12.1.1 PROTOCOL AND PROTOCOL AMENDMENTS

This appendix includes the following approved original protocol and protocol amendments

- Original Protocol – [redacted]

Clinical Trial Protocol: PT005003-00

Study Title:	A Randomized, Double-Blind, Single Dose, Six-Treatment, Placebo-Controlled, Cross-Over, Multi-Center Study to Assess Efficacy and Safety of Three Doses of PT005, in Patients with Moderate to Severe COPD, Compared with Foradil® Aerolizer® (12 and 24 µg Open-Label) as Active Controls
Study Number:	PT005003-00
Study Phase:	IIb
Product Name:	Formoterol Fumarate Inhalation Aerosol; PT005
IND Number:	105586
Indication:	COPD
Investigators:	Multicenter
Sponsor:	Pearl Therapeutics, Inc. [redacted]
Sponsor Contact:	[redacted]

	Version Number	Date
Original Protocol:	Version 1.0	[redacted]

Confidentiality Statement

SYNOPSIS

Sponsor:
Pearl Therapeutics

Names of Finished Products:
Formoterol Fumarate Inhalation Aerosol; PT005
Placebo for Formoterol Fumarate Inhalation Aerosol
Foradil® Aerolizer®

Name of Active Ingredients:
Formoterol Fumarate (FF)

Study Title:
A Randomized, Double-Blind, Single Dose, Six-Treatment, Placebo-Controlled, Cross-Over, Multi-Center Study to Assess Efficacy and Safety of Three Doses of PT005, in Patients with Moderate to Severe COPD, Compared with Foradil® Aerolizer® (12 and 24 µg Open-Label) as Active Controls

Study Number: PT005003-00

Study Phase: IIb

Study Objective(s):

Primary objective:

The primary objective of this study is to demonstrate efficacy relative to placebo of FF metered dose inhaler (MDI) in patients with moderate to severe chronic obstructive pulmonary disease (COPD) within the range of doses evaluated in this study. To this end, each dose of FF MDI will be compared to placebo with respect to the primary efficacy endpoint, the area under the curve from 0 to 12 hours (AUC_{0-12}) of the change in FEV_1 from baseline.

Secondary Objectives:

The secondary objective of the study is to characterize the dose-response curve of FF MDI, to conduct a non-inferiority assessment comparing FF MDI within the range of doses evaluated in this study to open-label Foradil Aerolizer 12 µg, and to select the most appropriate dose of FF MDI to carry forward into Phase III clinical studies.

Safety Objective:

The safety objective is to evaluate the safety of FF MDI (7.2, 9.6, and 19.2 µg) in patients with moderate to severe COPD compared with placebo MDI and open-label Foradil Aerolizer (12 and 24 µg). Safety will be assessed by adverse events (AEs), physical examination findings, tremor assessments, paradoxical bronchospasm, vital signs, electrocardiograms (ECGs), and laboratory assessments.

Pharmacokinetic Objective(s):

The pharmacokinetic (PK) objective is to characterize the concentration-time profile of FF MDI and Foradil Aerolizer, to define a dose of FF MDI that provides comparable systemic concentrations to Foradil Aerolizer 12 µg and to assess relative bioavailability for each dose of FF MDI relative to Foradil Aerolizer 12 µg.

Study Design:

This is a randomized, double-blind (test products and placebo), single dose, six-treatment, six period, placebo-controlled, cross-over, multi-center study to assess efficacy and safety of three doses of FF MDI (7.2, 9.6 and 19.2 µg) in patients with moderate to severe COPD (reversible to albuterol), compared with two doses of Foradil Aerolizer (formoterol fumarate inhalation powder 12 and 24 µg, open-label), as active controls.

This multi-center study will be conducted at approximately 2 to 6 sites, contributing approximately 6 to 24 patients per site, in the United States (US). Across these sites; it is planned that approximately 48 patients with moderate to severe COPD will be randomized into the study to provide the target of 36 evaluations per study treatment. The entire study period is scheduled to take a maximum of 12 weeks for each individual patient (see Figure 1). The study is anticipated to run for approximately 9 months and should not exceed 18 months.

Study Population:

Approximately 48 patients with moderate to severe COPD (reversible to albuterol) will be enrolled to provide approximately 36 patients to complete the study.

Test Product, Dose, and Mode of Administration:

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

Product Descriptions

Product Name & Potency	Dosage Form	Comments
Formoterol Fumarate 7.2 µg ex-actuator	MDI	Taken as 2 inhalations of the 3.6 µg per actuation strength MDI
Formoterol Fumarate 9.6 µg ex-actuator	MDI	Taken as 2 inhalations of the 4.8 µg per actuation strength MDI
Formoterol Fumarate 19.2 µg ex-actuator	MDI	Taken as 2 inhalations of the 9.6 µg per actuation strength MDI
Placebo	MDI	Formulation does not contain active ingredient
Formoterol Fumarate inhalation powder† 12 µg	DPI	Foradil Aerolizer Taken as 1 capsule. Each capsule contains 12 µg corresponding to 10 µg formoterol fumarate dihydrate delivered from the mouthpiece *Supplies are open-label.*
Formoterol Fumarate inhalation powder† 24 µg	DPI	Foradil Aerolizer Taken as 2 capsules. Each capsule contains 12 µg corresponding to 10 µg formoterol fumarate dihydrate delivered from the mouthpiece *Supplies are open-label.*
Albuterol Sulfate inhalation aerosol§ 90 µg ex-actuator	MDI	Ventolin HFA Each inhalation contains 108 µg corresponding to 90 µg albuterol base from the mouthpiece *Supplies are open-label.*

† Active controls
§ Rescue medication
Note: All study drugs will be administered by oral inhalation.

All placebos are created by Pearl Therapeutics in the image of the active test products.

The 19.2, 9.6, and 7.2 µg ex-actuator doses of formoterol fumarate are equivalent to 20, 10, and 7.5 µg of formoterol fumarate *dihydrate*, respectively. The corresponding ex-valve doses for formoterol fumarate are 24, 12 and 9 µg, respectively.

Duration of Treatment:

Each patient will receive a single dose of study treatment in each of the six separate treatment periods with a washout period of at least 3 days, but no more than 10 days between treatments. The entire study period is scheduled to take a maximum of 12 weeks for each individual patient (see Figure 1).

Efficacy Assessments:

Efficacy variables are defined in terms of change from baseline, where the baseline is defined as the average of pre-dose values obtained on the current test day (Visits 2, 3, 4, 5, 6 and 7).

Primary Efficacy Endpoint:

- Forced expiratory volume in 1 second (FEV_1) AUC_{0-12} relative to baseline. FEV_1 AUC_{0-12} will be based on nominal measurement times, and will be normalized by the nominal total period of evaluation (12 hours); the units of FEV_1 AUC_{0-12} will be L.

Secondary Efficacy Endpoints:

- Peak change from baseline in FEV_1 (defined as highest change value post-dose)
- Time to onset of action (≥10% improvement in FEV_1 relative to baseline)
- Change from baseline at trough FEV_1 (trough FEV_1 is defined as the mean of the FEV_1 assessments taken at 11.5 and 12 hours post-dose)
- Non-inferiority assessment comparing FF MDI to Foradil Aerolizer 12 µg based on FEV_1 AUC_{0-12}

Safety Assessments:

The safety assessments include ECGs, vital sign measurements, clinical laboratory tests, monitoring for paradoxical bronchospasm, assessment of tremor, in addition to recording AEs and serious adverse events (SAEs) (including physical examination findings).

Pharmacokinetic Assessments:

Pharmacokinetics will be evaluated in all patients. Each patient will undergo PK sampling in four of the six treatment periods. Each patient will be sampled during the FF MDI 9.6 µg treatment period, Foradil Aerolizer 12 µg treatment period and in two of the remaining three formoterol fumarate treatment periods (FF MDI 19.2 µg, FF MDI 7.2 µg and Foradil Aerolizer 24 µg) or the placebo treatment period. If the treatment during the first period was not FF MDI 9.6 µg or Foradil Aerolizer 12 µg, then the first treatment period will be one of these two other periods sampled. That is, all patients will be sampled in the first period, and in the period during which they receive FF MDI 9.6 or Foradil Aerolizer 12 µg.

Blood sampling for PK will be evaluated immediately prior to study drug administration, at 2, 6, 20 minutes, and 1, 2, 4, 8, 10, and 12 hours post-dose.

Statistical Methods:

Sample Size Consideration: Power calculations were based on the primary endpoint, FEV_1 $AUC_{0-12,}$ assuming a full cross-over design, and also on the properties of the PK endpoints: C_{max} and AUC_{0-12}.

Estimates of within subject standard deviation of FEV_1 AUC_{0-12} from published studies (D'Urzo et al, 2001; van Noord et al, 2005, Maesen et al 1995) suggest a within subjects standard deviation of approximately 0.13L, in a non-reversible population. A recent Pearl

study in a non-reversible population revealed a within subjects standard deviation of 0.1L; this is similar to the estimate of 0.1L obtained by Humerfelt et al (1998) for asymptomatic men. In a single dose study in a reversible population, Pearl achieved a within subjects standard deviation of 0.07L. These findings suggest that a within subjects standard deviation of 0.1L or less should be achievable in a reversible population.

Assuming a clinically relevant effect size of 0.1L, a sample size of 36 completing patients then delivers greater than 90% power for the primary efficacy objective (assuming a significance test at the 5% level, with no multiplicity adjustment).

Bioequivalence is not the primary objective of this study. Accordingly we relax the usual equivalence definition of relative bioavailability in the range (0.8-1.25). Instead we consider the power to demonstrate that relative bioavailability lies in the range (0.75-1.3333). Power was calculated assuming the two one-sided test (TOST) procedure (Phillips, 1990) will be applied on the log scale.

Earlier studies of single-dose and multiple dose treatment with FF MDI provided estimates of between subjects standard deviation for log AUC_{0-12} formoterol fumarate plasma concentration of 0.4. Power to demonstrate bioequivalence (using the 0.75-1.333 relative bioavailability interval) between Formoterol Fumarate MDI 9.6 µg and Foradil Aerolizer 12 µg was calculated assuming a true relative bioavailability of 1.05. A sample size of 36 patients then delivers power of 80%. The variability of C_{max} is somewhat higher; the between subjects standard deviation is approximately 0.45. A sample size of 36 completing patients produces a power of approximately 70%.

A total of 48 patients will be randomized to yield 36 completing patients. This sample size is a compromise between the needs of the efficacy objectives (the most important aspect of this study) and the needs of the pharmacokinetic objectives.

Primary Efficacy Analysis: Efficacy analysis will be based on a linear mixed model in which treatment will be a fixed effect, subject will be a random effect, and within subject errors are correlated, but between subject errors are independent. Unstructured, compound symmetry and first-order autoregressive error models will be considered, and the appropriate model selected using Akaike's information criterion (Akaike, 1974). Fixed and random effects will be estimated using the REML algorithm (Patterson and Thompson, 1971), which allows for the recovery of inter-block (subject) information.

The primary efficacy analysis will involve *a priori* comparisons between treatments for the primary endpoint, FEV_1 AUC_{0-12} :

1. FF MDI 19.2 µg vs. Placebo
2. FF MDI 9.6 µg vs. Placebo
3. FF MDI 7.2 µg vs. Placebo

Strong control of the family-wise Type I error will be achieved by hierarchical testing (Bauer et al, 1998). No efficacy claims will be advanced for any dose level of FF MDI unless all

higher dose levels are statistically significantly superior to the Placebo. Testing for unequal carry-over effects will be performed. Models will include a baseline measurement as a covariate. Two-sided 95% confidence intervals will be tabulated.

Secondary Efficacy Analysis: Secondary efficacy comparisons for FEV_1 AUC_{0-12} are:

1. FF MDI 19.2 µg non-inferiority vs. open-label Foradil Aerolizer 12 µg
2. FF MDI 9.6 µg non-inferiority vs. open-label Foradil Aerolizer 12 µg;
3. FF MDI 7.2 µg non-inferiority vs. open-label Foradil Aerolizer 12 µg.

A non-inferiority margin of 0.1L will be adopted. This margin has been selected because a change in pre-dose FEV_1 of approximately 0.1L can be perceived by patients, correlates with fewer relapses following exacerbations, and correlates with two year decline in lung function (Donohue, 2005). For this endpoint, strong control of the family-wise Type I error will be achieved by hierarchical testing (Bauer et al, 1998). No non-inferiority claims will be advanced for any dose level of Formoterol Fumarate unless all higher dose levels are statistically significantly non-inferior to Foradil Aerolizer 12 µg.

Other secondary efficacy analyses will involve the primary efficacy comparisons (each dose of FF MDI vs Placebo MDI) applied to secondary efficacy endpoints (*vide supra*). The statistical model and tabulations will be exactly as for the primary objectives (except for time to onset), except that no tests for unequal carry-over effects will be performed.

For time to onset of action, data will be analyzed using Murray's method for weighted integrated Kaplan-Meier curves for paired data (Murray, 2001).

Primary PK Analyses: Non-compartmental parameter estimates will be analyzed using a linear mixed model in which Treatment will be a fixed effect and within subject errors are correlated, but between subject errors are independent. Unstructured, compound symmetry and first-order autoregressive error models will be considered, and the appropriate model selected using Akaike's information criterion (Akaike, 1974). AUC and C_{max} will be ln-transformed before analysis.

Relative bioavailability will be calculated for each dose relative to the Foradil Aerolizer 12 µg treatment, using the mixed model results. A 90% confidence interval for each relative bioavailability (a ratio) will be calculated. Bioequivalence will be tested using the TOST procedure (Phillips, 1990).

Safety Analyses: Safety analyses will be based on descriptive statistics for ECGs, vital signs, and laboratory measurements as appropriate, and also on frequencies of adverse events and the number of patients with an adverse event. Tremor and paradoxical bronchospasm will be summarized by the number of patients experiencing the event during a particular treatment period.

Statistical Analysis Plan: All statistical analyses will be document in a statistical analysis plan, which will define study populations, endpoints, statistical models, table and listing formats and graphical presentations. All statistical analyses will be performed using SAS (Version 9.2 or higher). The PK data will be analysed using WinNonLin (Version 5.2 or higher).
Date of Original Approved Protocol: [redacted]
Date of Most Recent Protocol Amendment (if applicable): N/A
Prepared in: Microsoft Word 2007

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATS	American Thoracic Society
AUC	Area under the curve
AV	Atrioventricular block
BMP	Basic Metabolic Panel
BP	Blood Pressure
BPM	Beats per minute
BTPS	Body Temperature and Pressure Saturated
BUN	Blood urea nitrogen
CL/F	Apparent systemic clearance after oral inhalation administration
C_{max}	maximum concentration
$CaCl_2$	Calcium chloride
CFR	Code of Federal Regulations
CI	Confidence interval
CIR	Cumulative incidence ratio
CMP	Comprehensive Metabolic Panel
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case report form
CT	Computerized Tomography
DBP	Diastolic blood pressure
DPI	Dry Powder Inhaler
DSPC	Distearoylphophatidylcholine
e.g.	Exempli gratia, for example
ECG	Electrocardiogram
ERS	European Respiratory Society
EV	Back extrapolation volume

ex-actuator	dose delivered from the actuator (i.e., mouthpiece) of the MDI
FDA	Food and Drug Administration
FEV_1	Forced Expiratory Volume in 1 second
FF MDI	Formoterol Fumarate MDI
FRC	Functional Residual Capacity
FVC	Forced Vital Capacity
GCP	Good clinical practice
GFF MDI	Glycopyrrolate and Formoterol Fumarate MDI
GP MDI	Glycopyrrolate MDI
HCG	Human chorionic gonadotropin
HR	Heart Rate
HFA	Hydrofluroalkane
i.e.	*Id est,* that is
ICF	Informed consent form
ICH	International Conference on Harmonization
ICMJE	International Committee of Medical Journal Editors
ICS	Inhaled Corticosteroid
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITT	Intention-to-treat
IUD	Intrauterine device
IV	Intravenous
IWRS	Interactive Web Response System
K_e	terminal elimination rate constant
L	Liter
LABA	Long-acting beta agonist
LAMA	Long-acting antimuscarinic agents
LC/MS/MS	High Performance Liquid Chromatography tandem Mass Spectrometry
LTOT	Long Term Oxygen Therapy

MAO	Monoamine oxidase inhibitor
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MDI	Metered Dose Inhaler
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified ITT
mL	Milliliter
Msec (ms)	Millisecond
NHANES III	Third National Health and Nutrition Examination Survey
OTC	Over-the-counter
PEFR	Peak expiratory flow rate
PD	Pharmacodynamic
PFT	Pulmonary function test
PK	Pharmacokinetics
PP	Per protocol
PRN	pro re nata
Rx	Treatment
QTcF	QT corrected using Fridericia's formula ($QT/(RR^{1/3})$)
SABA	Short-acting beta agonist
SAE	Serious Adverse Event
SBP	Systolic blood pressure
SOP	Standard operating procedure
$t_{1/2}$	Apparent terminal elimination half-life
T_{max}	Time to C_{max}
TNFα	Tumor necrosis factor α
TOST	two one-sided test
US	United States
Vz/F	Apparent volume of distribution during the terminal phase

TRADEMARK INFORMATION

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Aerolizer

Certihaler

Foradil

Dulera

Handihaler

Spiriva

Symbicort

Ventolin

1 INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity and mortality at a global level and recent statistics suggest it will become more prevalent as smoking frequencies rise and the population ages (Calverly, 2003; Feenstra, 2001; Ferrer, 1997; Murray, 1997; Sullivan, 2000). In a systemic review and meta-analysis by Halbert and colleagues, the prevalence of physiologically defined COPD in adults aged ≥40 years was observed to be 9-10% (Halbert 2003 and 2006). The causes behind COPD are multi-factorial, where various risk factors and environmental stimuli have been identified and include smoking, air pollution, and occupational hazards. Hence, COPD is not only a smoker's disease with familial origins but one that worsens with age.

