12.1.1 PROTOCOL AND PROTOCOL AMENDMENTS

This appendix includes the following approved original protocol and protocol amendments

- Original Protocol – [redacted]
- Protocol Amendment 1 – [redacted]

Clinical Trial Protocol: PT003004-00

Study Title:	A Randomized, Double-Blind, Chronic Dosing (7 Days), Two-Period, Six-Treatment, Incomplete Block, Cross-Over, Multi-Center Study to Assess Efficacy and Safety of Four Doses of GFF MDI in Patients With Moderate to Severe COPD, Compared With Its Individual Components (FF MDI and GP MDI) as Active Controls
Study Number:	PT003004-00
Study Phase:	IIb
Product Name:	Glycopyrrolate and Formoterol Fumarate Inhalation Aerosol; PT003
IND Number:	107739
Indication:	COPD
Investigators:	Multicenter
Sponsor:	Pearl Therapeutics, Inc. [redacted]
Sponsor Contact:	[redacted]

	Version Number	Date
Original Protocol	Version 1.0	[redacted]

SYNOPSIS

Sponsor:
Pearl Therapeutics

Names of Finished Products:
Glycopyrrolate and Formoterol Fumarate Inhalation Aerosol; Glycopyrrolate and Formoterol Fumarate Metered Dose Inhaler; GFF MDI; PT003
Glycopyrrolate Inhalation Aerosol; Glycopyrrolate Metered Dose Inhaler; GP MDI; PT001
Formoterol Fumrate Inhalation Aerosol; Formoterol Fumarate Metered Dose Inhaler; FF MDI; PT005

Name of Active Ingredients:
Glycopyrrolate and Formoterol Fumarate
Glycopyrrolate
Formoterol Fumarate

Study Title:
A Randomized, Double-Blind, Chronic Dosing (7 Days), Two-Period, Six-Treatment, Incomplete Block, Cross-Over, Multi-Center Study to Assess Efficacy and Safety of Four Doses of GFF MDI in Patients With Moderate to Severe COPD, Compared With Its Individual Components (FF MDI and GP MDI) as Active Controls

Study Number: PT003004-00

Study Phase: IIb

Study Objective(s):

Primary objective:
The primary objective of this study is to demonstrate efficacy of GFF MDI relative to its individual components (GP MDI and FF MDI) in patients with moderate to severe COPD within the range of doses evaluated in this protocol. To this end, the primary efficacy endpoint, FEV_1 AUC_{0-12}, will be compared for each dose of GFF MDI relative to its individual components Glycopyrrolate Metered Dose Inhaler (GP MDI 36µg ex-actuator, BID) and Formoterol Fumarate Metered Dose Inhaler (FF MDI 9.6 µg ex-actuator, BID).

Secondary Objectives:
The secondary objective of the study is to characterize the dose-response curve for GFF MDI. The primary and secondary endpoints identified in Section 3.1 will be assessed for GFF MDI given as a twice-daily administration as compared to GP MDI and FF MDI.

Safety Objective:
The safety objective is to evaluate the safety of GFF MDI (36/7.2, 36/9.6, 18/9.6, and 9/9.6 µg ex-actuator, BID) in patients with moderate to severe COPD compared with GP MDI (36 µg ex-actuator, BID) and FF MDI (9.6 µg ex-actuator, BID). Safety will be assessed by adverse events (AEs), physical examination findings, assessments of dry mouth and tremor, monitoring for paradoxical bronchospasm, vital signs, electrocardiograms (ECGs), and laboratory assessments.

Study Design:

This is a randomized, double-blind, chronic dosing (7 days), two-period, six-treatment, balanced incomplete block, cross-over, multi-center study to assess efficacy and safety of four doses of GFF MDI (36/7.2, 36/9.6, 18/9.6, and 9/9.6 µg ex-actuator, BID) in patients with moderate to severe COPD, compared with its individual components, GP MDI (36 µg ex-actuator, BID) and FF MDI (9.6 µg ex-actuator, BID), as active controls.

This multi-center study will be conducted at approximately 10-15 sites, contributing approximately 10 to 15 patients per site in the United States. Across these sites, it is planned that approximately 175 patients with moderate to severe COPD will be randomized into the study to provide approximately 150 patients to complete the study. The entire study period is scheduled to take a maximum of 9 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 175 patients with moderate to severe COPD will be enrolled to provide approximately 150 patients to complete the study.

Test Product, Dose, and Mode of Administration:
Investigational materials will be provided by Pearl Therapeutics as summarized in the table below.

Product Name and Potency	Product Strength	Dosage Form	Comments
GFF MDI 36/7.2 µg ex-actuator	GFF MDI 18/ 3.6 µg per actuation	MDI	Taken as 2 inhalations.
GFF MDI 36/9.6 µg ex-actuator	GFF MDI 18/ 4.8 µg per actuation	MDI	Taken as 2 inhalations.
GFF MDI 18/9.6 µg ex-actuator	GFF MDI 9/4.8 µg per actuation	MDI	Taken as 2 inhalations.
GFF MDI 9/9.6 µg ex-actuator	GFF MDI 4.5/4.8 µg per actuation	MDI	Taken as 2 inhalations.
GP MDI 36 µg ex-actuator†	GP MDI 18 µg per actuation	MDI	Taken as 2 inhalations.
FF MDI 9.6 µg ex-actuator†	FF MDI 4.8 µg per actuation	MDI	Taken as 2 inhalations.
Albuterol Sulfate inhalation aerosol 90 µg ex-actuator§	US source: (Ventolin HFA) Each inhalation contains 108 µg corresponding to 90 µg albuterol base per actuation	MDI	Supplies are open-label.

FF MDI = Formoterol Fumarate Metered Dose Inhaler; GFF MDI = Glycopyrrolate and Formoterol Fumarate Metered Dose Inhaler; GP MDI = Glycopyrrolate Metered Dose Inhaler; MDI = Metered Dose Inhaler.
† Active control
§ Rescue medication during treatment periods.
Note: All study test medications will be administered by oral inhalation.

Duration of Treatment:
Each patient will receive 7 days of study treatment with each of their assigned treatments for a total of 2 separate treatment periods. A washout period of at least 7 days (up to 21 days) will occur between each treatment period. The entire study is scheduled to take a maximum of 9 weeks for each individual patient from the time of screening (see Figure 1).

Efficacy Assessments:
All efficacy assessments are relative to baseline, and will be compared with the individual components as active controls. Since pre-dose values are known to be variable, and an isolated time-point may not accurately reflect the true baseline, the following baseline will be used for statistical analyses unless otherwise specified for exploratory endpoints: the mean of available pre-dose values on the first day of each treatment cycle, i.e., the mean of pre-dose values at Visits 2 and 4, where the mean of the -60 and -30 minute value for each visit day is averaged and then both visit means are averaged. Previous studies showed that this average baseline was a more effective covariate than with the mean of pre-dose values on the current day, or the mean of pre-dose values during Visit 2 alone.

Primary Efficacy Endpoint Evaluated on Treatment Day 7 (Visits 3 and 5, following chronic dosing):

- Forced expiratory volume in 1 second area under the curve (FEV_1 AUC_{0-12}) relative to baseline following chronic dosing (1 week). 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:
Secondary Endpoints Evaluated on Treatment Day 1 (Visits 2 and 4) Relative to Baseline Defined as Average of Pre-Dose Values Across Visits 2 and 4*:*

- Peak change from baseline in FEV_1 (defined as change at highest value of FEV_1 post-dose)
- Time to onset of action (≥10% improvement in FEV_1 relative to baseline)
- Proportion of patients achieving ≥ 12% improvement in FEV_1 relative to baseline
- Peak change in Inspiratory Capacity (IC) (mean of 1 and 2 hour post-dose)

Secondary Endpoints Evaluated on Treatment Day 7 (Visits 3 and 5, following chronic dosing):

- Change from baseline in morning pre-dose FEV_1, defined as the average of the 60 and 30 minute pre-dose values on Treatment Day 7 – Baseline, defined as the average across Visits 2 and 4.
- Peak change from baseline in FEV_1 (defined as highest value of FEV_1 post-dose) where baseline is defined as the average of pre-dose values across Visits 2 and 4.

- Peak change from baseline in IC (mean of 1 and 2 hours post-dose assessments) where baseline is defined as the average IC pre-dose values across Visits 2 and 4.
- 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), where baseline is defined as the average of FEV_1 pre-dose values across Visits 2 and 4.
- Change from baseline morning (A.M.) pre-dose daily peak flow readings taken by subjects, during each treatment period (excluding reading taken pre-dose on Visit 2 (Treatment 1 Day 1), where baseline is defined as the pre-dose measurement on Treatment Day 1. Baseline is taken with the home instrument.
- Change from baseline morning (A.M.) post-dose daily peak flow readings taken by subjects, during each treatment period (excluding reading taken pre-dose on Visit 2 (Treatment 1 Day 1), where baseline is defined as the pre-dose measurement on Treatment Day 1. Baseline is taken with the home instrument.
- Change from baseline evening (P.M.) pre-dose daily peak flow readings taken by subjects, during each treatment period, where baseline is defined as the pre-dose measurement on Treatment Day 1. Baseline is taken with the home instrument.
- Change from baseline evening (P.M.) post-dose daily peak flow readings taken by subjects, during each treatment period, where baseline is defined as the pre-dose measurement on Treatment Day 1. Baseline is taken with the home instrument.

