	Formerly working and has had to stop working or has completely abandoned some of usual activities due to shortness of breath.
_____-1	*Minor Deterioration*	Has changed to a lighter job and/or has reduced activities in number or duration due to shortness of breath. Any deterioration less than preceding categories.
_____ 0	*No Change*	No change in functional status due to shortness of breath.
_____+1	*Minor Improvement*	Able to return to work at reduced pace or has resumed some customary activities with more vigour than previously due to improvement in shortness of breath.
_____+2	*Moderate Improvement*	Able to return to work at nearly usual pace and/or able to return to most activities with moderate restriction only.
_____+3	*Major Improvement*	Able to return to work at former pace and able to return to full activities with only mild restriction due to improvement of shortness of breath.
_____ Z	*Further Impairment for Reasons Other than Shortness of Breath*	Subject has stopped working, reduced work, or has given up or reduced other activities for other reasons. For example, other medical problems, being "laid off" from work, etc.

Change in Magnitude of Task

_____-3	*Major Deterioration*	Has deteriorated two grades or greater from baseline status.
_____-2	*Moderate Deterioration*	Has deteriorated at least one grade but fewer than two grades from baseline status.
_____-1	*Minor Deterioration*	Has deteriorated less than one grade from baseline. Subject with distinct deterioration within grade, but has not changed grades.
_____ 0	*No Change*	No change from baseline.
_____+1	*Minor Improvement*	Has improved less than one grade from baseline. Subject with distinct improvement within grade, but has not changed grades.
_____+2	*Moderate Improvement*	Has improved at least one grade but fewer than two grades from baseline.
_____+3	*Major Improvement*	Has improved two grades or greater from baseline.
_____ Z	*Further Impairment for Reasons Other than Shortness of Breath*	Subject has reduced exertion capacity, **but** not related to shortness of breath. For example, musculoskeletal problem or chest pain.

Change in Magnitude of Effort

_____-3	*Major Deterioration*	Severe decrease in effort from baseline to avoid shortness of breath. Activities now take 50-100% longer to complete than required at baseline.
_____-2	*Moderate Deterioration*	Some decrease in effort to avoid shortness of breath, although not as great as preceding category. There is greater pausing with some activities.
_____-1	*Minor Deterioration*	Does not require more pauses to avoid shortness of breath, but does things with distinctly less effort than previously to avoid breathlessness.
_____ 0	*No Change*	No change in effort to avoid shortness of breath.
_____+1	*Minor Improvement*	Able to do things with distinctly greater effort without shortness of breath. For example, may be able to carry out tasks somewhat more rapidly than previously.
_____+2	*Moderate Improvement*	Able to do things with fewer pauses and distinctly greater effort without shortness of breath. Improvement is greater than preceding category, but not of major proportion.
_____+3	*Major Improvement*	Able to do things with much greater effort than previously with few, if any, pauses. For example, activities may be performed 50-100% more rapidly than at baseline.
_____ Z	*Further Impairment for Reasons Other than Shortness of Breath*	Subject has reduced exertional capacity, but not related to shortness of breath. For example, musculoskeletal problem or chest pain.

Appendix 10 Sponsor Signatory

Study Title: A Randomized, Double-Blind, Chronic Dosing (28 Days), Four-Period, Five-Treatment, Incomplete Block, Multi-Center, Crossover Study to Assess the Efficacy and Safety of PT009, PT008, and PT005 in Subjects With Moderate to Severe COPD

Study Number: PT009001-01

Final Date: [redacted]

Signature: [redacted] Date: [redacted]

Name: [redacted]
Title:

Appendix 11 Investigator's Agreement and Signature Page

Study Title: A Randomized, Double-Blind, Chronic Dosing (28 Days), Four-Period, Five-Treatment, Incomplete Block, Multi-Center, Crossover Study to Assess the Efficacy and Safety of PT009, PT008, and PT005 in Subjects With Moderate to Severe COPD

Study Number: PT009001-01

Final Date: [redacted]

I agree:

- To assume responsibility for the proper conduct of the study at this site.
- To conduct the study in compliance with the protocol and with any other study conduct procedures provided by Pearl Therapeutics, Inc. (hereafter referred to as Pearl).
- Not to implement any changes to the protocol without agreement from the Sponsor and prior review and written approval from the IRB/IEC, except where necessary to eliminate an immediate hazard to the subjects, or for administrative aspects of the study (where permitted by all applicable regulatory requirements).
- That I am aware of, and will fully comply with GCP and all applicable regulatory requirements.
- That I am thoroughly familiar with the appropriate use of the investigational product(s), and other information provided by Pearl including, but not limited to, the following: the protocol and the current Investigator's Brochure (IB).
- To ensure that all persons assisting me with the study are qualified, adequately informed about the investigational product(s) and of their study-related duties and functions.
- To supply Pearl with any necessary information regarding ownership interest and financial ties; to promptly update this information if any relevant changes occur during the course of the study and for 1 year following completion of the study; and agree that Pearl may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- I agree to report all information or data in accordance with the protocol and any other study conduct procedures provided by Pearl.
- That since the information in this protocol and IB is confidential, I understand that its disclosure to any third parties, other than those involved in approval, supervision or conduct of the study is prohibited.
- To accurately transfer all required data from each subject's source document to the CRFs. The CRFs will be provided to the Sponsor in a timely manner at the completion of the study, or as otherwise specified by the Sponsor.
- To allow authorized representatives of Pearl or regulatory authority representatives to conduct on-site visits to review, audit and copy study documents. I will personally meet with these representatives to answer any study-related questions.

Signature:_____ Date:_____

Name:_____

Affiliation: _____