COPD is progressive in nature and only partially reversible at a functional level. This disease is characterized by premature loss of ventilatory function as determined by a decline in forced expiratory volume in the first second of exhalation (FEV_1). Pathological inflammatory changes are characterized by elevations in activated macrophages, neutrophils, elastases and CD8 lymphocytes. These molecular and cellular changes cause the destruction of small airways and surrounding alveoli. As expiratory airflow (FEV_1 or forced vital capacity [FVC]) is a function of pressure against resistance, airflow in COPD is diminished due to a loss of elastic recoil and airway constriction.

Traditionally, bronchodilator medications are central to the symptomatic management of COPD. The principal bronchodilator treatments are both short-acting and long-acting β_2-agonists (SABA and LABA, respectively), both short and long-acting anticholinergics, and methylxanthines used as monotherapy or in combination. Regular treatment with LABAs is more effective in the management of COPD than SABAs (GOLD, 2008).

Formoterol fumarate (Foradil® Aerolizer® and Foradil Certihaler®) is a potent and selective LABA approved in the United States (US) and worldwide for use in asthma and COPD. Formoterol is also approved in the US as part of two combination products, Symbicort® (budesonide and formoterol fumarate dihydrate) and Dulera® (mometasone furoate and formoterol fumarate).

Pearl Therapeutics, Inc. has licensed and developed a particle engineering technology that utilizes porous particles for pulmonary drug delivery via metered dose inhalers (MDI). This technology is based on spray-dried porous particles comprised of distearoylphophatidylcholine (DSPC) and calcium chloride ($CaCl_2$) that are cosuspended with crystalline active drug substances and formulated into suspension-based hydrofluoroalkane (HFA) MDIs. In vitro and in vivo testing suggests that the Pearl Therapeutics formulations will provide highly efficient, reproducible administration of therapeutics from MDIs in a wide dosing range (Hirst, 2002; Dellamary, 2000).

Pearl Therapeutics is currently evaluating Formoterol Fumarate Inhalation Aerosol (Pearl Therapeutics internal product code: PT005), hereafter referred to as FF MDI, in the porous particle platform for the long-term, twice-daily (morning and evening), maintenance

treatment of bronchoconstriction associated with COPD, including chronic bronchitis and emphysema.

Pearl Therapeutics has conducted two clinical studies with FF MDI.

Study PT0050801 was a randomized, double-blind, five-period, placebo and active-controlled, ascending dose, cross-over, multi-center study that was conducted in patients with moderate to severe COPD deemed clinically stable by their physician. This study was conducted in Australia and New Zealand. The primary objective was to evaluate the safety and tolerability of FF MDI at doses of 2.4, 4.8, and 9.6 µg ex-actuator compared to placebo MDI and Foradil Aerolizer 12 µg (corresponding to 10 µg delivered from the mouthpiece). Spirometry measures were performed at baseline, 15 and 30 minutes, and 1, 2, 4, 6, 8, 10, 11.5, and 12 hours post-dose. A total of 34 patients were enrolled (18 males, 16 females; mean age: 65 years), 29 of whom received all 5 treatments. All 3 doses of FF MDI demonstrated superior efficacy compared to placebo in terms of FEV_1 area under the curve from 0 to 12 hours (AUC_{0-12}), the primary endpoint of the study ($p<0.001$). Furthermore, the FF MDI 9.6 µg ex-actuator dose demonstrated non-inferior bronchodilator efficacy relative to Foradil Aerolizer 12 µg over the 12-hour period ($p<0.001$) and at every individual time point assessed ($p<0.05$). FF MDI at a dose of 9.6 µg ex-actuator also demonstrated a comparable pharmacokinetic (PK) profile to Foradil Aerolizer 12 µg, with similar concentration-time plots and similar area under the curve from 0 to 12 hours (AUC_{0-12}) and maximum concentration (C_{max}). No substantial differences were noted between the FF MDI treatment groups and placebo or Foradil Aerolizer in terms of safety, and there were no trends in QTc changes or changes in serum potassium values across the doses. Two serious adverse events (SAEs) were reported, one following placebo (small intestinal obstruction) and one following FF MDI 4.8 µg ex-actuator (exacerbation of COPD); neither were deemed related to study drug by the Investigator.

Study PT0031002 was a randomized, double-blind (test products and placebo) chronic dosing (7 days), four-period, eight-treatment, placebo-controlled, customized, unbalanced incomplete-block cross-over multi-center study that evaluated the efficacy, safety and PK of two doses of Glycopyrrolate and Formoterol Fumarate MDI (72 µg/9.6 µg and 36 µg/9.6 µg twice daily), two doses of Formoterol Fumarate MDI (9.6 µg and 7.2 µg twice daily), and one dose of Glycopyrrolate MDI (36 µg twice daily) in patients with moderate to very severe COPD, compared to Foradil Aerolizer (12 µg twice daily, open-label) and Spiriva® Handihaler® (18 µg once daily, open-label) as active controls. In this study, both doses of FF MDI were superior to placebo in terms of the primary endpoint, FEV_1 AUC_{0-12}. The FF MDI 9.6 µg dose was shown to be statistically non-inferior to Foradil Aerolizer in terms of improvement in FEV_1 at all time points tested with the *a priori* defined non-inferiority bound of 100 mL (mean difference = -16 mL; 95% confidence interval (CI) -54, +22 mL) and demonstrated bioequivalence to Foradil Aerolizer from a pharmacokinetic (PK) perspective. The FF MDI 7.2 µg dose also demonstrated non-inferiority compared to Foradil Aerolizer, but was numerically lower than FF MDI 9.6 µg (mean difference = -24mL; 95% CI: -62, +15 mL) and did not meet criteria for bioequivalence when compared to Foradil Aerolizer. The safety profile showed the compound was safe and well-tolerated.

Note: Unless otherwise indicated, throughout this document all references to doses of FF MDI will be to the ex-actuator or "delivered" doses, all references to the Foradil Aerolizer dose will be to the capsule content and all references to Ventolin® HFA (albuterol sulfate inhalation aerosol) will be 108 µg corresponding to 90 µg albuterol base from the mouthpiece.

1.1 Study Rationale

Formoterol fumarate is a well-established and extensively tested LABA that is approved for use in the management of COPD.

In Study PT0050801, FF MDI 9.6 µg showed similar efficacy and PK when compared with Foradil Aerolizer 12 µg, while the two lower doses studied (2.4 and 4.8 µg) were inferior to Foradil Aerolizer in terms of efficacy. These findings supported the evaluation of FF MDI 9.6 µg and a lower dose (i.e., 7.2 µg) in patients with COPD. In Study PT0031002, both FF MDI 7.2 and 9.6 µg doses were non-inferior to Foradil Aerolizer, and the FF MDI 7.2 µg dose was non-inferior to the FF MDI 9.6 µg dose. However, the FF MDI 9.6 µg dose had a more similar PK / pharmacodynamic (PD) profile to Foradil Aerolizer compared with the FF MDI 7.2 mcg dose.

Novel technology based on spray-dried porous particles comprised of DSPC and $CaCl_2$ that are cosuspended with crystalline active drug substances and formulated into suspension-based HFA MDIs has enabled the development of FF MDI and could have the potential to improve the delivery of drug to the lower respiratory tract, improve the physical stability of the drug, and improve dose uniformity. Pearl Therapeutics is evaluating FF MDI in this porous particle platform for the long-term, twice daily (morning and evening) administration in the maintenance treatment of bronchoconstriction in patients with COPD, including chronic bronchitis and emphysema.

In order to ensure that the dose of FF MDI selected for further evaluation provides a comparable PD response to Foradil Aerolizer 12 µg (which is less than Foradil Aerolizer 24 µg), has systemic exposure less than or comparable to Foradil Aerolizer 12 µg and to demonstrate separation between FF MDI doses and between Foradil Aerolizer 12 and 24 µg, Pearl Therapeutics plans to evaluate a range of FF MDI doses (7.2, 9.6, 19.2 µg), placebo and Foradil Aerolizer (12 and 24 µg) in a single dose study in patients with COPD that demonstrate reversibility to albuterol.

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of this study is to demonstrate efficacy relative to placebo of FF MDI in patients with moderate to severe COPD within the range of doses evaluated in this study. To this end, each dose of FF MDI will be compared to placebo with respect to the primary efficacy endpoint, forced expiratory volume in one second (FEV_1). The AUC_{0-12} of change in FEV_1 from baseline will be calculated. Baseline is defined as the average of pre-dose values obtained on the current test day.

2.2 Secondary Objectives

The secondary objective of the study is to characterize the dose-response curve of FF MDI, to conduct a non-inferiority assessment comparing FF MDI within the range of doses evaluated in this study to open-label Foradil Aerolizer 12 µg, and to select the most appropriate dose of FF MDI to carry forward into Phase III clinical studies.

2.3 Safety Objective

The safety objective is to evaluate the safety of FF MDI (7.2, 9.6, and 19.2 µg) in patients with moderate to severe COPD compared with placebo MDI and open-label Foradil Aerolizer (12 and 24 µg). Safety will be assessed by adverse events (AEs), physical examination findings, tremor assessments, paradoxical bronchospasm, vital signs, electrocardiograms (ECGs), and laboratory assessments.

2.4 Pharmacokinetic Objective

The PK objective is to characterize the concentration-time profile of FF MDI and Foradil Aerolizer, to define a dose of FF MDI that provides comparable systemic concentrations to Foradil Aerolizer 12 µg and to assess relative bioavailability for each dose of FF MDI relative to Foradil Aerolizer 12 µg.

3 STUDY ENDPOINTS

3.1 Efficacy Endpoints

Efficacy endpoints will be defined as change from baseline, where the baseline is defined as the average of pre-dose values obtained on the current test day (Visits 2, 3, 4, 5, 6 and 7).

3.1.1 Primary Efficacy Endpoint

- AUC_{0-12} of change in FEV_1 from baseline, which will be referred to as FEV_1 AUC_{0-12}. FEV_1 AUC_{0-12} will be based on nominal measurement times, and will be normalized by the nominal total period of evaluation (12 hours); the units of FEV_1 AUC_{0-12} will be L.

3.1.2 Secondary Endpoints

The following secondary endpoints will be evaluated:

- Peak change from baseline in FEV_1 (defined as highest change post-dose)
- Time to onset of action (≥10% improvement in FEV_1 relative to baseline
- Change from baseline at trough FEV_1 (trough FEV_1 is defined as the mean of the FEV_1 assessments taken at 11.5 and 12 hours post-dose)
- Non-inferiority assessment comparing FF MDI to Foradil Aerolizer 12 µg based on FEV_1 AUC_{0-12}

3.2 Safety Endpoints

The safety assessments include ECGs, vital sign measurements, clinical laboratory tests, monitoring for paradoxical bronchospasm, assessment of tremor, in addition to recording AEs and SAEs (including physical examination findings).

3.3 Pharmacokinetic Endpoints

Pharmacokinetics will be evaluated in all patients. Each patient will undergo PK sampling in four of the six treatment periods. The treatment periods selected for PK sampling will satisfy the following criteria:

- The period treated with FF MDI 9.6 µg will be sampled.
- The period treated with Foradil Aerolizer 12 µg will be sampled.
- The first period will be sampled.
- The remaining one or two periods sampled will be selected at random from amongst the periods not otherwise sampled. If Either FF MDI 9.6 µg or Foradil Aerolizer 12 µg occurs in the first period then there will be two remaining periods to sample, otherwise there will be one remaining period to sample.

The following blood sampling scheme will be adopted for each period sampled: immediately prior to study drug administration, at 2, 6, 20 minutes, and 1, 2, 4, 8, 10, and 12 hours post-dose.

The PK endpoints for this study include the following:

- AUC_{0-12}: Area under the plasma concentration versus time curve from time 0 to 12 hours post-dose, where time 0 is defined as the pre-dose measurement
- AUC_{0-inf}: Area under the plasma concentration versus time curve from time 0 to infinity, where time 0 is defined as the pre-dose measurement
- C_{max}: Maximum plasma concentration
- T_{max}: Time to C_{max}
- $t_{1/2}$: Apparent terminal elimination half-life
- CL/F: Apparent systemic clearance after oral inhalation administration
- Vz/F: Apparent volume of distribution during the terminal phase after oral inhalation administration.

The terminal elimination rate constant (k_e), the apparent terminal elimination half-life ($t_{1/2}$) and the area under the plasma concentration versus time curve from time 0 to infinity (AUC_{0-inf}) will be calculated only if the data permit.

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

This is a randomized, double-blind (test products and placebo), single dose, six-treatment, six period, placebo-controlled, cross-over, multi-center study to assess efficacy and safety of three doses of FF MDI (7.2, 9.6 and 19.2 μg) in patients with moderate to severe COPD with demonstrated reversibility to albuterol, compared with two doses of Foradil Aerolizer, (formoterol fumarate inhalation powder 12 and 24 μg, open-label) as active controls.

This multi-center study will be conducted at approximately 2 to 6 sites, contributing approximately 6 to 24 patients per site, in the US. Across these sites; it is planned that approximately 48 patients with moderate to severe COPD will be randomized into the study to provide the target of 36 evaluations per study treatment. The entire study period is scheduled to take a maximum of 12 weeks for each individual patient (see Figure 1). The study is anticipated to run for approximately 9 months and should not exceed 18 months.

All patients are to sign an informed consent form prior to the conduct of any screening assessments (Visit 1a). The Investigator 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 30 minutes following 4 puffs of Ventolin HFA will be assessed at Screening to determine eligibility to participate in the study. Patients who are not using a prohibited medication and meet all other entry criteria will return to the clinic at least 7 days [≥2 weeks if taking tiotropium or phosphodiesterase inhibitors (e.g. theophylline, roflumilast)] after screening for Visit 2 (Randomization).

Patients who meet all entry criteria but are using certain prohibited COPD medications [e.g., oral β_2 agonists, LABAs, corticosteroid/LABA combination products, phosphodiesterate inhibitors (e.g. theophylline, roflumilast), cromoglycate or nedocromil inhalers, leukotriene antagonists (e.g., zafirlukast, montelukast, zileuton), or tiotropium] will discontinue these medications for the duration of the trial and be switched to short-acting bronchodilators (albuterol MDI, ipratropium MDI or albuterol/ipratropium combination MDI) per the Investigator's discretion (see Section 5.4).

In order to allow for an adequate washout of previous maintenance medications, patients will undergo a washout period of at least 7 days (at least 2 weeks if taking tiotropium or phosphodiesterate inhibitors), but not greater than 21 days duration prior to returning to the clinic for Visit 2 (Randomization).

Patients who do not meet the entry criteria at Visit 1a can return to complete screening requirements at Visit 1b at the Investigator's discretion (e.g. patients who do not meet reversibility requirement at Visit 1a can repeat the reversibility attempt at Visit 1b).

At Visit 2 (Randomization Visit; Treatment [Rx] 1), patients will return to the clinic before 10:00 am. Patients 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. Patients will be randomized into one of 36 sequences. Each sequence will include all 6 treatment groups included in this study (placebo, Foradil Aerolizer 12 and 24 µg, and FF MDI at the following doses: 7.2 µg, 9.6 µg and 19.2 µg). On every treatment day the patient, clinical site personnel and Pearl Therapeutics will be unaware of the treatment to be assigned that day. If on a test day a patient is assigned FF MDI or matched placebo, it will not be possible to differentiate between these two treatments since they will be identical in all aspects. Blinding with regard to the active comparator, Foradil Aerolizer, will not be performed in order to avoid 'dummy/dummy' allocations.

Randomization will be centralized, through the use of an Interactive Web Response System (IWRS). Each of the 6 treatments will be administered as a single dose with a washout period of between 3 and 10 days between treatments.

During Visit 2 (Rx 1), patients will be dispensed study medication and will administer a single dose at the clinic under supervision. Patients will be required to remain at the clinic until completion of all protocol-defined assessments (see Table 5). Following discharge, patients will undergo a study medication washout period of at least 3 days but no more than 10 days prior to initiating the next treatment in their assigned treatment sequence.