Exploratory Endpoints Evaluated on Treatment Day 7 (Visits 3 and 5, following chronic dosing):

- Peak expiratory flow rate (PEFR) AUC_{0-12} and change from baseline by post-dose time point. AUC will be normalized by dividing by time so that the units of AUC will be L. Baseline is average of PEFR pre-dose values across Visits 2 and 4.
- Forced vital capacity (FVC) AUC_{0-12} and change from baseline by post-dose time point. AUC will be normalized by dividing by 12 so that the units of AUC will be L. Baseline is average of pre-dose FVC values across Visits 2 and 4.
- Change from baseline for mean morning trough IC (mean of -60 and -30 min pre-dose), where baseline is the average of pre-dose IC values across Visits 2 and 4.
- Change from baseline for mean evening trough IC (mean of 11.5 and 12 hours post-dose), where baseline is the average of IC pre-dose values across Visits 2 and 4.
- Mean number of puffs of rescue medication recorded in patient diaries, during each treatment period and by treatment and number of days treated.

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

Statistical Methods:

Sample Size Determination: Power calculations were based on the properties of the primary endpoint, FEV_1 $AUC_{0-12,}$ on the last day of each dosing period following administration of the study drug. Estimates of within subject standard deviation of FEV_1 AUC_{0-12} were obtained from published studies (D'Urzo et al, 2001; van Noord et al, 2005; Maesen et al 1995). A composite within-subjects variance component of 0.13L was adopted. A between-subjects variance component of FEV_1 AUC_{0-12} was obtained from Dahl et al, 2001 and from Calverley et al, 2003. A composite value of 0.13 L was adopted. This represents a total standard deviation of 0.18 L. Note that variance components here are expressed as the standard deviation of the relevant random effect (not the variance). Between and within patients variance components were assumed to have standard deviations of 0.13 L.

The standard error of each contrast was calculated, assuming a generalized least squares analysis in which the ratio of between and within patient variance components was known. The generalized least squares estimates also assumed spherical errors. This is an approximation to the standard error of the REML estimates. It was assumed that there are no carryover effects. The non-centrality parameter of the t-test was calculated, assuming the standard error from the generalized least squares analysis, and a difference of 0.1 L (the minimally clinically significant difference). A sample size of 150 patients achieves 91% power (assuming a significance test at the 5% level, with no multiplicity adjustment. Approximately 175 patients will be recruited in order to achieve 150 patients completing.

Efficacy Analyses: The primary efficacy analysis involves the comparison of the mean primary efficacy endpoint (FEV_1 AUC_{0-12} relative to baseline) for each combination treatment compared to GP MDI 36 µg ex-actuator and FF MDI 9.6 µg ex-actuator. Baseline 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.

For the primary objective, family-wise Type I error will be controlled as follows:

1. No efficacy or non-inferiority claims will be advanced unless the GFF MDI 36/9.6 µg ex-actuator treatment is statistically significantly superior to both the GP MDI 36 µg ex-actuator and the FF MDI 9.6 µg ex-actuator treatments. Both comparisons must be statistically significant before an improvement over the individual components is claimed for this combination therapy.

2. If an improvement over the individual components is detected for the GFF MDI 36/9.6 µg ex-actuator treatment, then the GFF MDI 36/7.2 µg ex-actuator treatments will be compared with the individual components. Both comparisons with the individual components must be statistically significant before an improvement over the individual components is claimed for

this combination therapy.

3. If an improvement over the individual components is detected for the GFF MDI 36/9.6 µg ex-actuator treatment, then the GFF MDI 18/9.6 µg ex-actuator treatments will be compared with the individual components. Both comparisons with the individual components must be statistically significant before an improvement over the individual components is claimed for this combination therapy.

4. If an improvement over the individual components is detected for the GFF MDI 18/9.6 µg ex-actuator treatment, then the GFF MDI 9/9.6 µg ex-actuator treatments will be compared with the individual components. Both comparisons with the individual components must be statistically significant before an improvement over the individual components is claimed for this combination therapy.

Secondary and exploratory efficacy analysis will involve the same comparisons on secondary efficacy endpoints. For endpoints other than time to onset and puffs of rescue medication from diary entries, these comparisons will be performed using the same mixed model and the same algorithms as for the primary efficacy objective. Hierarchical testing will not be imposed for secondary endpoints. For time to onset, comparisons will be based on Murray's method for weighted Kaplan-Meier statistics for paired data (Murray, 2001). The number of puffs of rescue mediation will be summarized using descriptive statistics only.

Safety analyses: Safety analyses will be based on descriptive statistics for ECG, vital sign and laboratory measurements as appropriate, and also on frequencies of adverse events and the number of patients reporting an adverse event.

Statistical Analysis Plans: All statistical analyses will be documented 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 [redacted]

Date of Original Approved Protocol: [redacted]

Date of Most Recent Protocol Amendment (if applicable): [redacted]

Prepared in: [redacted]

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AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATS	American Thoracic Society
AUC	Area under the curve
AV	Atrioventricular block
BID	bis in die, twice daily
BMP	Basic Metabolic Panel
BP	Blood Pressure
BPM	Beats per minute
BTPS	Body Temperature and Pressure Saturated
BUN	Blood urea nitrogen
$CaCl_2$	Calcium chloride
CFR	Code of Federal Regulations
CIR	Cumulative incidence ratio
CMP	Comprehensive Metabolic Panel
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case report form
CRO	Contract Research Organization
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
IC	Inspiratory Capacity
ICF	Informed consent form
ICH	International Conference on Harmonization
ICMJE	International Committee of Medical Journal Editors
ICS	Inhaled Corticosteroid
IEC	Independent Ethics Committee
IM	Intramuscular
IRB	Institutional Review Board
ITT	Intention-to-treat
IUD	Intrauterine device
IV	Intravenous
IWRS	Interactive Web Response System
L	Liter
LABA	Long-acting beta agonist
LAMA	Long-acting antimuscarinic agents
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
PFT	Pulmonary function test
PP	Per protocol
PRN	pro re nata
REML	Residual or restricted maximum likelihood
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
SVC	Slow Vital Capacity
TLC	Total Lung Capacity
TNFα	Tumor necrosis factor α
US	United States

TRADEMARK INFORMATION

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Aerolizer

Atrovent

Dulera

Foradil

Handihaler

PulmoSphere

Robinul

Robinul Forte

Spiriva

Symbicort

Ventolin

1 INTRODUCTION

Pearl Therapeutics is developing a combination product comprising the long acting β_2-agonist (LABA) formoterol fumarate and the long acting muscarcinic antagonist (LAMA) glycopyrrolate (Glycopyrrolate and Formoterol Fumarate Inhalation Aerosol [hereafter referred to as Glycopyrrolate and Formoterol Fumarate Metered Dose Inhaler [MDI] or GFF MDI) for the maintenance treatment of bronchospasm associated with Chronic Obstructive Pulmonary Disease (COPD), including chronic bronchitis and emphysema.

COPD is a disease state characterized by airflow limitation that is not fully reversible. The airflow limitation is usually both progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases (GOLD, 2008). None of the existing medications for COPD have been shown to modify the long-term decline in lung function that is the hallmark of this disease. Therefore, pharmacotherapy for COPD is used to decrease symptoms and/or complications (GOLD, 2008).

Bronchodilator medications are central to the symptomatic management of COPD. The principal bronchodilator treatments are β_2-agonists, anticholinergics, and methylxanthines used as single agents or in combination. Regular treatment with long-acting bronchodilators is more effective and convenient than treatment with short-acting bronchodilators (GOLD, 2008). Combining bronchodilators may improve efficacy and decrease the risk of side effects compared to increasing the dose of a single bronchodilator (GOLD, 2008). Anticholinergics and β_2-agonists reduce bronchoconstriction through different mechanisms and there is a long history of combination therapy for COPD with short-acting agents in these classes.

Formoterol is a potent and selective β_2-agonist approved in many countries worldwide for use in asthma and COPD. In patients with COPD, formoterol is typically administered at an orally inhaled dose of 12 µg twice daily with doses up to 24 µg twice daily approved in some countries. Formoterol is classified as a LABA, although it has a rapid onset of action similar to SABAs. Formoterol is also approved in the United States (US) as part of two combination products, Symbicort® (budesonide and formoterol fumarate dihydrate) and Dulera® (mometasone furoate and formoterol fumarate), for the treatment of COPD and asthma, respectively.

Five large, placebo controlled clinical studies of up to 12 months in duration in nearly 2,500 patients demonstrated that formoterol fumarate is effective and well tolerated in patients with COPD (Dahl, 2001; Rossi, 2002; Aalbers, 2002; Campbell, 2005; Campbell, 2007). Many of the adverse events (AEs) associated with β_2-agonists are pharmacologically predictable (Sears, 2002). Treatment with LABAs can result in tachycardia, arrhythmia, other cardiac AEs (e.g. ischemia, heart failure, cardiomyopathy), tremor, and metabolic imbalances, such as decreased serum potassium levels or increased glucose levels. Formoterol fumarate has been well tolerated in placebo-controlled studies, demonstrating a safety profile similar to placebo (Aalbers, 2002; Dahl, 2001; Campbell, 2005; and Rossi, 2002). In addition, a placebo-controlled cardiovascular safety study in over 200 patients with COPD demonstrated that formoterol fumarate had a good cardiovascular safety profile (Campbell, 2007).

Glycopyrrolate (Robinul® and Robinul Forte®) is an anticholinergic drug that is marketed in Australia and New Zealand as a parenteral formulation and in the US in both oral and parenteral formulations. Glycopyrrolate is a quaternary ammonium derivative that when inhaled results in minimal mucosal absorption and systemic side effects. Glycopyrrolate is not approved for respiratory inhalation. However, another anticholinergic drug, tiotropium bromide (Spiriva®), is licensed in the US, Europe (Hansel, 2002) and Australia (eMIMS 2008) as a powder for inhalation. It has been shown to reduce the rate of COPD exacerbations and to improve the effectiveness of pulmonary rehabilitation (Niewoehner, 2005; Casaburi, 2005).

Although glycopyrrolate is not approved for administration via inhalation, there is a large body of published data evaluating the safety and efficacy of inhaled glycopyrrolate in healthy volunteers, patients with COPD, and patients with asthma that support its safety. Inhaled glycopyrrolate has been safely administered to over 550 patients with COPD. The safety and efficacy of chronic daily administration are supported by two large, well-conducted, dose-ranging studies of 28 days duration that evaluated doses up to 240 µg administered via a dry powder inhaler (Kuna, 2007; Vogelmeier, 2008).

Pearl Therapeutics has recently completed clinical studies with its LABA/LAMA formulation (GFF MDI; Studies PT0030901 and PT0031002) as well as Phase IIa dose-ranging studies in patients with COPD with each of the individual component products (Formoterol Fumarate MDI [FF MDI] and Glycopyrrolate MDI [GP MDI]; Studies PT0050801 and PT0010801).

Study PT0030901 was a single center, randomized, double-blind, 4-period cross over study evaluating 4 single-dose inhaled treatments (GP MDI 72 µg, FF MDI 9.6 µg, and GFF MDI 72/9.6 µg delivered individually and GP MDI 72 µg and FF MDI 9.6 µg delivered together in separate inhalers) in healthy subjects. The objectives of this study were to evaluate safety and pharmacokinetics (PK) following each treatment. A total of 16 subjects were enrolled, 13 of whom completed the study. All 4 treatments were safe and well-tolerated in this study. Overall, the most frequently reported AEs were headache and dry mouth. No serious adverse events (SAEs) or AEs leading to withdrawal occurred following any treatment, and no clinically significant changes were noted in QTc values, vital signs, laboratory values, or serum potassium values.

Study PT0031002 was a randomized, double-blind, chronic dosing (7 days), four-period, eight-treatment, placebo and active-controlled, customized, unbalanced, incomplete block crossover multi-center study that evaluated the efficacy, safety and PK of two doses of GFF MDI (72 µg/9.6 µg and 36 µg/9.6 µg twice daily), two doses of FF MDI (9.6 µg and 7.2 µg twice daily) and one dose of GP MDI (36 µg twice daily) in patients with moderate to very severe COPD, compared to placebo, Foradil® Aerolizer® (12 µg twice daily, open label) and Spiriva® Handihaler® (18 µg once daily, open label) as active controls. No substantial differences were noted between any of the active treatments and placebo in terms of common AEs, SAEs, and AEs leading to withdrawal. The most commonly reported AEs (≥ 5% of subjects) overall were dry mouth, headache, COPD worsening, cough, and tremor. No deaths were reported in the study. Five subjects reported a total of 6 SAEs, none of which

were attributed to study treatment: inhaled foreign body, COPD exacerbation (for which the subject was withdrawn), ruptured appendix, atypical chest pain (for which the subject was withdrawn), and gastritis and abdominal aortic aneurysm reported in one subject. A total of 11 subjects were withdrawn from the study due to AEs: 8 subjects experienced COPD (increase/exacerbation); 2 subjects experienced lower respiratory tract infection (chest infection); and 1 subject experienced chest pain. All AEs leading to subject discontinuation from the study were considered unrelated to study treatment with the exception of one event of lower respiratory tract infection reported in 1 subject considered possibly due to treatment with FF MDI 9.6 µg. No clinically significant changes were noted in QTc values, vital signs, laboratory values, or serum potassium values.

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. The primary objective was to evaluate the safety and tolerability of FF MDI at doses of 2.4, 4.8, and 9.6 µg compared to placebo MDI and Foradil Aerolizer 12 µg. A total of 34 patients were enrolled, 29 of whom received all 5 treatments. 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. Changes in laboratory values and vital signs were generally small, and no important trends were noted for FF MDI at any dose. Headache was the most frequently reported AE with FF MDI treatment (5 events following 2.4 µg, 1 following 9.6 µg, 2 following Foradil Aerolizer, and 2 following placebo) followed by dyspnea (1 event following 2.4 µg, 1 following 4.8 µg, 1 following Foradil Aerolizer, and 2 following placebo). Two cases of migraine were reported in 1 patient following treatment with FF MDI 9.6 µg; however, this patient also reported a case of migraine at Screening prior to receiving any treatment. Two SAEs were reported, one following placebo (small intestinal obstruction) and one following FF MDI 4.8 µg (exacerbation of COPD); neither were deemed related to study drug by the Investigator. Two additional AEs resulted in withdrawal of the patient from the study: moderate dyspnea following treatment with Foradil Aerolizer 12 µg, and mild atrial fibrillation following treatment with placebo; both of these events were considered not related or unlikely related to study drug by the investigator. One patient experienced mild tremor following FF MDI 9.6 µg treatment.

Study PT0010801 was a randomized, double-blind, single ascending dose, four-period, six-treatment, balanced, incomplete block, cross-over, placebo and active-controlled, multi-center study that was conducted in patients with mild to severe COPD deemed clinically stable by their physician. The primary objective was to evaluate the efficacy and safety of four doses of GP MDI (18, 36, 72, and 144 µg) compared to placebo MDI and Spiriva Handihaler 18 µg. A total of 33 patients were enrolled, 30 of whom completed the study per protocol. No substantial differences were noted between the GP MDI treatment groups and placebo or Spiriva on any other safety parameter. Dry mouth was the most frequently reported AE with GP MDI treatment, although a clear dose relationship was not observed. Oropharyngeal pain was reported in 2 patients following Glycopyrrolate MDI treatment (18 µg and 144 µg). Changes in laboratory values, vital signs, and ECG parameters were generally small, and no important trends were noted for GP MDI at any dose compared to

placebo or Spiriva. No deaths, SAEs or AEs leading to withdrawal occurred during the study. One death due to complications of COPD occurred outside of the protocol specified reporting period (>30 days from last dose) and was deemed not related to study drug by the investigator.

Note: Unless otherwise indicated, throughout this document all references to doses of GFF MDI will be to the ex-actuator or "delivered" doses (36/7.2, 36/9.6, 18/9.6, and 9/9.6 µg); all references to the FF MDI dose will be to the ex-actuator or "delivered" doses (9.6 µg); all references to the GP MDI dose will be to the ex-actuator or "delivered" doses (36 µg); all references to doses of Ventolin HFA (albuterol sulfate inhalation aerosol) will be to the ex-actuator or "delivered" doses (90 µg).

1.1 Study Rationale

The GOLD guidelines and published literature support the rationale for developing a combination product containing a long-acting β_2-agonist and an anticholinergic in a single device.

Formoterol is a well-established and extensively tested LABA that is clinically indicated for the management of COPD. Glycopyrrolate is under clinical investigation for patients with asthma and patients with COPD. Pearl Therapeutics's clinical studies with the combination of formoterol fumarate and glycopyrrolate (GFF MDI) demonstrated superior efficacy to the individual components (GP MDI and FF MDI), Spiriva, and Foradil for change in FEV_1 AUC_{0-12} after 1 week of dosing. GFF MDI was safe and well-tolerated with a safety profile comparable to Spiriva and Foradil. These data support the further evaluation of GFF MDI in the management of patients with COPD.

Novel technology based on spray-dried porous particles comprised of distearoylphophatidylcholine (DSPC) and $CaCl_2$ that are cosuspended with crystalline active drug substances and formulated into suspension-based hydrofluoroalkane (HFA) MDIs has enabled the development of Glycopyrrolate and Formoterol Fumarate either alone or as fixed combination MDI products, 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 Glycopyrrolate and Formoterol Fumarate either alone or as fixed combination MDI products in this porous particle platform for the long-term, twice daily, maintenance treatment of bronchospasm associated with COPD, including chronic bronchitis and emphysema.

In the development of a combination product, the optimal dose of the individual components needs to be established and then the combination product is compared to the individual components in order to meet the combination rule as outlined in Title 21 CFR Part 300.50. However, in parallel to the dose ranging studies for the individual components, data with the combination product can also provide useful information to aid in dose selection and in the evaluation of efficacy and safety in further studies.

To this end, this study will dose range glycopyrrolate on a fixed background of formoterol fumarate 9.6 µg (GFF MDI 9/9.6, 18/9.6, and 36/9.6 µg versus FF MDI 9.6 µg) to assess the incremental benefit offered by each successive dose. Similarly, this study will assess the incremental benefit of formoterol fumarate on a fixed background of glycopyrrolate 36 µg (GFF MDI 36/7.2 and 36/9.6 µg versus GP MDI 36 µg).

In Study PT0031002, comparable efficacy results were demonstrated for GFF MDI 36/9.6 µg and GFF MDI 72/9.6 µg administered twice daily, thus GFF MDI 36/9.6 µg and lower doses (GFF MDI 18/9.6 and 9/9.6 µg) administered twice daily will be further evaluated in this study. The results from Study PT0031002 also demonstrated that both FF MDI doses (7.2 and 9.6 µg) were non-inferior to Foradil Aerolizer 12 µg for the primary endpoint, FEV_1 AUC_{0-12} at Day 7, (mean difference = -24mL, 90% CI: -62, +15 mL and mean difference = -16 mL, 95% CI: -54, +22 mL, respectively) with only FF MDI 9.6 µg demonstrating bioequivalence from a PK perspective with Foradil Aerolizer 12 µg. These data further support the inclusion of 9.6 µg of formoterol fumarate in the combination product, GFF MDI, and also support the inclusion of 7.2 µg of formoterol fumarate in the combination product to evaluate whether the addition of 7.2 µg of formoterol fumarate to 36 µg of glycopyrrolate (GFF MDI 36/7.2 µg) provides benefit.

Since the mean half-life of GP MDI, FF MDI and GFF MDI is less than 12 hours, a 1-week treatment period should ensure that steady state conditions are achieved. Similarly, a minimum of a 1-week (i.e., more than 10 half-lives) washout period between treatments should ensure that there is no residual carry over effect from one treatment period to another.