Following the washout period, patients will repeat a similar pattern of visits and assessments for the remaining five treatments in their assigned sequence, as follows:

Visit 3 (Rx 2): Administer Rx 2 study medication and remain at the clinic until completion of all protocol-defined assessments (see Table 5.). Following discharge, patients will undergo a study medication washout period of at least 3 days but no more than 10 days prior to initiating the next treatment in their assigned treatment sequence.

Visit 4 (Rx 3): Administer Rx 3 study medication and remain at the clinic until completion of all protocol-defined assessments (see Table 5). Following discharge, patients will undergo a study medication washout period of at least 3 days but no more than 10 days prior to initiating the next treatment in their assigned treatment sequence.

Visit 5 (Rx 4): Administer Rx 4 study medication and remain at the clinic until completion of all protocol-defined assessments (see Table 5). Following discharge, patients will undergo a study medication washout period of at least 3 days but no more than 10 days prior to initiating the next treatment in their assigned treatment sequence.

Visit 6 (Rx 5): Administer Rx 5 study medication and remain at the clinic until completion of all protocol-defined assessments (see Table 5). Following discharge, patients will undergo a study medication washout period of at least 3 days but no more than 10 days prior to initiating the next treatment in their assigned treatment sequence.

Visit 7 (Rx 6): Administer Rx 6 study medication and remain at the clinic until completion of all protocol-defined assessments (see Table 5). Following completion of Visit 7, patients should be returned to pre-study or appropriate COPD maintenance medications and return for the final/follow-up visit after at least 3 days but not greater than 14 days.

Visit 8: Visit 8 will serve as the final/follow-up visit. Patients will complete all post-study assessments, including a final physical examination and recording of any AEs, and will then be discharged from the study.

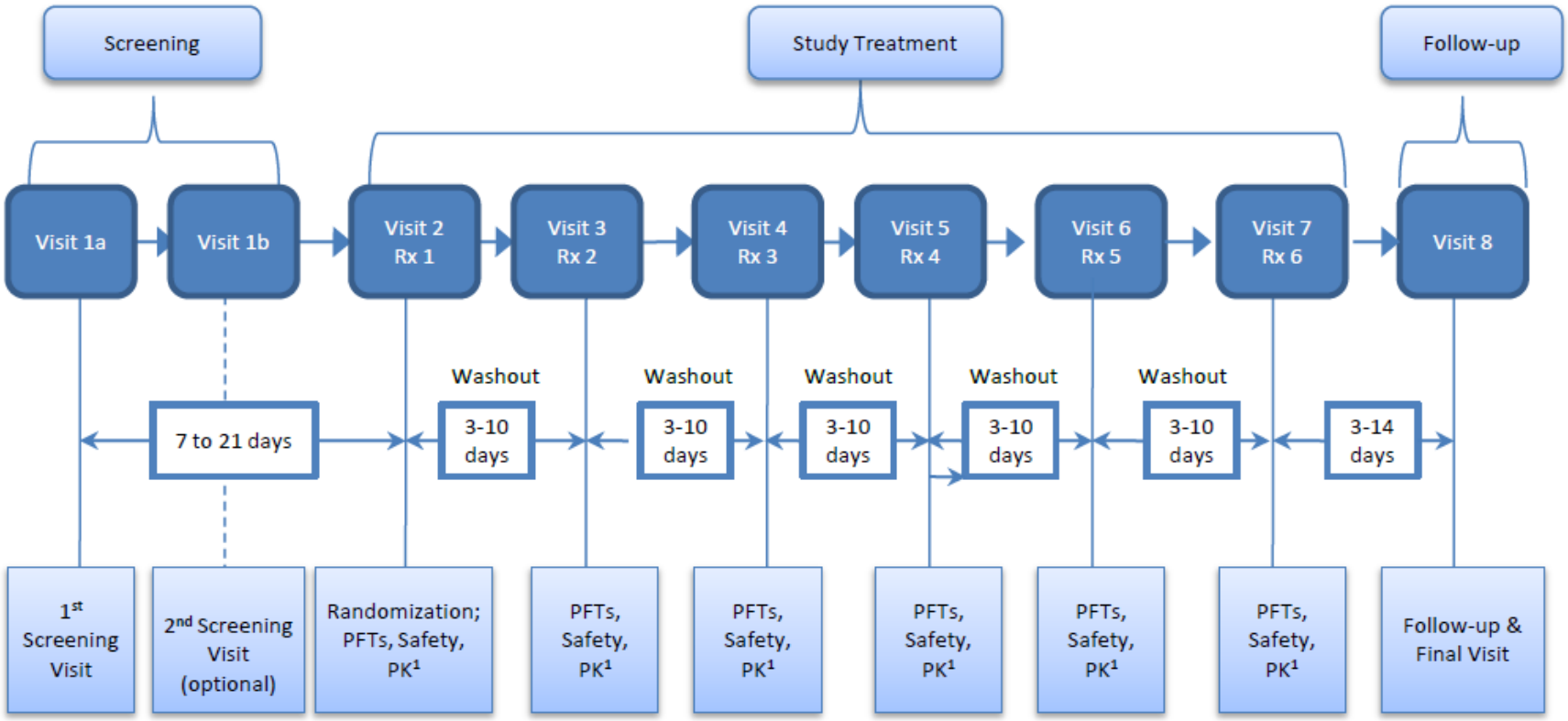
During the washout periods when subjects are not taking study drug (between Visits 2 and 3, Visits 3 and 4, Visits 4 and 5, Visits 5 and 6, and Visits 6 and 7), patients will be permitted to use short-acting bronchodilators (albuterol MDI, ipratropium HFA, or albuterol/ipratropium combination MDI) per the Investigator's discretion.

Protocol-adjusted inhaled corticosteroid (ICS) therapy defined at Screening, if any, should be continued and remain stable for the duration of the trial (see Section 5.4).

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

A Study Flow Diagram is displayed in Figure 1.

Figure 1. Study Flow Diagram



[1] Each patient will undergo PK assessments in 4 of the 6 treatment periods
PFT = pulmonary function test, Rx = treatment, PK = pharmacokinetic assessments

5 STUDY POPULATION SELECTION AND WITHDRAWAL CRITERIA

5.1 Inclusion Criteria

Patients eligible for enrollment in the study must meet all of the following criteria:

1. Give their signed written informed consent to participate.
2. Are between 40-80 years of age at Visit 1.
3. A female is eligible to enter and participate in the study if she is of:
   - Non-child bearing potential (i.e., physiologically incapable of becoming pregnant, including any female who is post-menopausal); or
   - Child bearing potential, has a negative serum pregnancy test at screening, and agrees to one of the following acceptable contraceptive methods used consistently and correctly (i.e., in accordance with the approved product label and the instructions of the physician for the duration of the study - screening to until 2 weeks after Visit 7:
     - Complete abstinence from intercourse from screening until 2 weeks after Visit 7 or
     - Implants of levonorgestrel inserted for at least 1 month prior to the study drug administration but not beyond the third successive year following insertion; or
     - Injectable progestogen administered for at least 1 month prior to study drug administration and administered for 1 month following study completion; or
     - Oral contraceptive (combined or progestogen only) administered for at least one monthly cycle prior to study drug administration; or
     - Double barrier method: condom or occlusive cap (diaphragm or cervical/vault caps) plus spermicidal agent (foam/gel/film/cream/suppository); or
     - An intrauterine device (IUD), inserted by a qualified physician, with published data showing that the highest expected failure rate is less than 1% per year; or
     - Estrogenic vaginal ring; or
     - Percutaneous contraceptive patches.
4. COPD Diagnosis: Patients with an established clinical history of COPD as defined by the American Thoracic Society (ATS)/European Respiratory Society (ERS) (Celli, 2004) characterized by:
   - Airflow limitation that is not fully reversible. Progressive airflow limitation associated with an abnormal inflammatory response of the lungs to noxious particles or gases, primarily caused by cigarette smoking.
5. Tobacco Use: Current or former smokers with a history of at least 10 pack-years of cigarette smoking. [Number of pack years = (number of cigarettes per day / 20) x number of years smoked (e.g., 20 cigarettes per day for 10 years, or 10 cigarettes per day for 20 years]. Former smokers are defined as those who have stopped smoking for at least 6 months prior to Screening (Visit 1).

6. Severity of Disease: Patients with an established clinical history of COPD and severity defined as:
   - Pre- and post-bronchodilator FEV_1/FVC ratio of <70%.
   - At Screening (Visit 1), post-bronchodilator FEV_1 must be greater than or equal to 30% and <80% predicted normal value calculated using the Third National Health and Nutrition Examination Survey (NHANES III) reference equations, and must also be greater than or equal to 750 mL.
   - At Baseline (Visit 2), pre-bronchodilator FEV_1 must be <80% predicted normal value calculated using NHANES III reference equations.
7. Demonstratead reversibility to short acting beta agonist (Ventolin HFA) (> 12% and >150 mL improvement in baseline FEV_1 approximately 30 minutes following administration of 4 puffs of Ventolin HFA or > 200 mL improvement in baseline FEV_1 30 minutes following administration of 2 puffs of Ventolin HFA)
8. Patient is willing and, in the opinion of the investigator, able to change current COPD therapy as required by the protocol and willing to use only albuterol/salbutamol, ipratropium or a combination thereof with or without ICS for maintenance therapy of COPD for at least 1 week prior to randomization.
9. Lab tests conducted at Screening must be acceptable to investigator. ECG performed at Screening must be acceptable to investigator. Chest X-ray or CT scan within 6 months prior to Screening must be acceptable to the investigator.
10. Compliance: Patients must be willing to remain at the study center as required per protocol to complete all visit assessments.

5.2 Exclusion Criteria

Patients meeting any of the following criteria are to be excluded:

1. Pregnancy: Women who are pregnant or lactating.
2. Asthma: Patients who have a primary diagnosis of asthma. (Note: Patients with a prior history of asthma are eligible if COPD is currently their primary diagnosis).
3. Alpha-1 Antitrypsin Deficiency: Patients who have alpha-1 antitrypsin deficiency as the cause of COPD.
4. Other Respiratory Disorders: Patients who have other active pulmonary disease such as active tuberculosis, lung cancer, bronchiectasis, sarcoidosis, lung fibrosis, primary pulmonary hypertension, interstitial lung disease and uncontrolled sleep apnea (i.e., in the opinion of the investigator severity of the disorder would impact the conduct of the study).
5. Lung Resection: Patients who have undergone lung volume reduction surgery at any time in the past.
6. Chest X-ray/CT Scan: Patients who have a chest X-ray (or CT scan) that reveal clinically significant abnormalities not believed to be due to the presence of COPD. A chest X-ray must be conducted if the most recent chest X-ray or CT scan are more than 6 months old at the time of Screening (Visit 1).

7. Hospitalization: Patients who have been hospitalized due to poorly controlled COPD within 3 months of Screening (Visit 1).
8. Poorly Controlled COPD: Patients who have poorly controlled COPD, defined as acute worsening of COPD that requires treatment with corticosteroids or antibiotics in the 6-week interval prior to Screening (Visit 1), or between Screening and Visit 2.
9. Lower Respiratory Tract Infection: Patients who had lower respiratory tract infections that required antibiotics within 6 weeks prior to Screening (Visit 1).
10. Spirometry Performance: Patients who cannot perform acceptable spirometry (at least 3 acceptable flow-volume curves with 2 or more meeting ATS reproducibility criteria).
11. Other Diseases: Patients who have clinically significant medical conditions including but not limited to cardiovascular, neurological, psychiatric, hepatic, gastrointestinal, renal (calculated creatinine clearance ≤ 50 mL/minute), immunological, endocrine (including uncontrolled diabetes or thyroid disease), or hematological medical problems.
12. Clinically significant abnormal ECG: Patients who in the opinion of the investigator have a clinically significant abnormal 12-lead ECG. A clinically significant abnormal ECG is defined as (but not limited to) any of the following:
    - Clinically significant conduction abnormalities (e.g., left bundle branch block, Wolff-Parkinson-White syndrome or evidence of second degree (Mobitz Type II) or third degree atrioventricular (AV) block)
    - Clinically significant arrhythmias (e.g., atrial fibrillation, ventricular tachycardia)
    - A mean corrected QT interval using Fridericia's correction factor (QTcF) value at screening >450 ms for males and >470 ms for females or an ECG that is not suitable for QT measurements (e.g., poorly defined termination of the T wave).
    - Ventricular rate <45 bpm.
    - Pathological Q waves of 1 year or less.
    - ST-T wave abnormalities (excluding non-specific ST-T wave abnormalities)
13. Uncontrolled Hypertension: Patients who have clinically significant uncontrolled hypertension.
14. Patient with abnormal liver function tests defined as AST, ALT, alkaline phosphatase or total bilirubin ≥ 1.5 times upper limit of normal on repeat testing.
15. Cancer: Patients who have cancer that has not been in complete remission for at least 5 years. Note: Patients with squamous cell carcinoma and/or basal cell carcinoma of the skin or localized prostate cancer that in the opinion of the investigator has been adequately worked up, is clinically controlled and the patient's participation in the study would not represent a safety concern, are eligible.
16. Drug Allergy: Patients who have a history of hypersensitivity to any β_2-agonists or any component of the MDI and/or constituents of the dry powder product (lactose).
17. Milk Allergy: Patients who have a history of severe milk protein allergy.
18. Substance Abuse: Patients with a known or suspected history of alcohol or drug abuse within the last 2-year period prior to Screening.

19. Medication Prior to Spirometry: Patients 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.
20. Prohibited COPD Medications: Patients taking the following medications within the specified time intervals prior to Screening (Visit 1) are to be excluded:
    - 3 months: depot corticosteroids, intra-articular corticosteroids
    - 6 weeks: parenteral and oral corticosteroids administered for a COPD exacerbation **Note:** Patients requiring chronic maintenance therapy with oral corticosteroids are excluded from participation in this study.
    - 6 weeks: antibiotics administered for a COPD exacerbation
21. Other Prohibited Medications:
    - Tricyclic antidepressants inhibitors for treatment of depression.
    - Monoamine oxidase (MAO) inhibitors.
    - Anticonvulsants (barbiturates, hydantoins, and carbamazepine) for the treatment of seizure disorder.
    - Non-selective beta-adrenergic antagonists.
    - Anti-tumor necrosis factor α (TNFα) antibodies (e.g., infliximab and any other members of this class of drugs).
    - Antipsychotic drugs (phenothiazines).
    - 1 month: systemic calcineurin inhibitors, systemic antifungal agents, protease inhibitors and cimetidine.
    - **Note**: Benzodiazepines are not exclusionary.
22. Oxygen: Patients receiving long-term-oxygen therapy (LTOT) or nocturnal oxygen therapy required for greater than 12 hours a day. As needed oxygen use is not exclusionary.
23. Pulmonary Rehabilitation: Patients who have participated in the acute phase of a Pulmonary Rehabilitation Program within 4 weeks prior to Screening (Visit 1) or who will enter the acute phase of a Pulmonary Rehabilitation Program during the study. Patients who are in the maintenance phase of a Pulmonary Rehabilitation program are not to be excluded.
24. Non-compliance: Patients unable to comply with study procedures, including an inability to abstain from smoking for 4 hours prior to each study visit and throughout the duration of each study visit as specified in the protocol.
25. 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.
26. Questionable Validity of Consent: Patients 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.

27. Investigational Drugs or Devices: Treatment with investigational study drug or participation in another clinical trial or study within the last 30 days or 5 half lives prior to Screening, whichever is longer.
28. A patient who requires the use of a spacer device to compensate poor hand-to-breath coordination with a MDI.
29. Patients who were previously enrolled in Pearl Therapeutics PT005 (FF MDI) studies or Part B of Study PT0031002.

5.3 Patient Identification

All patients who undergo screening will be assigned a unique screening identification number at the Screening visit (Visit 1). Only patients continuing to meet entry inclusion/exclusion criteria at Visit 2 will be assigned a unique patient randomization number.

5.4 Prior, Concomitant, and Prohibited Medications

All prescription and over-the-counter (OTC) medications taken by the patient during 30 days before Screening 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 below) and are approved by the Investigator. Patients should also be instructed to contact the Investigator if they develop any illnesses.

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

Prohibited COPD Medications:

A list of prohibited medications prior to Screening is provided in Section 5.2. The following medications used for the treatment of asthma and/or COPD are not permitted during this study:

- oral β_2 agonists*
- any LABAs*
- any corticosteroid/LABA combination products*
- phosphodiesterate inhibitors (e.g. theophylline, roflumilast)* (requires 2-week washout prior to randomization)
- cromoglycate or nedocromil inhalers*
- leukotriene antagonists (e.g., zafirlukast, montelukast, zileuton)*

- tiotropium (requires 2-week washout prior to randomization)*
- any formulation of oral (including prednisone) or intravenous/intramuscular (IV/IM) corticosteroids (see Section 5.2). **Note**: For patients maintained on ICS, the dose must remain stable for the duration of the trial.