The duration of exposure to GFF, GP, and FF MDIs in this study is supported by 14-day toxicology studies in rats and dogs conducted in compliance with Good Laboratory Practices regulations that include a full range of safety assessments including recovery groups, toxicokinetics and abbreviated safety pharmacology. In addition, weekly exposure to PulmoSpheres® in rats and dogs for up to 6 months has demonstrated the safety of the porous particle platform (summarized in the Investigator's Brochure).

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of this study is to demonstrate efficacy of GFF MDI relative to its individual components (GP MDI and FF MDI) in patients with moderate to severe COPD within the range of doses evaluated in this protocol. To this end, the primary efficacy endpoint, FEV_1 AUC_{0-12}, will be compared for each dose of GFF MDI relative to its individual components Glycopyrrolate Metered Dose Inhaler (GP MDI 36 µg ex-actuator, BID) and Formoterol Fumarate Metered Dose Inhaler (FF MDI 9.6 µg ex-actuator, BID).

2.2 Secondary Objectives

The secondary objective of the study is to characterize the dose-response curve for GFF MDI. The primary and secondary endpoints identified in Section 3.1 will be assessed for GFF MDI given as a twice-daily administration as compared to GP MDI and FF MDI.

2.3 Safety Objective

The safety objective is to evaluate the safety of GFF MDI (36/7.2, 36/9.6, 18/9.6, and 9/9.6 µg ex-actuator, BID) in patients with moderate to severe COPD compared with GP MDI (36 µg ex-actuator, BID) and FF MDI (9.6 µg ex-actuator, BID). Safety will be assessed by adverse events (AEs), physical examination findings, assessments of dry mouth and tremor, monitoring for paradoxical bronchospasm, vital signs, electrocardiograms (ECGs), and laboratory assessments.

3 STUDY ENDPOINTS

3.1 Efficacy Endpoints

All efficacy assessments are relative to baseline, and will be compared with the individual components as active controls. Since pre-dose values are known to be variable, and an isolated time-point may not accurately reflect the true baseline, the following baseline will be used for statistical analyses unless otherwise specified for exploratory endpoints: the mean of available pre-dose values on the first day of each treatment cycle, i.e., the mean of pre-dose values at Visits 2 and 4, where the mean of the -60 and -30 minute value for each visit day is averaged and then both visit means are averaged. Previous studies showed that this average baseline was a more effective covariate than with the mean of pre-dose values on the current day, or the mean of pre-dose values during Visit 2 alone.

3.1.1 Primary Efficacy Endpoint

Primary Efficacy Endpoint Evaluated on Treatment Day 7 (Visits 3 and 5, following chronic dosing):

- Forced expiratory volume in 1 second area under the curve (FEV_1 AUC_{0-12}) relative to baseline following chronic dosing (1 week). 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 Efficacy Endpoints

Secondary Endpoints Evaluated on Treatment Day 1 (Visits 2 and 4) Relative to Baseline Defined as Average of Pre-Dose Values Across Visits 2 and 4:

- Peak change from baseline in FEV_1 (defined as change at the highest value of FEV_1 post-dose)
- Time to onset of action (≥10% improvement in FEV_1 relative to baseline)
- Proportion of patients achieving ≥ 12% improvement in FEV_1 relative to baseline
- Peak change in Inspiratory Capacity (IC) (mean of 1 and 2 hour post-dose)

Secondary Endpoints Evaluated on Treatment Day 7 (Visits 3 and 5, following chronic dosing):

- Change from baseline in morning pre-dose FEV_1 , defined as the average of the 60 and 30 minute pre-dose values on Treatment Day 7 – Baseline, defined as the average across Visits 2 and 4.
- Peak change from baseline in FEV_1 (defined as highest value of FEV_1 post-dose) where baseline is defined as the average of pre-dose values across Visits 2 and 4.

- Peak change from baseline in IC (mean of 1 and 2 hours post-dose assessments) where baseline is defined as the average IC pre-dose values across Visits 2 and 4.
- 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), where baseline is defined as the average of FEV1 pre-dose values across Visits 2 and 4.
- Change from baseline morning (A.M.) pre-dose daily peak flow readings taken by subjects, during each treatment period (excluding reading taken pre-dose on Visit 2 (Treatment 1 Day 1), where baseline is defined as the pre-dose measurement on Treatment Day 1. Baseline is taken with the home instrument.
- Change from baseline morning (A.M.) post-dose daily peak flow readings taken by subjects, during each treatment period (excluding reading taken pre-dose on Visit 2 (Treatment 1 Day 1), where baseline is defined as the pre-dose measurement on Treatment Day 1. Baseline is taken with the home instrument.
- Change from baseline evening (P.M.) pre-dose daily peak flow readings taken by subjects, during each treatment period, where baseline is defined as the pre-dose measurement on Treatment Day 1. Baseline is taken with the home instrument.
- Change from baseline evening (P.M.) post-dose daily peak flow readings taken by subjects, during each treatment period, where baseline is defined as the pre-dose measurement on Treatment Day 1. Baseline is taken with the home instrument.

3.1.3 Other/Exploratory Endpoints

Exploratory Endpoints Evaluated on Treatment Day 7 (Visits 3 and 5, following chronic dosing):

- Peak expiratory flow rate (PEFR) AUC_{0-12} and change from baseline by post-dose time point. AUC will be normalized by dividing by time so that the units of AUC will be L. Baseline is average of PEFR pre-dose values across Visits 2 and 4.
- Forced vital capacity (FVC) AUC_{0-12} and change from baseline by post-dose time point. AUC will be normalized by dividing by 12 so that the units of AUC will be L. Baseline is average of pre-dose FVC values across Visits 2 and 4.
- Change from baseline for mean morning trough IC (mean of -60 and -30 min pre-dose), where baseline is the average of pre-dose IC values across Visits 2 and 4.
- Change from baseline for mean evening trough IC (mean of 11.5 and 12 hours post-dose), where baseline is the average of IC pre-dose values across Visits 2 and 4.
- Mean number of puffs of rescue medication recorded in patient diaries, during each treatment period and by treatment and number of days treated.

3.2 Safety Endpoints

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

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

This is a randomized, double-blind, chronic dosing (7 days), two-period, six-treatment, balanced incomplete block, cross-over, multi-center study to assess efficacy and safety of four doses of GFF MDI (36/7.2, 36/9.6, 18/9.6, and 9/9.6 µg ex-actuator, BID) in patients with moderate to severe COPD, compared with its individual components, GP MDI (36 µg ex-actuator, BID) and FF MDI (9.6 µg ex-actuator, BID), as active controls.

This multi-center study will be conducted at approximately 10-15 sites, contributing approximately 10 to 15 patients per site in the United States. Across these sites, it is planned that approximately 175 patients with moderate to severe COPD will be randomized into the study to provide approximately 150 patients to complete the study (see Study Flow Diagram). The entire study period is scheduled to take a maximum of 9 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 Inhalation Aerosol (Ventolin HFA) will be assessed at Screening to characterize the patient population but will not be used to determine eligibility to participate in the study. Patients who are not using a prohibited medication and meet all other entry criteria will return to the clinic at least 7 days (≥2 weeks if taking tiotropium) after screening for Visit 2 (Randomization).

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 1 week (at least 2 weeks if taking tiotropium or phosphodiesterase inhibitors), but not greater than 28 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 (e.g. follow-up on missing chest x-ray or CT scan) at a second Screening visit (Visit 1b) at the investigator's discretion.

At Visit 2 (Randomization Visit; Treatment [Rx] 1, Day 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 30 sequences. Each sequence will include exactly 2 of the 6 treatment groups included in this study. On every treatment day the patient, clinical site personnel and Pearl Therapeutics will be unaware of the treatment to be assigned that day.

Randomization will be centralized, through the use of an IWRS (Interactive Web Response System). All study test medications will be administered twice daily. Each of the 2 treatments will be administered for 7 days with a washout period of at least 7 days (up to 21 days) in between treatments.

During Visit 2 (Rx 1, Day 1), patients will be dispensed study medication and will administer their first 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). Patients will then be discharged from the clinic and will continue to administer study medication for 1 week at home.

Patients will return to the clinic following 1 week of treatment for Visit 3 (Rx 1, Day 7) at approximately the same time as Visit 2 (± 2 hours). Patients will receive their last dose of Rx 1 study medication that morning under supervision and will be required to remain at the clinic until completion of all protocol-defined assessments (see Table 6). Following discharge, patients will undergo a study medication washout period of at least 1 week but no more than 3 weeks duration 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 next treatment in their assigned sequence, as follows:

Visit 4 (Rx 2, Day 1): Administer first dose of Rx 2 study medication and remain at the clinic until completion of all protocol-defined assessments (see Table 5). Following discharge, patients will continue daily administration for 1 week.

Visit 5 (Rx 2, Day 7): Administer last dose of Rx 2 study medication and remain at the clinic until completion of all protocol-defined assessments (see Table 6). Following completion of Visit 5, patients should be returned to pre-study or appropriate COPD maintenance medications and return for the final/follow-up visit after at least 7 days but not greater than 14 days.

Visit 6 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.

Every effort must be made to ensure that patients return to the clinic on Day 7 (1 week) following initiation of each treatment arm. To accommodate scheduling conflicts a window of 7 ± 2 days is permitted (i.e., Treatment Day 7 procedures must be done within a minimum of 5 days and a maximum of 9 days from Treatment Day 1). If any patient exceeds 9 days of

treatment for any treatment, Pearl Therapeutics should be notified and the patient may be withdrawn from the study.

A sponsor-provided peak flow meter and appropriate training on the proper use of the device will be provided to the patient at the Screening Visit. Starting at the Screening Visit, patients will receive a diary in which they will be asked to maintain a daily record of their study medication dosing, rescue medication use, and collection of daily peak flow rates using a sponsor-provided portable peak flow meter.

During the treatment periods (between Visits 2 and 3, and Visits 4 and 5), patients will be permitted to use sponsor-provided Ventolin HFA on an as needed basis for relief of COPD symptoms.

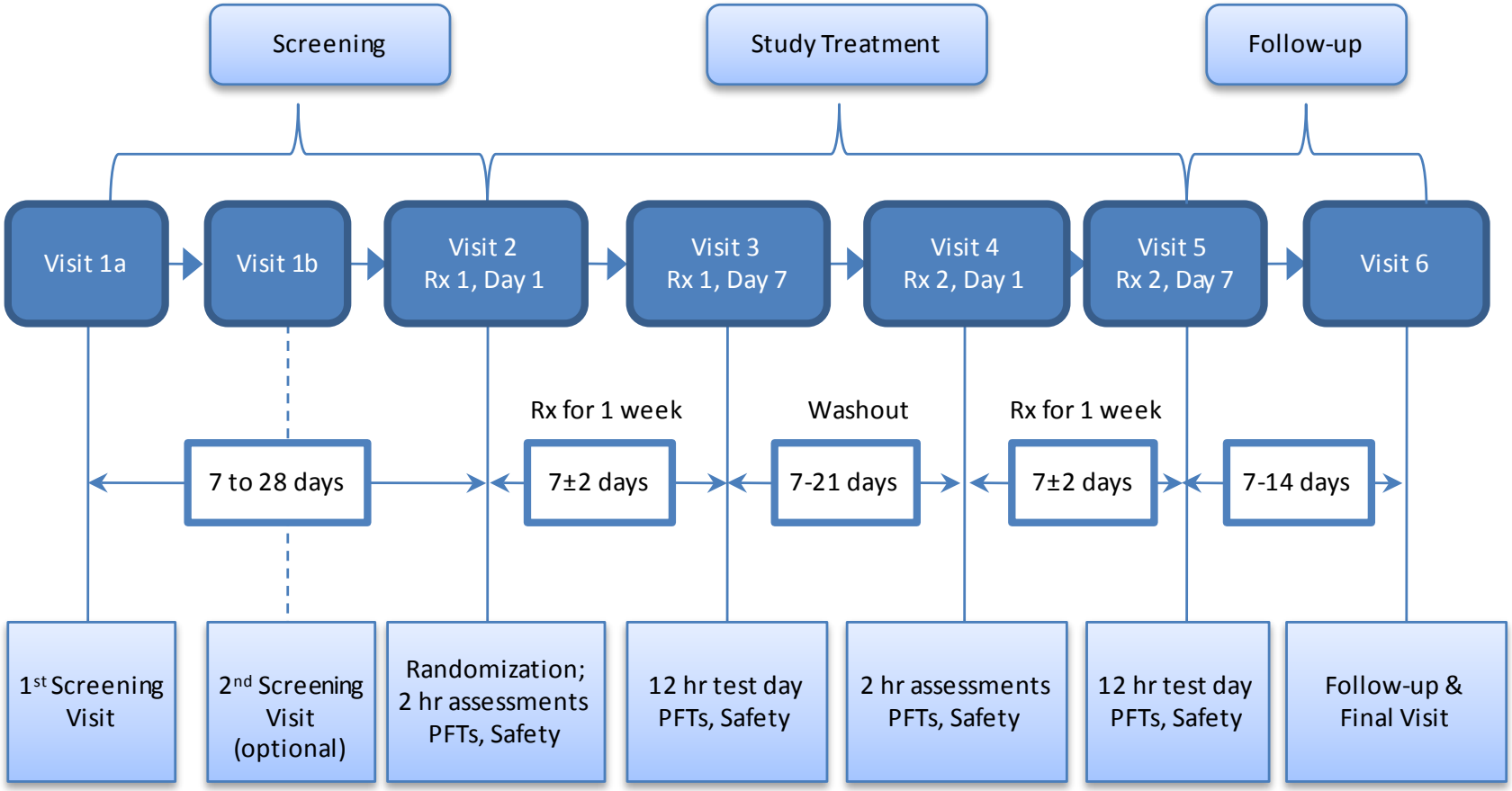
During the washout period when subjects are not taking study drug (between Visits 3 and 4), patients will be permitted to use short-acting bronchodilators (albuterol MDI, Atrovent HFA, or albuterol/ipratropium combination MDI) per the investigator's discretion.

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



PFT = pulmonary function test, Rx = treatment

5 STUDY POPULATION SELECTION AND WITHDRAWAL CRITERIA

5.1 Inclusion Criteria

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

1. Give their signed written informed consent to participate.
2. Are 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 2 years 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 until 2 weeks after Visit 6):
     - Complete abstinence from intercourse from screening until 2 weeks after Visit 6 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. 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 relief of COPD symptoms for at least 1 week prior to randomization and for the duration of the study.
8. 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.
9. Compliance: Patients must be willing to remain at the study center as required per protocol to complete all visit assessments.

5.2 Exclusion Criteria

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

1. 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, glaucoma, symptomatic prostatic hypertrophy (if treated and asymptomatic, the patient is eligible for enrollment), uncontrolled diabetes (random blood glucose > 200 mg/dL at screening), uncontrolled thyroid disease or other endocrine disorders, hematological medical problems, and urinary retention problems [including bladder-neck obstruction (e.g., difficulty passing urine, painful urination)].
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 basal cell carcinoma of the skin and 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, glycopyrrolate or other muscarinic anticholinergics, or any component of the MDI.
17. Substance Abuse: Patients with a known or suspected history of alcohol or drug abuse within the last 2-year period prior to Screening.

18. 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.
19. 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
20. 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.
21. 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.
22. 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.
23. 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.
24. 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.
25. 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.

26. 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.
27. A patient who requires the use of a spacer device to compensate for poor hand-to-breath coordination with a MDI.
28. Patients who were previously enrolled in a Pearl Therapeutics PT001 (Glycopyrrolate MDI), PT005 (Formoterol Fumarate MDI) 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*
- phosphodiesterase 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 corticosteroids 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, Atrovent HFA, 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 formoterol and budesonide will be switched to the corresponding dose of fluticasone, mometasone or budesonide administered as a single agent, with short-acting bronchodilators (albuterol MDI, Atrovent HFA, 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 LAMA (tiotropium) administered alone or as a loose combination will have these medications discontinued and replaced with short-acting bronchodilators (albuterol MDI, Atrovent HFA, or albuterol/ipratropium combination MDI) per the investigator's discretion.

Note: During study treatment (i.e., between Visits 2 and 3, and Visits 4 and 5), patients will receive study drug to be administered twice daily and are only allowed sponsor-provided Ventolin HFA to be used as needed for relief of symptoms. Patients are permitted to resume other short-acting bronchodilators during washout period.

Note: During the screening phase and washout period (i.e., between Visit 3 and 4), Albuterol, Atrovent HFA, or ipratropium/albuterol combination drugs 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 6 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 Interactive Web Response System (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 the Sponsor. 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 and Potency	Product Strength	Dosage Form	Comments
GFF MDI 36/7.2 µg ex-actuator	GFF MDI 18/ 3.6 µg per actuation	MDI	Taken as 2 inhalations.
GFF MDI 36/9.6 µg ex-actuator	GFF MDI 18/ 4.8 µg per actuation	MDI	Taken as 2 inhalations.
GFF MDI 18/9.6 µg ex-actuator	GFF MDI 9/4.8 µg per actuation	MDI	Taken as 2 inhalations.
GFF MDI 9/9.6 µg ex-actuator	GFF MDI 4.5/4.8 µg per actuation	MDI	Taken as 2 inhalations.
GP MDI 36 µg ex-actuator†	GP MDI 18 µg per actuation	MDI	Taken as 2 inhalations.
FF MDI 9.6 µg ex-actuator†	FF MDI 4.8 µg per actuation	MDI	Taken as 2 inhalations.
Albuterol Sulfate inhalation aerosol 90 µg ex-actuator§	US source: (Ventolin HFA) Each inhalation contains 108 µg corresponding to 90 µg albuterol base per actuation	MDI	Supplies are open-label.

FF MDI = Formoterol Fumarate Metered Dose Inhaler; GFF MDI = Glycopyrrolate and Formoterol Fumarate Metered Dose Inhaler; GP MDI = Glycopyrrolate Metered Dose Inhaler; MDI = Metered Dose Inhaler.
† Active control
§ Rescue medication during treatment periods.
Note: All study test medications will be administered by oral inhalation.

For 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 Sponsor as summarized in Table 2. Ventolin HFA supplies will be supplied as open-label MDIs.

Table 2. Packaging of Clinical Supplies

Product Name and Potency	Product Strength	Fill Count	Dosing Instructions
GFF MDI 36/7.2 µg ex-actuator	GFF MDI 18/ 3.6 µg per actuation	1 MDI 120 actuations	Take as directed in the morning and evening.
GFF MDI 36/9.6 µg ex-actuator	GFF MDI 18/ 4.8 µg per actuation	1 MDI 120 actuations	Take as directed in the morning and evening.
GFF MDI 18/9.6 µg ex-actuator	GFF MDI 9/4.8 µg per actuation	1 MDI 120 actuations	Take as directed in the morning and evening.
GFF MDI 9/9.6 µg ex-actuator	GFF MDI 4.5/4.8 µg per actuation	1 MDI 120 actuations	Take as directed in the morning and evening
GP MDI 36 µg ex-actuator[§]	GP MDI 18 µg per actuation	1 MDI 120 actuations	Take as directed in the morning and evening
FF MDI 9.6 µg ex-actuator[§]	FF MDI 4.8 µg per actuation	1 MDI 120 actuations	Take as directed in the morning and evening
Albuterol Sulfate inhalation aerosol 90 µg[†]	US source: (Ventolin HFA) Each inhalation contains 108 µg corresponding to 90 µg albuterol base per actuation	1 MDI 60 or 120 actuations	Use only as directed

[§] Active control
[†] Rescue medication during treatment periods.