Patients who meet all entry criteria but are using a prohibited COPD medication will have their maintenance therapy for COPD adjusted as follows:

- Patients taking the COPD medications denoted with * in the list above at Screening (Visit 1) will discontinue these medications for the duration of the trial and be switched to short-acting bronchodilators (albuterol MDI, ipratropium MDI or albuterol/ipratropium combination MDI) per the Investigator's discretion.
- Patients receiving a maintenance dose of an ICS as part of a fixed dose combination therapy containing fluticasone and salmeterol, mometasone and formoterol or budesonide and formoterol will be switched to the corresponding dose of fluticasone, mometasone or budesonide administered as a single agent, with short-acting bronchodilators (albuterol MDI, ipratropium MDI or albuterol/ipratropium combination MDI) per the Investigator's discretion provided they have been maintained on a stable dose for at least 4 weeks.
- Patients receiving a maintenance dose of an ICS that is not administered as a fixed dose combination together with a LABA will be permitted to continue the ICS provided they have been maintained on a stable dose for at least 4 weeks.
- All patients treated with either a LABA (salmeterol, formoterol) or long-acting anti-muscarinic agent (LAMA) (tiotropium) administered alone or as a loose combination will have these medications discontinued and replaced with short-acting bronchodilators (albuterol MDI, ipratropium MDI or albuterol/ipratropium combination MDI) per the Investigator's discretion.

Note: During the screening phase and washout periods (i.e. between Visit 2 and 3, Visit 3 and 4, Visit 4 and 5, Visit 5 and 6, and Visit 6 and 7), albuterol MDI, ipratropium MDI or albuterol/ipratropium combination MDI are acceptable based on the investigator's assessment, but must be withheld for at least 6 hours before each study visit.

5.5 Other Restrictions, Illicit Drugs or Drugs of Abuse

Illicit drugs or drugs of abuse will not be allowed from the start of Screening (Visit 1) to the end of Visit 7 or to whenever the patient discontinues the study. If any illicit drugs or drugs of abuse are used by the patient during the study, the dates of use and the amount will be documented.

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

Patients 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. Decaffienated beverages are acceptable.

Patients 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. Study participants may utilize various nicotine replacement treatments such as chewing gum and patches as needed (*prn)*, in accordance with recommendations from the Investigator during the entire study visit.

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

6.1 Patient Information

Clinical supplies will be packaged to support enrollment of the study.

Study personnel will have access to an IWRS to allocate patients, to assign drug to patients and to manage the distribution of clinical supplies. Clinical supplies will be packaged according to a component schedule generated by Pearl Therapeutics. Each person accessing the IWRS system must be assigned an individual unique PIN. They must use only their assigned PIN to access the system and they must not share their assigned PIN with anyone.

6.2 Product Descriptions

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

Table 1. Product Descriptions

Product Name & Potency	Dosage Form	Comments
Formoterol Fumarate 7.2 µg ex-actuator	MDI	Taken as 2 inhalations of the 3.6 µg per actuation strength MDI
Formoterol Fumarate 9.6 µg ex-actuator	MDI	Taken as 2 inhalations of the 4.8 µg per actuation strength MDI
Formoterol Fumarate 19.2 µg ex-actuator	MDI	Taken as 2 inhalations of the 9.6 µg per actuation strength MDI
Placebo	MDI	Formulation does not contain active ingredient
Formoterol Fumarate inhalation powder[†] 12 µg	DPI	Foradil Aerolizer Taken as 1 capsule. Each capsule contains 12 µg corresponding to 10 µg formoterol fumarate dihydrate delivered from the mouthpiece *Supplies are open-label.*
Formoterol Fumarate inhalation powder[†] 24 µg	DPI	Foradil Aerolizer Taken as 2 capsules. Each capsule contains 12 µg corresponding to 10 µg formoterol fumarate dihydrate delivered from the mouthpiece *Supplies are open-label.*
Albuterol Sulfate inhalation aerosol[§] 90 µg ex-actuator	MDI	Ventolin HFA Each inhalation contains 108 µg corresponding to 90 µg albuterol base from the mouthpiece *Supplies are open-label.*
[†] Active controls [§] Rescue medication **Note: All study drugs will be administered by oral inhalation.**		

All placebos were created by Pearl Therapeutics in the image of the active test product(s).

For open-label Foradil Aerolizer (formoterol fumarate inhalation powder, 12 and 24 µg), bulk commercial blister packs containing 6 individually sealed capsules will be provided. Manufacturer's instructions for study drug administration will be provided.

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

6.3 Primary Packaging and Labeling Information

Investigational materials will be packaged by the Pearl Therapeutics as summarized in Table 2. Foradil Aerolizer and Ventolin HFA supplies will be supplied as open-label MDIs.

Table 2. Packaging of Clinical Supplies

Interval ID	Product Name and Potency	Fill Count	Dosing Instructions
Treatment Period (Visit 2, 3, 4, 5, 6, and 7)	Formoterol Fumarate 7.2 µg ex-actuator	1 MDI 120 actuations	Take a single dose as directed in the clinic
Treatment Period (Visit 2, 3, 4, 5, 6, and 7)	Formoterol Fumarate 9.6 µg ex-actuator	1 MDI 120 actuations	Take a single dose as directed in the clinic
Treatment Period (Visit 2, 3, 4, 5, 6, and 7)	Formoterol Fumarate 19.2 µg ex-actuator	1 MDI 120 actuations	Take a single dose as directed in the clinic
Treatment Period (Visit 2, 3, 4, 5, 6, and 7)	Foradil Aerolizer† 12 µg	N/A	Take a single dose as directed in the clinic
Treatment Period (Visit 2, 3, 4, 5, 6, and 7)	Foradil Aerolizer† 24 µg	N/A	Take a single dose as directed in the clinic
Treatment Period (Visit 2, 3, 4, 5, 6, and 7)	Placebo	1 MDI 120 actuations	Take a single dose as directed in the clinic
Treatment Period (Visit 2, 3, 4, 5, 6, 7 and 8)	Albuterol Sulfate inhalation aerosol§ 90 µg	1 MDI 60 or 200 actuations	Use only as directed.

† Active control
§ Rescue medication

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

Open-label Supplies: Open-label Foradil Aerolizer will be provided as individually labeled DPIs and bulk labeled commercial blister packs packaged in sets of 1 blister pack per patient within a foil overwrap labeled with a two-part label. Each Foradil Aerolizer will have a single label.

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

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

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

6.4 Secondary Packaging and Labeling Information (Box)

Investigational drug or placebo supplies for Visit 2, 3, 4, 5, 6 and 7 will be packaged in boxes as outlined in Table 3. Open-label Foradil Aerolizer supplies will be packaged in boxes as outlined in Table 3. Open-label Ventolin HFA supplies will be provided as bulk MDI in boxes as outlined in Table 3. Box configuration is subject to change as a result of packaging constraints.

Table 3. Description of Boxes

Drug Supplies	Box Contents
Blinded	1 MDI
Bulk Foradil Aerolizer Device	12 DPI
Foradil Aerolizer Capsule (12 μg Dose)	1 Foil Pouch Containing 1 Capsule
Foradil Aerolizer Capsule (24 μg Dose)	1 Foil Pouch Containing 2 Capsules
Bulk Ventolin HFA	1 MDI

Each box will be labeled with a single 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 or DPI) • 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 patients and to unmask drug identity. Pearl Therapeutics will not provide a disclosure envelope with the clinical supplies. The investigator or treating physician may unblind a subject's treatment assignment **only in the case of an emergency**, when knowledge of the study treatment is essential for the appropriate clinical management or welfare of the subject. Whenever possible, the

investigator must first discuss options with the Medical Monitor or appropriate study personnel **before** unblinding the subject's treatment assignment. If this is impractical, the investigator must notify Pearl Therapeutics 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: Clinical supplies should be kept in a secured location at room temperature (store at 20ºC to 25ºC; excursions permitted to 15ºC to 30ºC). Do not refrigerate or freeze.

Foradil Aerolizer drug supplies: Prior to dispensing: Store in a refrigerator, 2°C-8°C (36°F-46°F). After dispensing to patient: Store at 20°C to 25°C (68°F to 77°F). Protect from heat and moisture. CAPSULES SHOULD ALWAYS BE STORED IN THE BLISTER AND ONLY REMOVED FROM THE BLISTER IMMEDIATELY BEFORE USE.

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

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

6.7 Instructions for Preparation of Treatments for Administration and Dispensing

Formoterol Fumarate (7.2, 9.6 or 19.2 µg) and placebo MDIs

Individual FF (7.2, 9.6 or 19.2 µg), and placebo MDIs will be packaged in a foil pouch and contained in an individual visit treatment box. Both the visit treatment box and the foil overwrap will have a label with a component ID number. Confirm that the identifier given by IWRS and the component ID number written on the label are the same. The foil overwrap is labeled with a two-part label. Write the patient number and treatment visit number on each of the two-part labels. The 'tear-off' part of the label is to be placed onto the IWRS confirmation report.

All 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's ready to use.

The MDI must be primed in a separate room from the patient treatment area. Since the MDI is primed in a separate room before dosing, there is a possibility that there may be delay between priming and dosing, and therefore to ensure consistency in the administration for all patients, the MDIs are to be gently shaken (5-10 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 2 puffs from the MDI. See Appendix 4 for instructions on the administration of FF MDI and Placebo MDI.

Foradil Aerolizer 12 and 24 µg

Foradil Aerolizer capsule(s) will be packaged in a foil overwrap contained in an individual visit treatment box. Both the visit treatment carton 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 foil overwrap is labeled with a two-part label. Write the patient number and treatment visit number on each of the two-part labels. The 'tear-off' part of the label is to be placed onto the IWRS confirmation report.

For the Foradil Aerolizer 12 µg dose, the contents of 1 capsule will be inhaled. For the Foradil Aerolizer 24 µg dose, the contents of 2 capsules will be inhaled with no more than a minute between the inhalation of each capsule. See Appendix 5 for the manufacturer's instructions on the administration of Foradil Aerolizer.

Ventolin HFA 90 µg

Bulk supplies of open-label Ventolin HFA will be provided by Pearl Therapeutics and stored in a secured location within the clinic or pharmacy facilities. Per the protocol patients will be dispensed Ventolin HFA to conduct reversibility testing at Screening (Visit 1). The Ventolin HFA dispensed at Screening will remain in the clinic and will only be used during treatment visits [Visit 2 (Rx 1), Visit 3 (Rx 2), Visit 4 (Rx 3), Visit 5 (Rx 4), Visit 6 (Rx 5) and Visit 7 (Rx 6] in situations where the investigator deems rescue medication is required. Ventolin HFA should be stored at room temperature. Ventolin HFA should be primed per manufacturer's instructions prior to dispensing to patient. See Appendix 6 for the manufacturer's instructions on the administration of Ventolin HFA.

6.8 Drug Accountability/Return of Clinical Supplies

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

Investigational clinical supplies must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated assistants have access. Storage conditions for the clinical

supplies should be observed, monitored and documented. Clinical supplies are to be dispensed only in accordance with the protocol. The investigator is responsible for keeping accurate records of the clinical supplies received from Pearl Therapeutics, the amount dispensed to and returned by the subjects/patients, and the amount remaining at the conclusion of the study. Study medication should be handled in accordance with Good Pharmacy Practices (i.e., gloves should always be worn by study personnel if directly handling tablets or capsules that are returned). The Clinical Monitor should be contacted with any questions concerning investigational products where special or protective handling is indicated. At the end of the study, all clinical supplies including partial and empty containers must be returned or destroyed as directed by Pearl Therapeutics.

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

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

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

7 STUDY PROCEDURES

A time and events schedule is provided in Table 4. Detailed schedules for pre- and post-dose procedures to be performed at treatment visits are provided in Table 5.

All assessments during Visits 2 through 7 will be conducted in the following order: tremor assessments, vital signs, ECGs, clinical laboratory assessments, and spirometry.

7.1 Efficacy Assessments

Both forced expiratory spirometry for derivation of FEV_1, FVC and PEFR will be assessed using a spirometer that meets or exceeds minimum performance recommendations of the American Thoracic Society (ATS) (See Appendix 1).

The volume accuracy of the spirometer is to be checked daily using a 3 L syringe across 3 flow ranges i.e., at <2 L/sec, 4-6 L/sec and >8 L/sec with temperature and barometric pressure correction. The calibration syringe must meet ATS specifications and must not be used beyond the expiry date. Required accuracy is ± 3%, i.e., 2.91 L to 3.09 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).

At all treatment visits (Visits 2, through 7), spirometry will be conducted 60 minutes and 30 minutes prior to study drug administration. The average of these two assessments will be used to establish test-day baseline FEV_1, FVC and PEFR. The baseline FEV_1 at Visits 3, 4, 5, 6 and 7 must be within ±15% or 150 mL of the baseline FEV_1 obtained at the Randomization Visit (Visit 2). On initial assessment if the patient fails to meet the reproducibility criteria, but the 30 minute pre-dose assessment is closer to the ±15% or 150 mL cut-off, another assessment may be conducted 30 minutes later. If the last 2 assessments meet the reproducibility requirements, the initial 60 minute pre-dose assessment will not be used and the last 2 assessments will be used to establish the eligibility criteria. If the test day FEV_1 is not within ± 15% or 150 mL, the visit may be rescheduled at the investigators discretion (e.g., within one week), or the patient discontinued. 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.

7.1.1 Pulmonary Function Tests

All pulmonary function tests including FEV_1, FVC and PEFR as defined in ATS/ERS guidelines (Miller, 2005) 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 pulmonary function testing will receive identical, detailed 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 pulmonary function tests (ATS criteria, Miller, 2005) prior to performing testing on study patients. 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 Therapeutics or designee for central data management.

Refer to Section 7.4 for specific FEV_1 criteria that prompt patients to be discontinued from the study.

7.2 Safety Assessments

The safety assessments include ECGs, vital signs, physical examination findings, clinical laboratory tests, monitoring for paradoxical bronchospasm, assessment of symptoms of tremor, in addition to recording AEs and SAEs.

7.2.1 Medical/Surgical History and Physical Examination

Medical history will be taken at Screening (Visit 1) and updated at the Randomization Visit (Visit 2). A complete physical examination will be performed at Screening and the Final/Follow-up Visit (Visit 8). 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 (including assessment of tremor pre-albuterol use). Weight, assessed in ordinary indoor clothing with shoes off, and height (Screening) will be recorded at the specified visits.

7.2.2 Vital Sign Measurements

Heart rate and systolic and diastolic blood pressure ('vital signs') will be assessed at each visit; assessments will be obtained after being supine for 5 minutes for the first 2 hours after study drug and thereafter measurements may be obtained in the supine or seated position. If in the opinion of the investigator a clinically significant vital sign change occurs, then the measurement will be repeated at medically appropriate intervals until the value returns to within an acceptable range**.** Refer to Section 7.4 for specific criteria for heart rate and systolic and diastolic blood pressure readings that prompt patients to be discontinued from the study.

Systolic and diastolic blood pressures and heart rate will be obtained at the same times as indicated for spirometry (i.e., 60 and 30 minutes prior to study drug (all visits); 15 and 30 minutes, and 1, 2, 4, 6, 8, 10, 11.5, and 12 hours after study drug at all treatment Visits. Temperature will be obtained at Screening and at pre-dose and 2 hours post-dose and will not be repeated at subsequent time points unless clinically indicated.

7.2.3 12-Lead Electrocardiogram (ECG)

An ECG will be obtained at Screening. At all treatment visits, ECGs will be obtained between 1 to 2 hours and 30 minutes to 1 hour prior to study drug and at 15 and 30 minutes, and 1, 2, 4, and 12 hours after study drug.

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 patients. 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 heart rate, RR interval, PR interval, QRS axis, QRS interval, and QT/QTcF (Fridericia's Formula) interval.

QT intervals and calculated QTcF (Fridericia's Formula) intervals will be reviewed and checked for gross inaccuracies by the investigator or designated ECG reviewer. If the calculated QTcF intervals are greater than 500 msec, and have increased by 60 msec or more over baseline value, the investigator will make a determination on the suitability of continuing the patient in the study. If QTcF interval prolongation exceeding these limits is verified during treatment, the patient'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. Refer to Section 7.4 for specific criteria for QTcF that prompt patients to be discontinued from the study.

Additional ECGs will be obtained if the patient's heart rate is less than 60 beats/minutes (bpm) and is more than 20 bpm below test day baseline or is greater than 100 bpm and is more than 20 bpm above the test day baseline value (where baseline is defined as the mean of the heart rate assessments obtained 60 and 30 minutes prior to study drug administration on the same test day).

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 Therapeutics Medical Monitor.

The decision to continue the treatment of any patient with prolonged QT or QTcF interval must be discussed and agreed upon by the investigator and the Pearl Therapeutics Medical Monitor. All such patients, including patients 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 Therapeutics Medical Monitor must be contacted.

7.2.4 Clinical Laboratory Tests

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

Hematology (Complete Blood Count) and chemistry (Comprehensive Metabolic Panel) will be obtained within 60 minutes prior to dosing and at 2 hours post-dosing at each treatment visit (Visits 2, 3, 4, 5, 6 and 7). A basic metabolic panel (BMP) will be obtained at 30 minutes post-dose at each treatment visit (Visits 2, 3, 4, 5, 6 and 7).