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 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 and 4 will be packaged in boxes as outlined in Table 3. Open-label Ventolin HFA supplies will be provided 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 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)
- 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.

Ventolin HFA supplies:

Store at room temperature, 59-77°F (15-25°C), with mouthpiece down. 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

GFF MDI, GP MDI, and FF MDI

Individual GFF, GP, and FF 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 a 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.

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. Patients will be dispensed the MDI and instructed to continue taking study medication twice daily, 2 puffs in the morning and 2 puffs in the evening approximately 12 hours apart, for 7 days at home. The MDI should be stored at room temperature by the patient, avoiding temperature extremes and storage in direct sunlight. See Appendix 3 for instructions on the administration of GFF MDI, GP MDI, and FF MDI.

Ventolin HFA (albuterol sulfate inhalation aerosol)

Bulk supplies of open-label Ventolin HFA will be provided by the sponsor and stored in a secured location within the clinic or pharmacy facilities. Patients will be dispensed Ventolin HFA MDI to take as rescue medication between Visits 2 and 3 and Visits 4 and 5. Ventolin HFA should be stored at room temperature by the patient. Ventolin HFA should be primed per manufacturer's instructions prior to dispensing to patient. See Appendix 4 for the manufacturer's instructions on the administration of Ventolin HFA. Study personnel will record number on the dose counter at the time of dispensing (following priming) and upon return.

6.8 Drug Accountability/Return of Clinical Supplies

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

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

Sites should check with the Pearl Therapeutic 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 on Day 1 (Visits 2 and 4) and Day 7 (Visits 3 and 5) of each treatment period are provided in Table 5 and Table 6, respectively.

All assessments during Visits 2 through 5 will be conducted in the following order: dry mouth and tremor assessments, vital signs, ECGs, clinical laboratory assessments, and spirometry (IC, when conducted should be obtained prior to all other spirometry assessments).

7.1 Efficacy Assessments

Both forced expiratory spirometry for derivation of FEV_1, FVC and PEFR, and Slow Vital Capacity (SVC) maneuvers for IC determination will be assessed using a spirometer that meets or exceeds minimum performance recommendations of the 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., 3.09 L to 2.91 L (ATS/ERS). The results will be printed and maintained in a calibration log, which will be monitored for compliance during the monitoring visits (Refer to Appendix 2, Spirometry Assessment Criteria).

On Day 1 of each treatment period (Visits 2 and 4), spirometry will be conducted 60 minutes and 30 minutes prior to study drug administration. The average of these two assessments will be used to establish test-day baseline FEV_1, FVC and PEFR. **The baseline FEV_1 at Visits 4 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 within 20% of the baseline FEV_1 obtained at Randomization, 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 <u>not</u> 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 investigator's 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 and 2 hours post-dosing of study drug.

On Day 7 of each treatment period (Visits 3 and 5), spirometry will be conducted 60 and 30 minutes prior to study drug administration. The average of these two assessments will be used to establish Day 7 pre-dose FEV_1, FVC, and PEFR. 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. Specifically, FEV_1, FVC and PEFR data will be analyzed for primary and secondary assessments.

On Day 1 of each treatment period (Visits 2 and 4), IC assessments will be obtained at 60 and 30 minutes prior to study drug and at 1 and 2 hours after study drug

On Day 7 of each treatment period (Visits 3 and 5), IC assessments will be obtained at 60 and 30 minutes prior to study drug and at 1, 2, 11.5, and 12 hours after study drug. IC assessments are to precede spirometry assessments.

All patients will be instructed on the performance of the IC maneuver. Subjects must be tested in the seated position wearing a nose clip with no air leaks between the mouth and mouthpiece. Subjects should be relaxed with shoulders down and asked to breathe regularly for several breaths until the end-expiratory lung volume (FRC) is stable (this usually requires at least five tidal maneuvers). They are then urged to take a deep breath to total lung capacity (TLC) with no hesitation. From at least three acceptable trials, the two largest IC measurements should agree within 5% or 100 mL, both of these IC values will be captured and analyzed. Change in peak IC is a secondary endpoint.

7.1.1 Pulmonary Function Tests

All pulmonary function tests including FEV_1, FVC, PEFR, SVC and IC 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 standardized training at the investigator meetings. All technicians are required to demonstrate proficiency in the use of the equipment and the ability to perform technically acceptable 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 7.3 for specific FEV_1 criteria that prompt patients to be discontinued from the study.

7.1.2 Patient Diary

The study coordinator will be responsible for explaining to the patient the proper methods for completing the diary. The diary contains questions concerning actual time of dosing, rescue Ventolin HFA use, and collection of home peak flow measurements using a sponsor-provided home peak flow meter.

Beginning with the Screening Visit (Visit 1) and at Visits 2 and 4, the patient will be given a diary to be completed daily and returned at the next visit. The patient diary will not be dispensed at Visits 3 and 5. Before giving the diary to the patient, the study coordinator will be responsible for entering the patient's identification (screening number [Visit 1] and randomization number [Visits 2 and 4]), and dates of the week(s) the diary is to be completed.

The diary should be completed on the designated dates prefilled by the study site personnel. Upon arriving at the site for Visits 3 and 5, patients will return the diary provided at the previous visit. For example, patients returning for Visit 5 will return the diary given to them at Visit 4.

At or prior to Visit 2 only, patients must demonstrate acceptable use of the diary to be eligible for randomization. Diary data is considered acceptable if the requisite data is completed on at least 4 of 7 consecutive days and patient data would qualify for chronic dosing assessments. Patients who fail their first demonstration of proper diary use may at the investigator's discretion be retrained and Visit 2 rescheduled. Patients who fail to demonstrate proper diary use ≥2 times will be excluded from the study.

The patient is to return the completed diary at each scheduled visit. The study coordinator will be responsible for reviewing the diary for completeness and accuracy with the patient. All data fields should be completed by the patient. The patient will sign (initial) and date each page of the diary on the day it was completed and the study coordinator will initial and date each diary page at the site visit when the diary is returned to validate the authenticity of the entries. If discrepancies or *omissions of data are observed at this review, **the patient**, not the study coordinator, should make the corrections. The patient should draw a single line through the error and initial and date all corrections. The patient should make all entries on the diary card in blue or black ink—**correction fluid or pencil should never be used**. The diary card is considered a source document and should be retained in the appropriate section of the patient binder*.

Furthermore, in conjunction with review of the diary, the patient will be prompted for missed doses of study medication and additional COPD medication. The patient should be instructed to record this information in the diary card. Missing data from >24 hours prior to the site visit should be left blank. Subjects should be instructed to record the time of measurements and doses of study medication and rescue medication in hours and minutes a.m. or p.m., not in 24-hour clock time. P.M. medications taken after midnight but before 6 a.m. on a diary day should be noted as taken on the previous diary day.

7.1.3 Rescue Ventolin HFA Use

The patient will record the total number of "puffs" of rescue Ventolin HFA used on a daily basis. The number of "puffs" of rescue Ventolin HFA to be recorded is the number of actuations of the canister. For example, when rescue Ventolin HFA is required and 2 actuations are inhaled, this should be recorded as 2 "puffs." In the event the patient requires 4

actuations this should be recorded as 4 "puffs." Patients requiring more than 8 puffs per day on 3 or more consecutive days with worsening symptoms should contact the site.

7.1.4 Home Peak Expiratory Flow Rate

The peak flow meter will be provided to all study patients for measurement of PEFR at home. Under supervision and with coaching from the site staff, the patient will be instructed to perform peak expiratory flow efforts using the peak flow meter at Visit 1.

The peak flow meter will be used by all patients for home measurements of pre- and post-dose morning and evening assessments. At each study visit, the site will download data from the home peak flow meter onto a laptop provided by [redacted]. The investigator or designee will print a copy of the PEFR readings and review. Any findings will be discussed with the patient and clinical relevance determined. Patients will bring their peak flow meter to the clinic at each visit.

On each day starting with Day 1 of each treatment, the patient will measure PEFR immediately before and 30 minutes after dosing with study medication. Note: The 30 minute post-dose PEFR on Day 1 should be obtained after spirometry assessments allowing enough time for the patient to recover from the pulmonary function test maneuvers. The patient will be instructed to forcefully exhale from total lung capacity 3 times into the peak flow meter and confirm the collection of PEFR measurements on the diary card.

7.1.5 Medication Compliance

Time of dosing with study medication will be recorded in the patient diary for each day of treatment. Study medication compliance will be checked at all visits and any issues identified will be noted in the appropriate study files.

7.2 Safety Assessments

The safety assessments include ECGs, vital signs, physical examination findings, clinical laboratory tests, monitoring for paradoxical bronchospasm, and assessment of symptoms of dry mouth and 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 6). 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 7.3 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 and 2 hours after study drug [Visits 2 and 4]; 15 and 30 minutes, and 1, 2, 4, 6, 8, 10, 11.5, and 12 hours after study drug on Day 7 of each treatment period [Visits 3 and 5]) 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. On Day 1 of each treatment period (Visits 2 and 4), 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, and 2 hours after study drug. On Day 7 of each treatment period (Visits 3 and 5), 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. Original ECGs with interval printouts and rhythm strip run at 25 mm/sec must be attached to the appropriate CRF.

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. Refer to Section 7.3 for specific criteria for QTcF that prompt patients to be discontinued from 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.

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.

On Day 1 of each treatment period (Visits 2 and 4), hematology (Complete Blood Count) and chemistry (Comprehensive Metabolic Panel) will be obtained within 60 minutes prior to dosing. A basic metabolic panel (BMP) with focus on potassium and glucose parameters will be obtained at 2 hours post-dosing on all patients (see Table 5).

On Day 7 of each treatment period (Visits 3 and 5), hematology (Complete Blood Count) and chemistry (Comprehensive Metabolic Panel) will be obtained within 60 minutes prior to dosing and collect a BMP at 30 minutes and a CMP at 2 hours post-dosing (see Table 6).

Serum pregnancy testing will be performed at Screening and at the Final Visit (Visit 6) with Urine HCG testing occurring prior to the start of each treatment sequence (Visits 2 and 4) 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.

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 an SAE as defined below.

7.2.5.4 Severity

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

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

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

Severe: Associated with inability of 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 7.2.5.10.

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

7.2.5.8 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 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 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 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 may occur following inhalation from an MDI. Dry Mouth is a known side effect following administration of a LAMA. 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 specifically asked about the presence of dry mouth at baseline and at specified intervals (pre-dose and at 1 and 2 hours post-dose on Day 1 and on Day 7). On Day 7 if dry mouth persists at 2 hours additional assessments will be conducted every 2 hours until resolution of symptoms or completion of the test day (see Table 5 and Table 6) and if present, the severity (mild, moderate, and severe) of dry mouth symptoms will be assessed. If dry mouth is not noted at 2 hours post study drug administration, further dry mouth assessments do not need to be collected. All reports of dry mouth exceeding baseline will be recorded as AEs.

Instructions for Recording Dry Mouth AE:

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

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

    a. Patient has a history of dry mouth at Screening, and the event is considered a worsening of pre-existing dry mouth.

    b. Patient has no history of dry mouth at Screening.

3) The investigator should follow all AEs of dry mouth to resolution. An AE of dry mouth 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).

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, severe and very 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 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 document may include, but not be limited to the investigators brochure and approved product labeling for GFF MDI, GP MDI, and FF MDI.

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 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 8.6 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.

7.4 Termination of the Study

The study may be terminated prematurely with sufficient notice in advance by the investigator for any reason as per the terms of the contract with Pearl 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 on Day 1 (Visits 2 and 4) and Day 7 (Visits 3 and 5) of each treatment period are provided in Table 5 and Table 6, respectively.

Table 4. Schedule of Events

Procedures	Screening[a]		Treatment Period 1[a]		Treatment Period 2[a]		Follow-Up/ Final
	Visit 1a	Visit 1b (optional)	Visit 2 Randomization (Rx 1, Day 1)	Visit 3 (Rx 1, Day 7)	Visit 4 (Rx 2, Day 1)	Visit 5 (Rx 2, Day 7)	Visit 6 Final Visit
Informed Consent	X						
Eligibility Criteria	X	X	X				
Verify Continued Eligibility				X	X	X	
Dispense Peak Flow Meter	X						
Reversibility to Ventolin HFA[b]	X						
Demographics & Medical/Surgical History	X	X					
Concomitant Medications[c]	X	X	X	X	X	X	X
Spirometry[d]	X	X	X	X	X	X	
Physical Examination[e]	X						X
Vital Signs[f]	X		X	X	X	X	X
12-Lead ECG[g]	X		X	X	X	X	X
Pregnancy Test[h]	X		X	X	X	X	X
Clinical Laboratory Testing[h]	X		X	X	X	X	X
Adjust COPD Medications[i]	X					X	X
Adverse Events	X	X	X	X	X	X	X
Inhalation Device Training	X		X				
Study Drug Administration			X	X	X	X	
Dispense Patient Diary	X		X		X		
Collect/Review Patient Diary			X	X		X	
Download Peak Flow Meter Data and Review				X		X	
Study Drug Dispensing			X		X		
Study Drug Collection				X		X	
Dry Mouth/Tremor Assessment	X		X	X	X	X	
Paradoxical Bronchospasm[j]			X	X	X	X	

Table 4. Schedule of Events (continued)

a. Screening period of at least 7 days and up to 28 days. Patients are to return to the clinic within 7 days following initiation of each treatment arm. If any patient exceeds 9 days of treatment for any treatment, the Sponsor should be notified and the patient may be withdrawn. There must also be at least 7 days (not to exceed 21 days) between Visits 3 and 4 to allow for appropriate washout of study drug.

b. Assess reversibility of FEV_1 at 30 minutes following 4 puffs Ventolin HFA (to characterize the patient population only; not to be used to determine eligibility to participate in the study).

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 and 4. See Table 6 for spirometry assessments and specific time points to be performed at Visits 3 and 5.

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 hours 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 and 4. See Table 6 for SBP, DBP, and HR assessments and specific time points to be performed at Visits 3 and 5. At Visits 2-5, oral and/or tympanic 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 and 4. See Table 6 for ECG assessments and specific time points to be performed at Visits 3 and 5.

h. All clinical laboratory tests will be obtained at Screening and Follow-up. At Visits 2 through 5, hematology (Complete Blood Count) and chemistry (Comprehensive Metabolic Panel) will be obtained within 60 minutes prior to dosing. At Visits 2 and 4 (Treatment Day 1), BMP with focus on potassium and glucose parameters will be obtained at 2 hour post-dose on all patients (see Table 5). On Treatment Day 7 (Visits 3 and 5), BMP with focus on potassium and glucose parameters will be obtained at 30 minutes and a CMP at 2 hour post-dose (see Table 6). 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). At the end of the Visit 5, return patient to pre-study or other appropriate inhaled maintenance COPD medications.

j. Please refer to Section 7.2.6 for definition of paradoxical bronchospasm.

Table 5. Visit Procedures on Day 1 of Each Treatment Period (Visits 2 and 4)

	Pre-dosing		Post-dosing			
Clinical Variable[a]	**-1 hour**	**-30 minutes**	**15 minutes**	**30 minutes**	**1 hour**	**2 hours**
Dry Mouth and Tremor Assessment		X			X	X[b]
Vital Signs[c]	X	X	X	X	X	X
12- Lead ECG	X[c]	X[d]	X	X	X	X
Clinical Laboratory Testing[e]	X					X
Spirometry (FEV_1, FVC, PEFR)[g]	X[f]	X	X	X	X	X
Paradoxical Bronchospasm[h]			X	X		
Inspiratory Capacity	X	X			X	X
Peak Flow Meter Assessment		X		X		

a. Safety assessments (dry mouth and tremor assessments, vital signs, and ECG) 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 dry mouth or tremor is noted at the 2-hour time point, no further assessment is required. If dry mouth or tremor persists at 2 hours additional assessments will be conducted every 2 hours until resolution of symptoms or completion of the test day.

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

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

e. All clinical laboratory parameters will be obtained within 60 minutes prior to study drug administration; BMP with focus on potassium and glucose parameters will be obtained at 2 hours post-dose **on all patients**.

f. The baseline FEV_1 at Visits 4 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 within 20% of the baseline FEV_1 obtained at Randomization, 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 investigator's discretion (e.g., within one week), or the patient discontinued.

g. The 30 minute post-dose PEFR on Day 1 should be obtained after spirometry assessments allowing enough time for the patient to recover from the pulmonary function test maneuvers.

h. Please refer to Section 7.2.6 for definition of paradoxical bronchospasm.

Note: Where data collection time-points are concurrent, variables must be collected in the following order: Dry mouth and tremor assessment, vital signs, ECG, clinical laboratory assessments, and spirometry (IC when conducted, should be done prior to all other spirometry assessments).

Table 6. Visit Procedures on Day 7 of Each Treatment Period (Visits 3 and 5)

	Pre-dosing		Post-dosing									
Clinical Variable[a]	**-1 hr**	**-30 min**	**15 min**	**30 min**	**1 hr**	**2 hr**	**4 hr**	**6 hr**	**8 hr**	**10 hr**	**11.5 hr**	**12 hr**
Dry Mouth and Tremor Assessment[b]	X	X	X		X	X						
Vital Signs[c]	X	X	X	X	X	X	X	X	X	X	X	X
12- Lead ECG	X[d]	X[d]	X	X	X	X	X					X
Clinical Laboratory Testing[e]	X			X		X						
Spirometry (FEV_1, FVC, PEFR)[f]	X	X	X	X	X	X	X	X	X	X	X	X
Paradoxical Bronchospasm			X	X								
Inspiratory Capacity	X	X			X	X					X	X
Peak Flow Meter Assessment		X		X								

a. Safety assessments (dry mouth and tremor assessment, vital signs, and ECG) 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 dry mouth or tremor is noted at the 2-hour time point, no further assessment is required. If dry mouth or tremor persists at 2 hours additional assessments will be conducted every 2 hours until resolution of symptoms or completion of the test day.

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

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

e. All specified clinical laboratory parameters will be obtained within 60 minutes prior to study drug administration. A BMP with focus on potassium and glucose parameters will be obtained at 30 minutesand a CMP at 2 hours post-dose.

f. The 30 minute post-dose PEFR on Day 1 should be obtained after spirometry assessments allowing enough time for the patient to recover from the pulmonary function test maneuvers

Note: Where data collection time-points are concurrent, variables must be collected in the following order: Dry mouth and tremor assessment, vital signs, ECG, clinical laboratory assessments, and spirometry (IC when conducted, should be done prior to all other spirometry assessments).

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 dry mouth, glaucoma 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 (to characterize the patient population only; not to be used to determine eligibility to participate in the study).

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.
- Dispense patient diary, peak flow meter and provide instructions on use of peak flow meter and diary completion.