Serum pregnancy testing will be performed at Screening and at the Final Visit with Urine HCG testing occurring prior to the start of each treatment (Visits 2, 3, 4, 5, 6 and 7) in women of child-bearing potential.

The following clinical laboratory parameters will be assessed:

Hematology	
Hemoglobin	Mean corpuscular hemoglobin (MCH)
Hematocrit	Mean corpuscular hemoglobin concentration (MCHC)
White Blood Cell count with differential	Mean corpuscular volume (MCV)
Red Blood Cell count	
Platelet Count	
Clinical Blood Chemistry	
Liver Enzyme and Other Function Tests	**Other Clinical Blood Chemistry**
Alanine aminotransferase (ALT)	Albumin
Aspartate aminotransferase (AST)	Blood urea nitrogen (BUN)[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
	Urea
Other Tests:	
Pregnancy test (women of child-bearing potential only): serum [human chorionic gonadotropin (HCG)] at Screening and Final Visit only and Urine HCG at all other visits	
Creatinine clearance will be estimated by the central laboratory using a published formula.	

[a] Parameters included in the Basic Metabolic Panel (BMP).

7.2.5 Adverse Events

7.2.5.1 Performing Adverse Events Assessments

The investigator is responsible for promptly documenting and reporting all AEs observed during the study in the subject's case report form and on the AE Reporting Form. If the AE is "alarming", the investigator must report the AE immediately to Pearl Therapeutics. In addition, certain AEs (as described in Section 7.2.5.7) are classified as "serious" and must be reported no later than 24 hours after the investigator recognizes/classifies the event as a serious adverse event to Pearl Therapeutics or its designee (Sponsor).

In the case of serious adverse events, after discussing the details of the AE, the investigator and the Medical Monitor may discontinue the patient prematurely.

7.2.5.2 Adverse Event Definitions

The following definitions of terms are guided by the International Conference on Harmonization and the U.S. Code of Federal Regulations [21 CFR 312.32] and are included herein.

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

Adverse events include, but are not limited to:

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

An AE does **not** include:

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

7.2.5.3 Pre-Randomization Adverse Events

Adverse events that occur between the time the patient signs the informed consent form for the study and the time when that patient is randomized will be summarized as medical history and not as a study adverse event unless the event meets the definition of a serious adverse event (SAE) as defined below.

7.2.5.4 Severity

The investigator must categorize the severity of each AE according to the following guidelines:

Mild: Associated with no limitation of usual activities or only slight discomfort; generally not requiring alteration or cessation of study drug administration; and/or not needing therapeutic intervention.

Moderate: Associated with limitation of usual activities or significant discomfort; generally requiring alteration or cessation of study drug administration; and/or requiring therapeutic intervention.

Severe: Associated with inability of patient to carry out usual activities or very marked discomfort; considered to be life-threatening; resulting in significant disability or incapacity; and requiring therapeutic intervention.

7.2.5.5 Relationship

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

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

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

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

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

7.2.5.6 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 (e.g., elevated BUN and creatinine in the setting of an adverse event of renal failure, or decreased hemoglobin in a case of bleeding esophageal varices). In such cases, the laboratory abnormality itself (e.g., elevated creatinine in a setting of renal failure) does not need to be recorded as an AE. However, isolated

laboratory abnormalities should be reported as AEs if they are considered to be clinically significant by the investigator.

Criteria for a "clinically significant" laboratory abnormality are:

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

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

7.2.5.7 Serious Adverse Events

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

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

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon appropriate judgment, they may jeapordize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in 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 adverse event 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 Pearl Therapeutics's Medical Monitor or designee. All SAEs must be reported to Pearl Therapeutics no later than 24 hours after the investigator recognizes/classifies the event as a serious adverse event. At a minimum, a description of the event and the investigator's judgment of causality must be provided at the time of the initial report using the appropriate form (e.g., 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 Therapeutics as described in Section 7.2.5.9.

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

7.2.5.8 Supplemental Investigations of SAEs

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

7.2.5.9 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 patient 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 patient's safety or until the event stabilizes or resolves. If resolved, a resolution date should be documented on the case report form or reported to Pearl Therapeutics if the case report forms have been collected. The investigator is responsible to ensure that follow-up includes any supplemental investigations as may be indicated to elucidate the nature and/or causality of the AE. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals as is practical.

7.2.5.10 Notification of Post-Study Serious Adverse Events

Investigators are not obligated to actively follow patients 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 they must be reported to Pearl Therapeutics, whether or not the event is attributable to study drug. All SAEs must be reported to Pearl Therapeutics no later than 24 hours after the investigator recognizes/classifies the event as a serious adverse event.

7.2.5.11 IRB/IEC Notification of Serious Adverse Events

The investigator is responsible for promptly notifying her/his investigational review board/independent ethics committee (IRB/IEC) of all SAEs, including any follow-up information, occurring at her/his site and any SAE regulatory report, including any follow-up reports that he/she receives from Pearl Therapeutics. Documentation of the submission to the IRB/IEC must be retained for each safety report. The investigator is also responsible for notifying Pearl Therapeutics if their IRB/IEC requires revisions to the informed consent form or other measures based on its review of an SAE report.

7.2.5.12 Health Authority Safety Reports

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

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

7.2.6 AEs of Interest - Paradoxical Bronchospasm and Tremor

Paradoxical bronchospasm may occur following inhalation from either an MDI or DPI. Tremor is a known side effect following administration of a LABA.

Monitoring for paradoxical bronchospasm will occur at every visit for the first 30 minutes post-dose. In this study, paradoxical bronchospasm is defined as a reduction in FEV_1 of >20% from test day baseline (i.e., the mean FEV_1 values obtained 60 and 30 minutes prior to study drug administration) with associated symptoms of wheezing, shortness of breath, or cough. All AEs and SAEs will be recorded as appropriate.

Patients will be asked about symptoms of tremor at baseline and at specified intervals (pre-dose and at 1 and 2 hours post-dose at treatment Visits. If tremor persists at 2 hours post-dose additional assessments will be conducted every 2 hours until resolution of symptoms or completion of the test day (see Table 5) and if present, the severity (mild, moderate, and severe) of tremor symptoms will be assessed. If tremor is not noted at 2 hours post study

drug administration, further tremor assessments do not need to be collected. All reports of tremor exceeding baseline will be recorded as AEs.

Instructions for Recording Tremor AEs:

1) Investigator should assess patients for history of tremor at screening and prior to dosing at Visit 2 (Randomization). If yes, record tremor in the patients medical history.

2) If patient reports an event of tremor post-randomization capture as an AE if:

    a. Patient has a history of tremor at screening, and the event is considered a worsening of pre-existing tremor.

    b. Patient has no history of tremor at screening.

3) The investigator should follow all AEs of tremor to resolution. An AE of tremor is considered resolved when the patient reports the event has returned to baseline (absent or as described in medical history).

4) Duration is captured from onset (when first reported by patient) to resolution (when patient reports event has returned to baseline as described above).

7.2.7 Overdose

An overdose is defined as a dose greater than the high dose level evaluated in this study as described in Section 6.2 of the protocol (Product Descriptions) which results in clinical signs and symptoms. In the event of an overdose of study medication, the investigator should use clinical judgment in treating the overdose and contact the study Medical Monitor. The investigator should refer to the relevant document(s) for detailed information regarding warnings, precautions, contraindications, adverse events, and other significant data pertaining to the study drug(s) being used in this study. Such documentation may include, but not be limited to the investigators brochure and approved product labeling for FF MDI and Foradil Aerolizer.

7.2.8 Pregnancy

Any pregnancy that occurs from screening until study completion must be reported to Pearl Therapeutics.

To ensure subject safety, each pregnancy must be reported to Pearl Therapeutics within 2 weeks of learning of its occurrence. The pregnancy must be followed up to determine outcome (including premature termination) and status of mother and child.

7.3 Pharmacokinetic Assessments

7.3.1 Plasma Collection and Plasma Sample Handling

Approximately 5 mL of whole blood will be collected by direct venipuncture or may be obtained from an indwelling intravenous cannula (per site SOP after review by Pearl Therapeutics Medical Monitor or designee) using a vacuum collection tube (for example Vacutainer plasma collection tube) containing EDTA tripotassium according to the Schedule of Events (Table 4). After processing, the plasma for 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 3 for Plasma Collection, Storage and Handling.

Samples are to be shipped frozen by overnight courier to the bioanalytical laboratory [redacted] for analysis. Plasma levels of formoterol will be determined using a validated High Performance Liquid Chromatography tandem Mass Spectrometry (LC/MS/MS) method. Refer to Appendix 3 for sample shipping details.

7.3.2 Pharmacokinetic Evaluations

Each patient will undergo PK sampling in four of the six treatment periods. Each patient will be sampled during the FF MDI 9.6 µg treatment period, Foradil Aerolizer 12 µg treatment period and in two of the remaining three formoterol fumarate treatment periods (FF MDI 19.2 µg, FF MDI 7.2 µg and Foradil Aerolizer 24 µg) or the placebo treatment period. Blood sampling for PK will be evaluated immediately prior to study drug administration, at 2, 6, 20 minutes, and 1, 2, 4, 8, 10, and 12 hours post-dose.

7.4 Reasons and Procedures for Early Termination

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

If a patient is lost-to-follow-up, i.e., fails to return for study visits, reasonable efforts must be made to contact the patient and complete study termination procedures.

All patients 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 patients who prematurely discontinue the study after being randomized, regardless of the cause, should undergo only the assessments outlined in Section 8.4 on the date of discontinuation.

A patient 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 (SBP) 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.
- FEV_1 decrease by more than 20% from test day baseline (before taking study drug) on two consecutive spirometry assessments obtained at least 15 minutes apart with associated symptoms of dyspnea at any time within the first 2-hour interval after taking study drug.

7.5 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 Therapeutics. The reason should be communicated in writing to Pearl Therapeutics.

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

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

1. 4 or more deaths deemed to be cardiac or respiratory in origin at any point before 50 patients have been randomized; or
2. 9 or more deaths from any cause at any time during the course of the study.

Stopping criteria based on deaths from any source were based on estimates of instantaneous rates of mortality taken from the TORCH (Calverley, 2007) and UPLIFT (Tashkin, 2008) studies. These criteria imply a 1% 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 4. Detailed schedules for pre- and post-dose procedures to be performed at treatment visits are provided in Table 5.

Table 4. Schedule of Events

Procedures	Screening[a]		Treatment Period[a]						Follow-Up/ Final
	Visit 1a	Visit 1b (optional)	Visit 2 Randomization (Rx 1)	Visit 3 (Rx 2)	Visit 4 (Rx 3)	Visit 5 (Rx 4)	Visit 6 (Rx 5)	Visit 7 (Rx 6)	Visit 8 Final Visit
Informed Consent	X								
Eligibility Criteria	X	X							
Verify Continued Eligibility			X	X	X	X	X	X	
Reversibility to Ventolin HFA[b]	X								
Demographics & Medical/Surgical History	X	X							
Concomitant Medications[c]	X	X	X	X	X	X	X	X	X
Spirometry[d]	X	X	X	X	X	X	X	X	
Physical Examination[e]	X								X
Vital Signs[f]	X		X	X	X	X	X	X	X
12-Lead ECG[g]	X		X	X	X	X	X	X	X
Pregnancy Test[h]	X		X	X	X	X	X	X	X
Clinical laboratory testing[h]	X		X	X	X	X	X	X	X
Adjust COPD Medications per Protocol[i]	X								
Resume pre-study COPD medications as appropriate[j]								X	
Adverse Events	X	X	X	X	X	X	X	X	X
Inhalation Device Training	X		X						
Study Drug Administration			X	X	X	X	X	X	
PK Blood Samples[k]			X	X	X	X	X	X	
Tremor	X		X	X	X	X	X	X	
Paradoxical Bronchospasm[l]			X	X	X	X	X	X	

Table 4. Schedule of Events (continued)

a. Screening period of at least 7 days and up to 21 days. Patients are to return to the clinic within 3 to 10 days following initiation of each treatment arm.
b. Assess reversibility of FEV_1 at approximately 30 minutes following 4 puffs Ventolin HFA.
c. 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).
d. Spirometry (FEV_1, FVC, and PEFR) will be assessed at Screening. See Table 5 for spirometry assessments and specific time points to be performed at Visits 2, 3, 4, 5, 6 and 7.
e. Includes evaluation of height and weight at Screening.
f. All vital signs will be obtained at Screening. SBP, DBP and HR will be obtained in the supine position at all time points preceding and including the 2 hour time point post-dose. SBP, DBP and HR measurements obtained after the first 2 hours post-dose may be obtained in either the supine or the seated position. See Table 5 for SBP, DBP, and HR assessments and specific time points to be performed at Visits 2, 3, 4, 5, 6 and 7. At Visits 2-7, temperature will be obtained at pre-dose and 2 hours post-dose and will not be repeated at subsequent time points unless clinically indicated.
g. An ECG will be conducted at Screening. See Table 5 for ECG assessments and specific time points to be performed at Visits 2, 3, 4, 5, 6 and 7.
h. All clinical laboratory tests will be obtained at Screening and Follow-up. At Visits 2 through 7, hematology (Complete Blood Count) and chemistry (Comprehensive Metabolic Panel) will be obtained within 60 minutes prior to dosing and 2 hours post-dose and a basic metabolic panel (BMP) will be obtained at 30 minutes post-dose on all patients (see Table 5). Pregnancy test (women of child-bearing potential only): serum [human chorionic gonadotropin (HCG)] at Screening and Final Visit only and Urine HCG at all other visits
i. At screening, stop prohibited COPD medications and change COPD medications as specified in protocol Section 5.4 (i.e., short-acting bronchodilators with or without ICS).
j. At the end of the Visit 7, return patient to pre-study or other appropriate inhaled maintenance COPD medications.
k. See Table 5 for PK sample collection times at Visits 2, 3, 4, 5, 6 and 7. Note: PK will be evaluated in all patients at 4 of the 6 treatment visits; all patients will have PK sample collection at visit 2. Upon randomization IWRS will provide a schedule of which additional 3 treatment periods will require PK sample collection
l. Please refer to Section 7.2.6 for definition of paradoxical bronchospasm.

Table 5. Treatment Visit Procedures (at Visits 2, 3, 4, 5, 6 and 7)

	Pre-dosing		Post-dosing												
Clinical Variable[a]	**-1 hr**	**-30 min**	**2 min**	**6 min**	**15 min**	**20 min**	**30 min**	**1 hr**	**2 hr**	**4 hr**	**6 hr**	**8 hr**	**10 hr**	**11.5 hr**	**12 hr**
Tremor Assessments		X[b]			X		X	X	X[b]						
Paradoxical Bronchospasm							X[c]								
Vital Signs[d]	X	X			X		X	X	X	X	X	X	X	X	X
12- Lead ECG	X[e]	X[e]			X		X	X	X	X					X
PK Sampling[f]		X	X	X		X		X	X	X		X	X		X
Clinical Laboratory Testing[g]	X[g]						X[g]		X[g]						
Spirometry (FEV_1, FVC, PEFR)	X	X			X		X	X	X	X	X	X	X	X	X

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

b. If tremor is not noted at the 2-hour time point, no further assessment is required. If tremor persists at 2 hours additional assessments will be conducted every 2 hours until resolution of symptoms or completion of the test day.

c. Monitoring for paradoxical bronchospasm will occur at every visit for the first 30 minutes post-dose. Please refer to Section 7.2.6 for a definition of paradoxical bronchospasm

d. Temperature will be obtained pre-dose and 2 hours post-dose; no further temperature assessments required unless clinically indicated.

e. Two Baseline ECGs should be conducted, one between 60 to 120 minutes and another between 30 to 60 minutes prior to dosing.

f. Pharmacokinetics (PK) will be evaluated in all patients at 4 of the 6 treatment visits. All patients will have PK sample collection at visit 2. Upon randomization IWRS will provide a schedule of which additional 3 treatment periods will require PK sample collection.

g. All clinical laboratory parameters will be obtained within 60 minutes prior to study drug administration and at 2 hours after study drug. A basic metabolic panel (BMP) will be obtained at 30 minutes post-dose on all patients.

Note: Where data collection time-points are concurrent, variables must be collected in the following order: Tremor assessment, vital signs, ECG, clinical laboratory assessments, PK blood samples and spirometry.

8.1 Screening Visit (Visit 1a-1b)

- Obtain informed consent.
- Check inclusion/exclusion criteria.
- Obtain demographic data, including age, race, smoking history, medical/surgical history including tremor and age of onset of COPD.
- Obtain medication history, including COPD medications.
- Conduct a serum pregnancy test for all female patients unless it is documented in the medical history that the patient 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 (heart rate and blood pressure after being supine for 5 minutes, and oral or tympanic temperature).
- Obtain a 12-lead ECG.
- Conduct baseline spirometry assessments.
- Administer 4 puffs Ventolin HFA:
    - Confirm patient's ability to use MDI correctly (provide coaching as needed).
    - Repeat spirometry assessments 30 minutes following 4 puffs Ventolin HFA

If patient still meets inclusion/exclusion criteria perform the following:

- Obtain laboratory samples (hematology and chemistry).
- Complete Chest X-ray or CT scan if not performed within the last 6 months.
- Stop prohibited COPD medications and change concurrent COPD medications as specified in protocol (see Section 5.4).
- Arrange date of Visit 1b or Visit 2 as appropriate.
- Complete Screening Log (basic demographics, spirometry, medications and reasons for screen failure) for patients who do not meet eligibility criteria.

- Adverse events must be recorded during the screening period, that is, from the time of consent to the start of study treatment.

8.2 Randomization Visit (Visit 2; Rx 1)

- Review inclusion/exclusion criteria to confirm protocol eligibility.
- Review of clinical laboratory results from Visit 1. Please note whether the results are clinically significant and include comments where applicable.
- Record adverse events (if any).
- Review concomitant medications to ensure adherence to COPD regimen.
- Note time of last dose of short-acting bronchodilator and other COPD medications on the CRF (if <6 hours, Visit 2 must be rescheduled).
- Perform urine pregnancy test (women of child-bearing potential only).
- Perform all pre-dose assessments (refer to Table 5).
- **Note:** All patients will have PK sample collection at Visit 2. Upon randomization IWRS will provide a schedule of which additional 3 treatment periods will require PK sample collection
- Obtain patient treatment assignment information from IWRS. The patient is then considered randomized.
- At 15-30 minutes prior to dosing, the seal around the study day treatment box is to be opened and the instructions for administration of study drug on the inner flap of the study day treatment box are to be followed.
    - Refer to Section 6.7 for detailed instructions for preparation of treatments for administration. These instructions are to be adhered to and are relevant to all study treatment visits.
- Patient will administer a single dose of newly assigned study drug at the clinic.
- Perform all post-dosing assessments (refer to Table 5).
- Schedule Visit 3.

8.3 Visit 3, 4, 5, 6 and 7 (Rx 2, Rx 3, Rx 4, Rx 5 and Rx 6)

- Note time of last dose of short-acting bronchodilator and other COPD medications on CRF (if <6 hours, reschedule visit).

- Review concomitant medications and ensure adherence to COPD regimen.
- Review inclusion/exclusion criteria to confirm eligibility to continue.
- Review clinical laboratory results from previous visit. Please note whether the results are clinically significant and include comments where applicable.
- Record adverse events (if any).
- Perform urine pregnancy test (women of child-bearing potential only).
- Perform all pre-dose assessments (refer to Table 5).
- Obtain patient treatment assignment information from IWRS.
- At 15-30 minutes prior to dosing, the seal around the study day treatment box is to be opened and the instructions for administration of study drug on the inner flap of the study day treatment box are to be followed.
    - Refer to Section 6.7 for detailed instructions for preparation of treatments for administration. These instructions are to be adhered to and are relevant to all study treatment visits.
- Patient will administer a single dose of newly assigned study drug at the clinic.
- Perform all post-dosing assessments (refer to Table 5)
- **At Visit 3, 4 5, and 6 only**: Schedule next visit.
- **At Visit 7 only**: Schedule a final/follow-up visit at least 3 days but no longer than 10 days from Visit 7 and return patient to pre-study or appropriate inhaled maintenance COPD medications.

8.4 Follow-Up (Final) Visit/Premature Discontinuation (Visit 8)

- 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.
- Inform patient about reporting all SAEs up to 14 days following the last dose of study drug.

- If not adjusted following Visit 7, return patient to pre-study or appropriate inhaled maintenance COPD medications.

- Complete study completion page

8.5 Completion of the Study

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

- Patient discretion (document reason)
- Investigator considers it to be in the best interest of the patient
- Adverse events(s)
- Administrative reasons (e.g., early termination of the study)
- Patient lost-to-follow-up
- Major protocol violation
- Death
- Completion of the study
- Protocol-specific criteria such as QTc prolongation, heart rate, systolic or diastolic blood pressure, or FEV_1 changes (see Section 7.4).

9 PLANNED STATISTICAL METHODS

9.1 Introduction

This study will be conducted as a 6-period, 6-treatment, randomized block cross-over design evaluating the following 6 treatments in approximately 36 completing patients:

- FF MDI 7.2 µg ex-actuator
- FF MDI 9.6 µg ex-actuator
- FF MDI 19.2 µg ex-actuator
- Placebo MDI
- Foradil Aerolizer 12 µg
- Foradil Aerolizer 24 µg

The primary objective of this study is to demonstrate efficacy relative to placebo of FF MDI in patients with moderate to severe COPD within the range of doses evaluated in this protocol. To this end, each dose of FF MDI will be compared to placebo with respect to the primary efficacy endpoint, FEV_1 AUC_{0-12} relative to baseline. Baseline FEV_1 will be defined as the mean pre-dose values on the day of dosing (Visits 2, 3, 4, 5, 6 and 7). The secondary objective of the study is to characterize the dose-response curve of FF MDI and to conduct a non-inferiority assessment comparing FF MDI within the range of doses evaluated in this study to open-label Foradil Aerolizer 12 µg. The primary and secondary endpoints identified in Section 3.1 will be assessed for FF MDI as compared with placebo.

With 6 treatments in 6 periods there are 720 unique treatment sequences. A subset of 36 of these sequences will be generated as 6 replicates of a William Square design. In order to reduce the impact of multiple blood samples, each patient will be sampled for PK in only four of the six treatment periods. Each patient will be sampled during the FF MDI 9.6 µg treatment, during their Foradil Aerolizer 12 µg treatment, and in two periods selected from the remaining three formoterol fumarate treatments (FF MDI 19.2 µg, FF MDI 7.2 µg and Foradil Aerolizer 24 µg), and the placebo treatment. Treatments will be assigned to the remaining periods. The remaining three formoterol fumarate treatments and placebo will be allocated for PK sampling in a two-period four-treatment incomplete block.

9.2 Protocol Variables

9.2.1 Efficacy Endpoints

All efficacy assessments are defined as change from baseline. For each endpoint, baseline is given by the average of pre-dosing values on the current treatment day (Visits 2, 3, 4, 5, 6 and 7).

9.2.1.1 Primary Efficacy Endpoint

The primary endpoint is AUC_{0-12} of change in FEV_1 from baseline, which will be referred to as FEV_1 AUC_{0-12}. FEV_1 AUC_{0-12} will be based on nominal measurement times, and will be normalized by the nominal total period of evaluation (12 hours); the units of FEV_1 AUC_{0-12} will be L. The baseline will be defined by the average of the pre-dose values on the day of testing (Visits 2, 3, 4, 5, 6 and 7).

9.2.1.2 Secondary Efficacy Endpoints

- Peak change in FEV_1 from baseline (defined as highest change value post-dose)
- Time to onset of action (≥10% improvement in FEV_1 relative to baseline
- Change from baseline at trough FEV_1 (trough FEV_1 is defined as the mean of the FEV_1 assessments taken at 11.5 and 12 hours post-dose)
- Non-inferiority assessment comparing FF MDI to Foradil Aerolizer 12 μg based on FEV_1 AUC_{0-12} relative to baseline.

9.2.2 Pharmacokinetic Endpoints

PK analyses will be performed using actual time points calculated relative to dose. Assuming there are sufficient numbers of measurable plasma concentrations, the following PK parameters will be calculated for Formoterol Fumarate for each treatment using non-compartmental analysis methods.

Parameter	Description
AUC_{0-12}	Area under the plasma concentration versus time curve from time 0 to 12 hours post-dose
$AUC_{0-tlast}$	Area under the plasma concentration versus time curve from time 0 to time of the last quantifiable concentration
AUC_{0-inf}	Area under the plasma concentration versus time curve from time 0 to infinity
C_{max}	Maximum observed plasma concentration
T_{max}	Time to C_{max}
λ_z	The terminal elimination rate constant, calculated from the slope of the terminal log-linear portion of the plasma versus time curve
$t_{1/2}$	Apparent terminal half-life, calculated as $\ln 2/\lambda_z$
CL/F	Apparent systemic clearance, calculated as dose/AUC_{0-inf}
Vz/F	Apparent volume of distribution

The terminal elimination rate constant (k_e), the apparent terminal elimination half-life ($t_{1/2}$) and the area under the plasma concentration versus time curve from time 0 to infinity (AUC_{0-inf}) will be calculated if the data permit.

9.2.3 Exploratory Pharmacodynamic Endpoints

The major objective of these analyses will be to define an optimal therapeutic ratio based on outcomes from pharmacodynamic (FEV_1)/pharmacokinetic (AUC or C_{max}) determinants.

Details will be defined prospectively in a separate Statistical Analysis Plan.

9.2.4 Safety Endpoints

The safety endpoints for this study include:

1. **Adverse Events:** The safety measurements include both the numbers of adverse events as observed by the investigational team or reported by the patient, and the numbers of patients experiencing adverse events. Adverse events will be collected from the time of study enrolment at Screening, that is, once informed consent is obtained until the time of study termination or exit. Adverse events will be characterized by severity and relationship to study drug. The incidence of an adverse event will be defined by the number of patients experiencing an event.
2. **Paradoxical Bronchospasm and Tremor** will be regarded as adverse events of special significance, and tabulated separately. The incidence will be defined by the number of patients experiencing an event during a treatment..
3. **12 Lead ECG:** Change from baseline heart rate, RR interval, PR interval, QRS axis, QRS interval, QT intervals and QTcF (Fridericia Corrected QT) intervals, where baseline is defined as the average of the values prior to dosing for each treatment.
4. **Concomitant Medications:** All medications (including complementary medicines and other health supplements) that were used to treat acute or chronic conditions will be recorded at screening (Visit 1) and updated throughout the study as required.
5. **Clinical Laboratory Testing:** Full clinical laboratory testing at every visit including hematology and clinical chemistry, characterized by change from baseline, where the baseline is defined as the value prior to dosing for each treatment..
6. **Vital Sign Measurements:** Change from baseline values where baseline is defined as the average of the values prior to dosing for each treatment.

9.3 Analysis

9.3.1 Primary Efficacy Analysis

The primary efficacy analysis involves the comparison of the mean primary efficacy endpoint (FEV_1 AUC_{0-12} relative to baseline) for each experimental treatment with Placebo. Baseline FEV_1 will be included in the statistical model as a covariate.

Efficacy analysis will be based on a linear mixed model in which Treatment will be a fixed effect, subject will be a random effect, and within subject errors are correlated, but between

subject errors are independent. Unstructured, compound symmetry and first-order autoregressive error models will be considered, and the appropriate model selected using Akaike's information criterion (Akaike, 1974). Fixed and random effects will be estimated using the REML algorithm (Patterson and Thompson, 1971), which allows for the recovery of inter-block (subject) information.

The primary efficacy analysis will involve *a priori* comparisons between treatments for the primary endpoint, FEV_1 AUC_{0-12}:

1. FF MDI 19.2 µg vs. Placebo
2. FF MDI 9.6 µg vs. Placebo
3. FF MDI 7.2 µg vs. Placebo

Strong control of the family-wise Type I error will be achieved by hierarchical testing (Bauer et al, 1998). No efficacy claims will be advanced for any dose level of FF MDI unless all higher dose levels are statistically significantly superior to the Placebo. Testing for unequal carry-over effects will be performed. Models will include baseline as a covariates. Two-sided 95% confidence intervals will be tabulated.

9.3.2 Secondary Efficacy Analysis

Secondary efficacy comparisons for FEV_1 AUC_{0-12} are:

1. FF MDI 19.2 µg non-inferiority vs. open-label Foradil Aerolizer 12 µg
2. FF MDI 9.6 µg non-inferiority vs. open-label Foradil Aerolizer 12 µg;
3. FF MDI 7.2 µg non-inferiority vs. open-label Foradil Aerolizer 12 µg.

A non-inferiority margin of 0.1L will be adopted for FEV_1 AUC_{0-12}. This margin has been selected because a change in pre-dose FEV_1 of approximately 0.1L can be perceived by patients, correlates with fewer relapses following exacerbations, and correlates with two year decline in lung function (Donohue, 2005). For this endpoint, strong control of the family-wise Type I error will be achieved by hierarchical testing (Bauer et al, 1998). No non-inferiority claims will be advanced for any dose level of FF MDI unless all higher dose levels are statistically significantly non-inferior to Foradil Aerolizer 12 µg.

No non-inferiority comparisons will be performed for other endpoints.

Other secondary efficacy analyses will involve the primary efficacy comparisons (superiority of each FF MDI treatment group to placebo) applied to secondary efficacy endpoints (*vide supra*). The statistical model and tabulations will be exactly as for the primary objectives (except for time to onset), except that no tests for unequal carry-over effects will be performed. The false discovery rate for all secondary efficacy comparisons will be controlled using the Benjamini Hochberg procedure (Benjamini and Hochberg, 1995).

For time to onset of action, data will be analyzed using Murray's method for weighted Kaplan-Meier statistics for paired data (Murray, 2001). For each pair of treatments being compared, the cumulative incidence Kaplan-Meier curves will be plotted, along with their ratio, the cumulative incidence ratio (CIR).

9.3.3 Primary Pharmacokinetic Analysis

Non-compartmental parameter estimates will be analyzed using a linear mixed model in which Treatment will be a fixed effect and within subject errors are correlated, but between subject errors are independent. Unstructured, compound symmetry and first-order autoregressive error models will be considered, and the appropriate model selected using Akaike's information criterion (Akaike, 1974). AUC and C_{max} will be ln-transformed before analysis.

Relative bioavailability will be calculated for each dose relative to the Foradil Aerolizer 12 µg treatment, using the mixed model results. A 90% confidence interval for each relative bioavailability (a ratio) will be calculated. Details will be provided in a separate PK statistical analysis plan.

9.3.4 Safety Analysis

9.3.4.1 Adverse Events

Adverse events during each treatment regimen will be summarized by the number of patients experiencing an event. They will be tabulated at the level of the MedDRA preferred term, and the MedDRA System Organ Class. The version of MedDRA at the time of database lock will be used for the final analysis of the data. Tabulations will be broken down by severity and by relationship to study drug. No hypothesis tests will be performed. Tables will show the overall incidence of adverse events and the incidence for each treatment. Incidence will be defined by the number of patients experiencing an event during the period between administration of the current treatment, and administration of the next treatment. No hypothesis tests will be performed.

9.3.4.2 Paradoxical Bronchospasm

Paradoxical Bronchospasm will be considered as an adverse event of special interest, and will be tabulated separately. Bronchospasm will be summarized by the number of patients experiencing the event during a particular treatment period. Bronchospasm that occurs outside a treatment period will be listed separately. No hypothesis tests will be performed, but an appropriate confidence interval may be provided.

9.3.4.3 Tremor

The incidence of tremor will be summarized by the number of patients experiencing the event during a particular treatment period. No hypothesis tests will be performed, but an appropriate confidence interval may be provided.

9.3.4.4 Clinical Laboratory Measurements

Summary statistics (mean, median, standard deviation and range) of change from baseline values will be tabulated for each treatment and each assessment time. For clinical laboratory measurements, baseline values will be defined by the value prior to dosing for each treatment period. Male and female patients will be tabulated separately. Clinically notable change from test day baseline in serum potassium (> 0.5 mmol/L reduction from baseline and serum potassium < 3.5 mmol/L) will be listed and tabulated by treatment. Similarly, clinically notable blood glucose values (> 9.99 mmol/L) will also be listed and tabulated by treatment.

9.3.4.5 Vital Signs

Summary statistics (mean, median, standard deviation and range) for absolute values and of change from baseline values will be tabulated for each treatment and assessment time. For vital signs, baseline values will be defined by the last available value prior to dosing for each treatment.

9.3.4.6 ECGs

The ECG parameters that will be assessed include heart rate, RR interval, PR interval, QRS axis, QRS interval, and corrected QT interval (QTcF). Summary statistics (mean, median, standard deviation and range) of change from baseline values will be tabulated for each treatment and each assessment time.

Summary statistics (mean, median, standard deviation and range) for absolute values and change from baseline values will be tabulated for each treatment and assessment time. For ECG parameters, baseline values will be defined as the average of the value(s) obtained prior to dosing for each treatment period.

In addition, all ECGs will be periodically reviewed by Pearl Therapeutics or designee to assess whether any patient has experienced a notable change in QTcF from test day baseline, i.e. ECG's with > 30 msec increase in QTcF from test day baseline and QTcF intervals greater than 450 msec for males and 470 msec for females. For any patient meeting these criteria all ECGs collected on that test day will be reviewed by a cardiologist and summary findings documented.

9.3.5 Pharmacodynamic Analysis

All pharmacodynamic endpoints are considered exploratory.

Pharmacodynamic endpoints will be analyzed using a linear mixed model in which treatment will be a fixed effect and within subject errors are correlated, but between subject errors are independent. Unstructured (for period), compound symmetry and first-order autoregressive error models will be considered, and the appropriate model selected using Akaike's information criterion (Akaike, 1974). Fixed and random effect (subject) parameter estimates will be obtained using the REML algorithm (Patterson and Thompson, 1971). Ratios will be ln-transformed before analysis.

A separate statistical analysis plan will be provided for pharmacodynamic analyses.

9.4 Randomization

Patients will be randomly assigned to a treatment sequence using an IWRS.

The treatment sequences are shown in Table 6. These sequences have been generated as a set of 6 Williams squares, and are therefore balanced for Period and for first-order carry-over effects.

Table 6. Treatment Selections By Period

	Period:					
Sequence	1	2	3	4	5	6
1	FF7.2	FF9.6	Placebo	FF19.2	FA24	FA12
2	FF9.6	FF19.2	FF7.2	FA12	Placebo	FA24
3	FF19.2	FA12	FF9.6	FA24	FF7.2	Placebo
4	FA12	FA24	FF19.2	Placebo	FF9.6	FF7.2
5	FA24	Placebo	FA12	FF7.2	FF19.2	FF9.6
6	Placebo	FF7.2	FA24	FF9.6	FA12	FF19.2
7	FF9.6	FF7.2	Placebo	FF19.2	FA24	FA12
8	FF7.2	FF19.2	FF9.6	FA12	Placebo	FA24
9	FF19.2	FA12	FF7.2	FA24	FF9.6	Placebo
10	FA12	FA24	FF19.2	Placebo	FF7.2	FF9.6
11	FA24	Placebo	FA12	FF9.6	FF19.2	FF7.2
12	Placebo	FF9.6	FA24	FF7.2	FA12	FF19.2
13	FF9.6	FF7.2	Placebo	FF19.2	FA12	FA24
14	FF7.2	FF19.2	FF9.6	FA24	Placebo	FA12
15	FF19.2	FA24	FF7.2	FA12	FF9.6	Placebo
16	FA24	FA12	FF19.2	Placebo	FF7.2	FF9.6
17	FA12	Placebo	FA24	FF9.6	FF19.2	FF7.2
18	Placebo	FF9.6	FA12	FF7.2	FA24	FF19.2
19	FF9.6	FF7.2	FA12	FF19.2	Placebo	FA24
20	FF7.2	FF19.2	FF9.6	FA24	FA12	Placebo
21	FF19.2	FA24	FF7.2	Placebo	FF9.6	FA12
22	FA24	Placebo	FF19.2	FA12	FF7.2	FF9.6
23	Placebo	FA12	FA24	FF9.6	FF19.2	FF7.2
24	FA12	FF9.6	Placebo	FF7.2	FA24	FF19.2
25	FF9.6	FF7.2	FA12	FA24	Placebo	FF19.2
26	FF7.2	FA24	FF9.6	FF19.2	FA12	Placebo
27	FA24	FF19.2	FF7.2	Placebo	FF9.6	FA12
28	FF19.2	Placebo	FA24	FA12	FF7.2	FF9.6
29	Placebo	FA12	FF19.2	FF9.6	FA24	FF7.2
30	FA12	FF9.6	Placebo	FF7.2	FF19.2	FA24
31	FF7.2	FF9.6	FA12	FA24	Placebo	FF19.2
32	FF9.6	FA24	FF7.2	FF19.2	FA12	Placebo
33	FA24	FF19.2	FF9.6	Placebo	FF7.2	FA12
34	FF19.2	Placebo	FA24	FA12	FF9.6	FF7.2
35	Placebo	FA12	FF19.2	FF7.2	FA24	FF9.6
36	FA12	FF7.2	Placebo	FF9.6	FF19.2	FA24

The allocation of PK samples to treatments and periods is shown in Table 7. The allocation has been chosen to satisfy the following constraints:

1. Every subject will have PK samples during the first period;

2. Every subject will have PK samples during the period in which Formoterol Fumarate MDI 9.6 µg is administered;

3. Every subject has PK samples during the period in which Foradil Aerolizer 12 µg is administered.

This sample design has been chosen to maximize the power for the comparison of FF MDI 9.6 µg with Foradil Aerolizer 12 µg.

The PK design is not balanced for period or for first-order carry-over effects, although the two treatments of greatest interest for pharmacokinetic analysis (FF MDI 9.6 µg with Foradil Aerolizer 12 µg) each occur six times in each of the six treatment periods. The incidence of PK samples by treatment and period is shown in Table 8.

Table 7. Allocation of PK Samples to Timepoint and Treatment

	Period					
Sequence	**1**	**2**	**3**	**4**	**5**	**6**
1	FF7.2	FF9.6	Placebo	----	----	FA12
2	FF9.6	FF19.2	FF7.2	FA12	----	----
3	FF19.2	FA12	FF9.6	FA24	----	----
4	FA12	FA24	FF19.2	----	FF9.6	----
5	FA24	Placebo	FA12	----	----	FF9.6
6	Placebo	FF7.2	----	FF9.6	FA12	----
7	FF9.6	FF7.2	Placebo	----	----	FA12
8	FF7.2	FF19.2	FF9.6	FA12	----	----
9	FF19.2	FA12	FF7.2	----	FF9.6	----
10	FA12	FA24	FF19.2	----	----	FF9.6
11	FA24	Placebo	FA12	FF9.6	----	----
12	Placebo	FF9.6	FA24	----	FA12	----
13	FF9.6	FF7.2	Placebo	----	FA12	----
14	FF7.2	FF19.2	FF9.6	----	----	FA12
15	FF19.2	FA24	----	FA12	FF9.6	----
16	FA24	FA12	FF19.2	----	----	FF9.6
17	FA12	Placebo	FA24	FF9.6	----	----
18	Placebo	FF9.6	FA12	FF7.2	----	----
19	FF9.6	----	FA12	----	Placebo	FA24
20	FF7.2	----	FF9.6	----	FA12	Placebo
21	FF19.2	----	----	Placebo	FF9.6	FA12
22	FA24	----	----	FA12	FF7.2	FF9.6
23	Placebo	FA12	----	FF9.6	----	FF7.2
24	FA12	FF9.6	----	----	FA24	FF19.2
25	FF9.6	----	FA12	----	Placebo	FF19.2
26	FF7.2	----	FF9.6	----	FA12	Placebo
27	FA24	----	----	Placebo	FF9.6	FA12
28	FF19.2	----	----	FA12	FF7.2	FF9.6
29	Placebo	FA12	----	FF9.6	----	FF7.2
30	FA12	FF9.6	----	----	FF19.2	FA24
31	FF7.2	FF9.6	FA12	----	----	FF19.2
32	FF9.6	----	----	FF19.2	FA12	Placebo
33	FA24	----	FF9.6	----	FF7.2	FA12
34	FF19.2	----	----	FA12	FF9.6	FF7.2
35	Placebo	FA12	----	----	FA24	FF9.6
36	FA12	----	----	FF9.6	FF19.2	FA24

---- indicates no sample

Table 8. Incidence of PK Samples by Treatment and Period

	Period					
Treatment	1	2	3	4	5	6
FA12	6	6	6	6	6	6
FA24	6	3	2	1	2	3
FF19.2	6	3	3	1	2	3
FF7.2	6	3	2	1	3	3
FF9.6	6	6	6	6	6	6
Placebo	6	3	3	2	2	3

9.5 Sample Size Consideration

Power calculations were based on the primary endpoint, FEV_1 $AUC_{0\text{-}12,}$ and also on the properties of the pharmacokinetic endpoints: C_{max} and $AUC_{0\text{-}12}$.

Estimates of within subject standard deviation of FEV_1 $AUC_{0\text{-}12}$ from published studies (D'Urzo et al, 2001; van Noord et al, 2005, Maesen et al 1995) suggest a within subjects standard deviation of approximately 0.13L, in a non-reversible population. A recent Pearl study in a non-reversible population revealed a within subjects standard deviation of 0.1L; this is similar to the estimate of 0.1L obtained by Humerfelt et al (1998) for asymptomatic men. The relatively low standard deviation obtained by Pearl is a reflection of the rigorous QA process adopted for spirometry data. In a single dose study on a reversible population, Pearl achieved a within subjects standard deviation of 0.07L. These findings suggest that a within subjects standard deviation of 0.1L or less should be achievable in a reversible population. Accordingly, all power calculations for spirometry endpoints have been performed assuming a within subjects standard deviation of 0.1L.

The primary efficacy comparisons are:

1. FF MDI 19.2 µg vs. Placebo
2. FF MDI 9.6 µg vs. Placebo
3. FF MDI 7.2 µg vs. Placebo

Assuming a clinically relevant effect size of 0.1L, a sample size of 24 completing patients then delivers approximately 90% power for each of the primary efficacy comparisons. A sample size of 36 patients yields approximately 98% power.

Since the comparison will be performed in a pre-determined hierarchy (i.e., Comparison 2 will not be performed unless Comparison 1 is statistically significant etc), the power for Comparisons 2 and 3 are reduced. Power estimates were obtained by simulation of the decision hierarchy. 100,000 realisations of the treatment means were generated, and *t* tests were performed assuming a known variance. The results for 24 and 36 samples are shown in Table 9. Note that the power differences between the primary endpints are generated only by the testing hierarchy. A sample size of 24 patients is clearly adequate for the primary efficacy objective.

Table 9. Power for Primary Efficacy Comparisons by Sample Size.

Power calculations assume a closed test hierarchy.

Comparison	24 Patients	36 Patients
FF MDI 19.2 µg vs. Placebo	92%	99%
FF MDI 9.6 µg vs. Placebo	87%	98%
FF MDI 7.2 µg vs. Placebo	83%	97%

Bioequivalence is not the primary objective of this study. Accordingly we relax the usual equivalence definition of relative bioavailability in the range (0.8-1.25). Instead we consider the power to demonstrate that relative bioavailability lies in the range (0.75-1.3333). Power was calculated assuming that the two one-sided test (TOST) procedure (Phillips, 1990) will be applied on the log[1] scale. A significance level of 0.05 was assumed for each of the two tests, giving a composite error rate of 10%.

Earlier studies of single-dose and multiple dose treatment with FF MDI provided estimates of between subjects standard deviation for log AUC_{0-12} formoterol fumarate plasma concentration of 0.4. Power to demonstrate bioequivalence between Formoterol Fumarate MDI 9.6 µg and Foradil Aerolizer 12 µg was calculated assuming a true relative bioavailability of 1.05. A sample size of 36 patients then delivers power of approximately 80%. The within subjects standard error of C_{max} is slightly greater than that of AUC_{0-12}, 0.45. With 36 patients the power to demonstrate bioequivalence for C_{max} is approximately 70%.

A total of 48 patients will be randomized to yield 36 completing patients. This sample size is regarded as a compromise; it is larger than required to generate adequate power for efficacy, and smaller than required to generate adequate power for a conventional bioequivalence analysis.

9.6 Analysis Plan

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

9.7 Study Populations

The following analysis populations are defined in this study:

- The **Intent-To-Treat (ITT) Population** is defined as all subjects who are randomized to treatment and receive at least one dose of the study treatment. (Note that a subject who

[1] All references to logarithims in this protocol should be interpreted as natural logarithms.

used a study treatment, but took less than one full dose of treatment will qualify for this population).

- A **Modified ITT (MITT) Population** will be used for analysis of PK and efficacy variables; where subjects must have completed at least 3 treatment periods, with adequate data to support 12 hour assessments for each of these treatment periods. Any evaluability criteria with a potential impact on efficacy or PK results will be indentified in a blinded fashion from review of data listings prior to database lock. Protocol deviations, therefore, can result in exclusion of all (e.g. spirometry) data from a particular subject from the analysis population or require exclusion of data from a specific treatment period or from a particular timepoint within a treatment period. Protocol deviations for exclusion of data from the MITT Population will be agreed by the investigator, Pearl Therapeutics and the biostatistician prior to database lock and will be pre-specified in the Statistical Analaysis Plan written prior to database lock.

  Any patient who has less than 4 test days (with twelve hours on each day) before terminating the study will be considered not to have sufficient efficacy data and will be replaced.

Evaluability criteria for efficacy measurements are defined in Table 10.

Table 10. Evaluability Criteria for Efficacy Endpoints

Endpoint	Evaluability Criteria
Peakchange from baseline in FEV_1	No more than one missing FEV_1 value from pre-dose to 2 hours post-dosing inclusive.
FEV_1 AUC_{0-12}	• Must satisfy the Peak criterion (See above); • No more than two missing FEV1 values at adjacent sample times, up to and including 12 hours post-dose; • No more than four missing FEV_1 values from pre-dose to the 12 hours post-dose inclusive.
Change from baseline at trough FEV_1	At least one of the 12 hours and 11.5 hours post-dosing FEV_1 values must be available.

Any FEV_1 measurement which does not meet quality criteria will be considered missing.

For pharmacokinetic data, C_{max} and T_{max} will be calculated whenever there are no missing values in the first four hours post-dosing (inclusive). Terminal elimination rate and parameters derived from it (e.g. AUC_{0-inf}) will be calculated whenever the pharmacokineticist judges that there are sufficient sample points in the terminal elimination phase to warrant analysis.

- The **Per-Protocol (PP) Population** is defined as all subjects who completed all treatment periods of the study as specified in the protocol. The PP Population will be used for sensitivity analyses. The PP Population will also exclude any measurements excluded from the MITT Population.

The Safety Population is defined identically to the ITT Population (all subjects who are randomized to treatment and receive at least one dose of the study treatment). (Note that a subject who used a study treatment, but took less than one full dose of treatment will qualify for this population). This population will be used to do safety tabulations (adverse events, and laboratory, vital sign, and ECG tabulations).

Analyses will be performed as follows:

Demographics will be summarized for the Intent-To-Treat (ITT), Modified Intent-To-Treat (MITT), and Per-Protocol (PP) patient populations. Extent of exposure will be summarized for the ITT population. The Safety population will be used to summarize safety.

Efficacy Analyses will be performed for the MITT and PP patient populations, with the MITT Population being considered the primary population for these analyses. The primary endpoint analysis will be repeated using the ITT Population. The ITT anlaysis of the primary endpoint and the PP analyses will be used as sensitivity analyses.

In the event of documented mis-dosings (that is, situations in which a patient is known to have received a dose different from that scheduled in the protocol) efficacy analyses will be based on the dose actually received, rather than the dose scheduled.

9.8 Handling of Missing Data

Missing data will not be imputed. Efficacy endpoints not meeting the evaluability criteria defined in Table 10 will be considered missing.

9.9 Statistical Software

Data processing, data screening, descriptive reporting and analysis of the efficacy and safety data will be performed using SAS (Version 9.2 or higher). The pharmacokinetic data will be analyzed using WinNonLin (Version 5.2 or higher).

10 ADMINISTRATIVE INFORMATION

10.1 Regulatory Authority Approval

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

10.2 Ethical Conduct of the Study and Institutional Review Board (IRB) or Independent Ethics Committee (IEC) Approval

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

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

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

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

10.3 Patient Information and Consent

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

The investigator will be responsible for obtaining written informed consent from potential patients prior to any study-specific screening and entry into the study. A copy of the signed ICF will be provided to the patient. 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 Therapeutics that information furnished to the investigator by Pearl Therapeutics will be maintained in confidence and such information will be divulged to the IRB/IEC, or similar or expert committee; affiliated institution; and employees only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees. Data generated by this study will be considered confidential by the investigator, except to the extent that it is included in a publication.

10.4.2 Confidentiality of Subject/Patient Records

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

10.5 Quality Control and Assurance

Pearl Therapeutics is responsible for implementing and maintaining quality control and quality assurance systems with written SOPs to ensure that trials are conducted and data are generated, documented, and reported in compliance with the protocol, accepted standards of Good Clinical Practice, 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 Therapeutics.

10.7 Study Monitoring

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

During these contacts, the monitor will:

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

This will be done in order to verify that the:

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

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

Upon completion of the study, the monitor will conduct the following activities innconjunction with the investigator or site staff, as appropriate:

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

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

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

10.9 Financial Disclosure

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

10.10 Investigator's Final Report

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

10.11 Publication Policy

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

In recent years, issues about conflicts of interest and accuracy of the study data have been raised in the medical press. Accordingly, Pearl Therapeutics has developed publication guidelines for clinical studies that are appropriate for this study.

Key issues include:

1. **Responsibility:** Each Principal investigator is responsible for the accuracy and completeness of all data from their site. Pearl Therapeutics (or its representatives) is responsible for the accuracy of the data entered into the study databases and for the accuracy of the analyses conducted.

2. **Authorship and Publication Committee:** Pearl Therapeutics, in collaboration with the investigators, will establish the appropriate authorship and responsibility for drafting study documents in accordance with the principles of the ICMJE. It is anticipated that a publication committee will be formed to assume oversight of these activities. All manuscripts will be reviewed and agreed upon before submission for publication by all authors.
3. **Sponsor Review of External Manuscripts:** Consistent with the previous bullet point, drafts of any and all publications or presentations that may arise from this study must be submitted at least 30 days prior to submission for publication or presentation to Pearl Therapeutics for review, approval, and to ensure consistency with the policy in this protocol. Pearl Therapeutics will have the right to request appropriate modification to correct facts and to represent its opinions, or the opinions of the publication committee, if these differ with the proposed publication.
4. **Confidentiality:** Investigators will conduct all interactions with Pearl Therapeutics and with third parties consistent with the executed confidentiality agreements. While publication, by intention, presents the critical scientific data in a public forum, some information (such as future plans, results of nonclinical studies, or chemical formulae) may still need to remain confidential.
5. **Medical Journal Review:** Consistent with the intention of Pearl Therapeutics to publish the study in a fair and accurate manner, Pearl Therapeutics supports diligence in the publication review process of medical journals. Accordingly, upon request, all pertinent study data and information will be made available as supplemental information for journal editors and reviewers to evaluate and audit, e.g., protocol and amendments, data tabulations, *etc*. The journal and reviewers will need to make arrangements to maintain the confidentiality of such supplemental information, where relevant, and Pearl Therapeutics will make suitable arrangements to ensure that the identity of journal reviewers is kept confidential. Records will be maintained of reviewers and the respective documents and datasets that were reviewed by each of them.
6. **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..

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Appendix 1 Spirometry Performance Recommendations

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

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

FEV_1 AND FVC MANEUVERS

Equipment Requirements

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

Display

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

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

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

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

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

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

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

Validation

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

Quality control

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

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

Table A1-2. Summary of Equipment Quality Control

Test	Minimal Interval	Action
Volume	Daily	Calibration check with a 3 L syringe
Leak	Daily	2 cm H_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, e.g., $\pm$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 $\pm$15 mL or $\pm$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 (e.g., monthly) leak tested at more than one volume up to their maximum; this can be done by attempting to empty them with the outlet corked. A dropped or damaged syringe should be considered out of calibration until it is checked.

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

Quality control for volume-measuring devices

The volume accuracy of the spirometer must be checked at least daily, with a single discharge of a 3-L calibrated syringe. Daily calibration checking is highly recommended so that the onset of a problem can be determined within 1 day, and also to help define day-to-day laboratory variability. More frequent checks may be required in special circumstances, such as: 1) during industrial surveys or other studies in which a large number of subject maneuvers are carried out, the equipment's calibration should be checked more frequently than daily; and 2) when the ambient temperature is changing (e.g., 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 cmH2O (0.3 kPa) with the spirometer outlet occluded (preferably at or including the mouthpiece). Any observed volume loss of .30 mL after 1 minute indicates a leak and needs to be corrected.

At least quarterly, volume spirometers must have their calibration checked over their entire volume range using a calibrated syringe or an equivalent volume standard. The measured volume should be within ±3.5% of the reading or 65 mL, whichever is greater. This limit includes the 0.5% accuracy limit for a 3-L syringe. The linearity check procedure provided by the manufacturer can be used if it is equivalent to one of the following procedures: 1) consecutive injections of 1-L volume increments while comparing observed volume with the corresponding cumulative measured volume, e.g., 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, e.g., 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-s^{-1} (with 3-L injection times of 6 s and 0.5 s). The volume at each flow should meet the accuracy requirement of ±3.5%. For devices using disposable flow sensors, a new sensor from the supply used for patient tests should be tested each day.

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

TECHNICAL CONSIDERATIONS

Minimal recommendations for spirometry systems

Accurate results require accurate equipment. Spirometer equipment recommendations apply to all spirometers and are minimal requirements. In some circumstances, it may be

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

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

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

FEVt: forced expiratory volume in t seconds

BTPS correction

All spirometry values should be reported at BTPS by any method (measuring temperature and barometric pressure) proven effective by the manufacturer. For volume-type spirometers, the temperature inside the spirometer should be measured for each breathing maneuver. Regardless of the BTPS correction technique used, the ambient temperature must always be recorded with an accuracy of $\pm$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

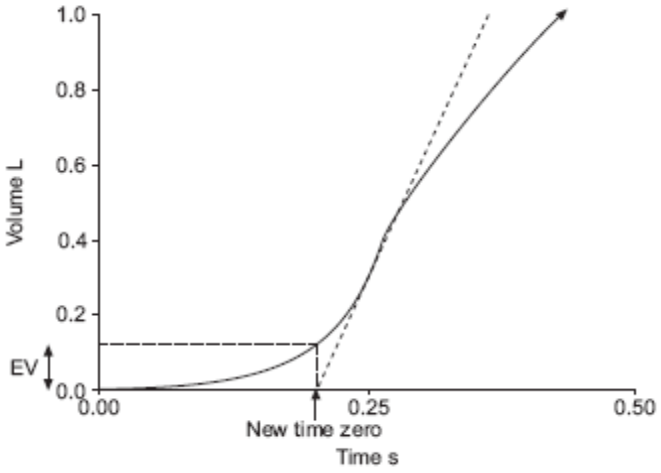
***Acceptable* Tests must meet the following 7 Criteria:**

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

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

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

Figure A2-1. Example of a Usable Spirogram



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

Between-Maneuver Reproducibility Criteria

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

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

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

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

Appendix 3 Plasma Collection, Storage and Handling (PK Samples)

- Collect approximately 5 mL of blood in a tube containing EDTA tripotassium (4×10^3M 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. The rotor chamber of the centrifuge must be refrigerated to maintain a temperature of approximately 4^oC.
- 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 patient.
- 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.
- 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.

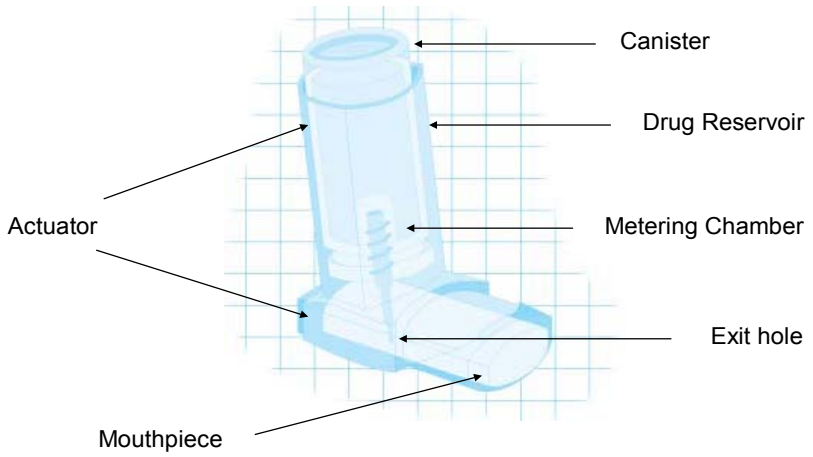
Shipping Address:

[redacted]

Appendix 4 Patient Instructions for Use of Formoterol Fumarate and Placebo MDI Devices

1. The inhaler should be stored at room temperature.
2. Take the cap off the mouthpiece of the actuator.
3. Inspect the front of the inhaler and make sure there is nothing inside the mouthpiece of the inhaler. Make sure the canister is fully and firmly inserted into the actuator.
4. All MDIs must be primed before the first use. Priming involves releasing a certain number of sprays (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's ready to use. 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.
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 8, with gentle shaking for 5-10 seconds prior to each spray.
10. Put the cap back on the mouthpiece after every time the inhaler is used.

METERED DOSE INHALER SCHEMA



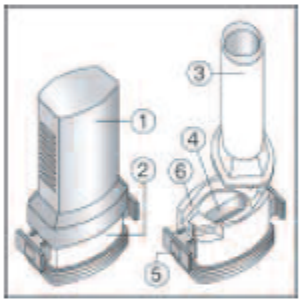
Appendix 5 Instructions for Use of Foradil Aerolizer Device

FORADIL AEROLIZER

- **FORADIL AEROLIZER consists of FORADIL capsules and a AEROLIZER Inhaler.**
- **FORADIL capsules come on blister cards and are wrapped in foil pouches. Do not open a foil pouch until you are ready to use FORADIL AEROLIZER.**
- **Keep your FORADIL and AEROLIZER Inhaler dry. Handle with DRY hands.**

Aluminum pouch covering the foil blister cards

Foil blister card



The Aerolizer consists of the following parts:

1. A cap to protect the mouth-piece of the base
2. A base that allows the proper release of medicine from the capsule

The base consists of:

3. A mouth piece
4. A capsule chamber
5. A button with "winglets" (projecting side pieces) and pins on each side
6. An air inlet channel.

With each new prescription of FORADIL AEROLIZER or refill, your pharmacist should have written the "Use by" date on the sticker on the outside of the FORADIL AEROLIZER box. Remove the "Use by" sticker on the box and place it on the AEROLIZER Inhaler cover that comes with FORADIL. If the sticker is blank, count 4 months from the date you got your FORADIL AEROLIZER from the pharmacy and write this date on the sticker. Also, check the expiration date stamped on the box. If this date is less than 4 months from your purchase date, write this date on the sticker.

Do not use FORADIL capsules with any other capsule inhaler, and do not use the AEROLIZER inhaler to take any other capsule medicine.

Taking a dose of FORADIL AEROLIZER requires the following steps:

1. Open the foil pouch containing a blister card of FORADIL capsules. Do not remove a FORADIL capsule until you are ready for a dose.

2. Pull off the AEROLIZER Inhaler cover. (Figure 1)

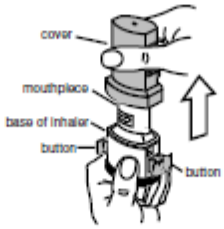


Figure 1

3. Hold the base of the AEROLIZER Inhaler firmly and twist the mouthpiece in the direction of the arrow to open. (Figure 2) Push the buttons in on each side to make sure that you can see 4 pins in the capsule well of the AEROLIZER Inhaler.

Figure 2

4. Separate one FORADIL capsule blister by tearing at the pre-cut lines. (Figure 3)

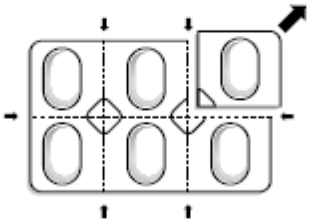


Figure 3

5. Peel the paper backing that covers one FORADIL capsule on the blister card. Push the FORADIL capsule through the foil. (Figure 4)

Figure 4

6. Place the FORADIL capsule in the capsule-chamber in the base of the AEROLIZER Inhaler. **Never place a capsule directly into the mouthpiece.** (Figure 5)

Figure 5

7. Twist the mouthpiece back to the closed position. (Figure 6)

Figure 6

8. Hold the mouthpiece of the AEROLIZER Inhaler upright and press both buttons at the same time. Only press the buttons **ONCE**. You should hear a click as the FORADIL capsule is being pierced. (Figure 7)

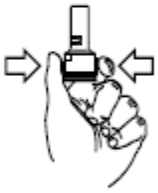


Figure 7

9. Release the buttons. If the buttons stay stuck, grasp the wings on the buttons and pull them out of the stuck position before the next step. Do not push the buttons a second time. This may cause the FORADIL capsule to break into small pieces. There is a screen built into the AEROLIZER Inhaler to hold these small pieces. It is possible that tiny pieces of a FORADIL capsule might reach your mouth or throat when you inhale the medicine. This will not harm you, but to avoid this, only pierce the capsule once. The FORADIL capsules are also less likely to break into small pieces if you store them the right way (See "How do I store FORADIL AEROLIZER?").

10. Breathe out (exhale) fully. **Do not exhale into the AEROLIZER mouthpiece.** (Figure 8)

Figure 8

11. Tilt your head back slightly. Keep the AEROLIZER Inhaler level, with the blue buttons to the left and right (**not up and down**). Place the mouthpiece in your mouth and close your lips around the mouthpiece. (Figures 9 and 10)

Figure 9

Figure 10

12. Breathe in quickly and deeply (Figure 11). This will cause the FORADIL capsule to spin around in the chamber and deliver your dose of medicine. You should hear a whirring noise and experience a sweet taste in your mouth. If you do not hear the whirring noise, the capsule may be stuck. If this occurs, open the AEROLIZER Inhaler and loosen the capsule allowing it to spin freely. **Do not try to loosen the capsule by pressing the buttons again.** (You will have to repeat steps 10 to 12 again to get your dose.)

Figure 11

13. Remove the AEROLIZER Inhaler from your mouth. Continue to hold your breath as long as you can and then exhale.

14. Open the AEROLIZER Inhaler to see if any powder is still in the capsule. If any powder remains in the capsule repeat steps 10 to 13. Most people are able to empty the capsule in one or two inhalations.

15. After use, open the AEROLIZER Inhaler, remove and discard the empty capsule. Do not leave a used capsule in the chamber.

16. Close the mouthpiece and replace the cover.

Appendix 6 Instructions for Use of Ventolin HFA Inhaler

The Parts of Your VENTOLIN HFA Inhaler

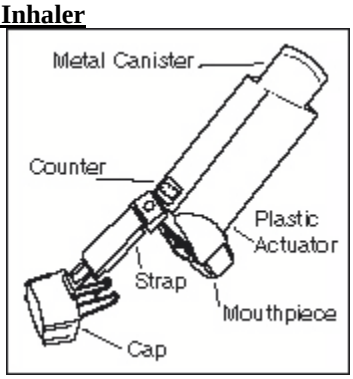


Figure 1

There are 2 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. And 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:

- 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.*
- 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.

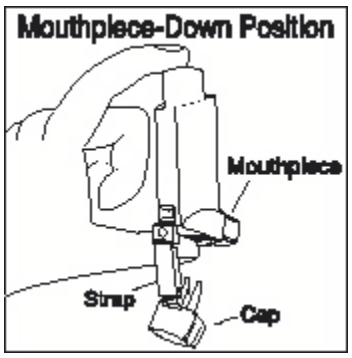


Figure 2

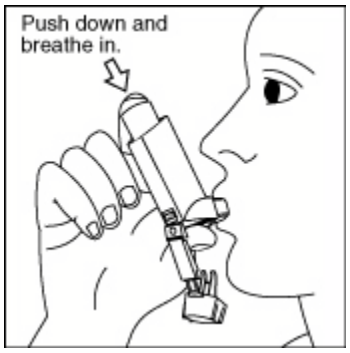


Figure 3

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

- **When the counter reads 020**, you should refill your prescription or ask your doctor if you need another prescription for VENTOLIN HFA.
- **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.
- **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).

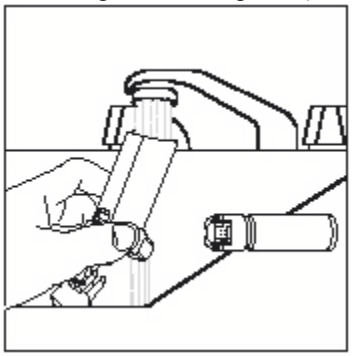


Figure 4

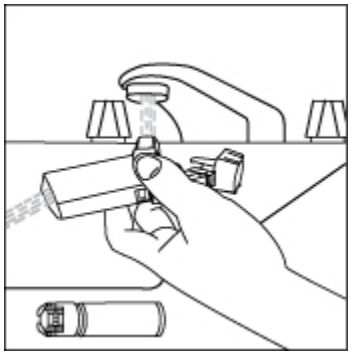


Figure 5

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).

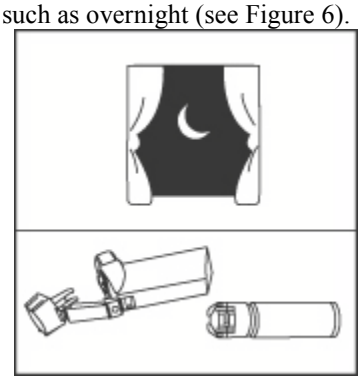


Figure 6

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 1-5.

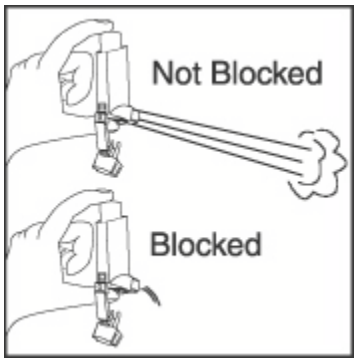


Figure 7

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 Sponsor Signatory

Study Title: A Randomized, Double-Blind, Single Dose, Six-Treatment, Placebo-Controlled, Cross-Over, Multi-Center Study to Assess Efficacy and Safety of Three Doses of PT005, in Patients with Moderate to Severe COPD, Compared with Foradil® Aerolizer® (12 and 24 µg Open-Label) as Active Controls

Study Number: PT005003-00

Final Date: Version 1.0, [redacted]

Amendment 1 Date: N/A

Signature:_____ Date:_____

Name: [redacted]

Title: [redacted]

Appendix 8 Investigator's Ageement and Signature Page

Study Title: A Randomized, Double-Blind, Single Dose, Six-Treatment, Placebo-Controlled, Cross-Over, Multi-Center Study to Assess Efficacy and Safety of Three Doses of PT005, in Patients with Moderate to Severe COPD, Compared with Foradil® Aerolizer® (12 and 24 μg Open-Label) as Active Controls

Study Number: PT005003-00

Final Date: Version 1.0, [redacted]

Amendment 1 Date: N/A

I agree:

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

Signature:_____ Date:_____

Name:_____

Affiliation: _____

_____