8.2 Randomization Visit (Visit 2; Rx 1, Day 1)

- Collect and review patient diary (if diary is not completed, re-train patient and Visit 2 must be rescheduled).
- Review inclusion/exclusion criteria to confirm patient eligibility.
- Obtain patient treatment assignment information from IWRS.
- 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).
- Dispense patient diary and provide instructions on diary completion if appropriate.
- 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 first dose of newly assigned study drug at the clinic.
    - The patient is to be considered randomized after receiving study medication.
- Perform all post-dosing assessments (refer to Table 5).
- Schedule Visit 3 and ensure patient has adequate supply of study drug and rescue Ventolin HFA.

8.3 Visit 3 (Rx 1, Day 7)

- Collect and review patient diary.
- Note time of last dose of short-acting bronchodilator and other COPD medications on CRF (if <6 hours, reschedule visit).
- Download and review data from Peak Flow Meter
- Confirm patient eligibility to continue.
- Record adverse events (if any).
- Perform urine pregnancy test (women of child-bearing potential only).
- Perform all pre-dose assessments (refer to Table 6).
- Patient will administer final dose of previously dispensed study drug at the clinic under supervision.
- Perform all post-dosing assessments (refer to Table 6).
- Collect previously dispensed study drug.
- Schedule next visit (following a washout period of at least 1 week but no longer than 3 weeks) and ensure patient has adequate supply of COPD medication.

8.4 Visit 4 (Day 1 of Rx 2)

- Collect and review patient diary
- Review inclusion/exclusion criteria to confirm patient eligibility to continue.
- Download and review data from Peak Flow Meter
- Review of clinical laboratory results from previous visit. Please note whether the results are clinically significant and include comments where applicable.

- Record adverse events (if any).
- Review concomitant medications and ensure adherence to COPD regimen.
- Note time of last dose of short-acting bronchodilator and other COPD medications on CRF (if <6 hours, reschedule visit).
- Perform urine pregnancy test (women of child-bearing potential only).
- Perform all pre-dose assessments (refer to Table 5).
- Dispense patient diary and provide instructions on diary completion if appropriate.
- 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 first dose of newly assigned study drug at the clinic.
- Perform all post-dosing assessments (refer to Table 5).
- Schedule next visit and ensure patient has adequate supply of study drug and rescue Ventolin HFA.

8.5 Visit 5 (Day 7 of Rx 2)

- Collect and review patient diary.
- Note time of last dose of short-acting bronchodilator and other COPD medications on CRF (if <6 hours, reschedule visit).
- Download and review data from Peak Flow Meter
- Review concomitant medications and ensure adherence to COPD regimen.
- Confirm patient eligibility to continue.
- Record adverse events (if any).
- Perform urine pregnancy test (women of child-bearing potential only).

- Perform all pre-dose assessments (refer to Table 6).
- Patient will administer final dose of previously dispensed study drug at the clinic.
- Perform all post-dosing assessments (refer to Table 6).
- Collect previously dispensed study drug.
- Schedule the final/follow-up visit at least 1 week but no longer than 2 weeks from Visit 5. At completion of all Visit 5 assessments, return patient to pre-study or appropriate inhaled maintenance COPD medications.

8.6 Follow-Up (Final) Visit/Premature Discontinuation (Visit 6)

- 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 5, return patient to pre-study or appropriate inhaled maintenance COPD medications.
- Complete study completion page.

8.7 Completion of the Study

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

- 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 7.3).

9 PLANNED STATISTICAL METHODS

9.1 Introduction

This study will be conducted as a 2-period, 6-treatment, balanced incomplete block cross-over design evaluating the following treatments in approximately 175 patients (it is anticipated that 175 patients will be randomized to obtain complete data on 150 patients):

- GFF MDI 36/7.2 µg ex-actuator
- GFF MDI 36/9.6 µg ex-actuator
- GFF MDI 18/9.6 µg ex-actuator
- GFF MDI 9/9.6 µg ex-actuator
- GP MDI 36 µg ex-actuator
- FF MDI 9.6 µg ex-actuator

The overall objectives of this study are to determine the efficacy of the combination GFF MDI therapy, relative to its individual components (GP MDI 36 µg ex-actuator and FF MDI 9.6 µg ex-actuator), and to characterize the dose response of GFF MDI. To this end, each dose of GFF MDI will be compared to both GP MDI 36 µg ex-actuator and FF MDI 9.6 µg ex-actuator, with respect to the primary efficacy endpoint, FEV_1 AUC_{0-12}, relative to baseline.

A balanced incomplete block design will be adopted, in which each of the fifteen pairs of treatments (i.e., in Period 1 and Period 2 of the crossover) is expected to be administered to 10 patients (N=150 patients in total to receive a pair of treatments). The fifteen treatment selections (ignoring order) are shown in Table 7. Each pair of treatments will be used to generate five replicates of a Williams design. Let the treatments be numbered 1…6, then for each pair of treatments i,j (i,j,$\in$ 1, 6), there are 5 subjects receiving i in Period 1 and j in Period 2, and a further 5 subjects receiving j in Period 1 and i in Period 2.

Table 7. Treatment Selections (Ignoring Order)

Selection	Treatments	
1	GFF MDI 36/7.2	GFF MDI 36/9.6
2	GFF MDI 36/7.2	GFF MDI 18/9.6
3	GFF MDI 36/7.2	GFF MDI 9/9.6
4	GFF MDI 36/7.2	GP MDI 36
5	GFF MDI 36/7.2	FF MDI 9.6
6	GFF MDI 36/9.6	GFF MDI 18/9.6
7	GFF MDI 36/9.6	GFF MDI 9/9.6
8	GFF MDI 36/9.6	GP MDI 36
9	GFF MDI 36/9.6	FF MDI 9.6
10	GFF MDI 18/9.6	GFF MDI 9/9.6
11	GFF MDI 18/9.6	GP MDI 36
12	GFF MDI 18/9.6	FF MDI 9.6
13	GFF MDI 9/9.6	GP MDI 36
14	GFF MDI 9/9.6	FF MDI 9.6
15	GP MDI 36	FF MDI 9.6

GP MDI=Glycopyrrolate MDI; FF MDI = Formoterol Fumarate MDI; GFF MDI = Glycopyrolate and Formoterol Fumarate MDI.

9.2 Protocol Variables

9.2.1 Efficacy Endpoints

All efficacy assessments are relative to baseline, and will be compared with the individual components as active controls. Since pre-dose values are known to be variable, and an isolated time-point may not accurately reflect the true baseline, the following baseline will be used for statistical analyses unless otherwise specified for exploratory endpoints: the mean of available pre-dose values on the first day of each treatment cycle, i.e., the mean of pre-dose values at Visits 2 and 4, where the mean of the -60 and -30 minute value for each visit day is averaged and then both visit means are averaged. Previous studies showed that this average

baseline was a more effective covariate than with the mean of pre-dose values on the current day, or the mean of pre-dose values during Visit 2 alone.

9.2.1.1 Primary Efficacy Endpoint

Primary Efficacy Endpoint Evaluated on Treatment Day 7 (Visits 3 and 5, following chronic dosing)

- Forced expiratory volume in 1 second area under the curve (FEV_1 AUC_{0-12}) relative to baseline following chronic dosing (1 week). 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.

9.2.1.2 Secondary Efficacy Endpoints

Secondary Endpoints Evaluated on Treatment Day 1 (Visits 2 and 4) Relative to Baseline Defined as Average of Pre-Dose Values Across Visits 2 and 4:

- Peak change from baseline in FEV_1 (defined as change at highest value of FEV_1 post-dose)
- Time to onset of action (≥10% improvement in FEV_1 at baseline)
- Proportion of patients achieving ≥ 12% improvement in FEV_1 at baseline
- Peak change in Inspiratory Capacity (IC) (mean of 1 and 2 hour post-dose)

Secondary Endpoints Evaluated on Treatment Day 7 (Visits 3 and 5, following chronic dosing):

- Change from baseline in morning pre-dose FEV_1, defined as the average of the 60 and 30 minute pre-dose values on Treatment Day 7 – Baseline, defined as the average across Visits 2 and 4.
- Peak change from baseline in FEV_1 (defined as highest value of FEV_1 post-dose) where baseline is defined as the average of pre-dose values across Visits 2 and 4.
- Peak change from baseline in IC (mean of 1 and 2 hours post-dose assessments), where baseline is defined as the average IC pre-dose values across Visits 2 and 4.
- 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), where baseline is defined as the average of FEV_1 pre-dose values across Visits 2 and 4.
- Change from baseline morning (A.M.) pre-dose daily peak flow readings taken by subjects, during each treatment period (excluding reading taken pre-dose on Visit 2 (Treatment 1 Day 1), where baseline is defined as the pre-dose measurement on Treatment Day 1, taken with the home instrument.

- Change from baseline morning (A.M.) post-dose daily peak flow readings taken by subjects, during each treatment period (excluding reading taken pre-dose on Visit 2 (Treatment 1 Day 1), where baseline is defined as the pre-dose measurement on Treatment Day 1, taken with the home instrument.
- Change from baseline evening (P.M.) pre-dose daily peak flow readings taken by subjects, during each treatment period, where baseline is defined as the pre-dose measurement on Treatment Day 1, taken with the home instrument.
- Change from baseline evening (P.M.) post-dose daily peak flow readings taken by subjects, during each treatment period, where baseline is defined as the pre-dose measurement on Treatment Day 1, taken with the home instrument.

9.2.1.3 Exploratory Endpoints Evaluated on Treatment Day 7 (Visits 3 and 5, following chronic dosing)

- Peak expiratory flow rate (PEFR) AUC_{0-12} and change from baseline by post-dose time point. AUC will be normalized by dividing by time so that the units of AUC will be L. Baseline is average of PEFR pre-dose values across Visits 2 and 4.
- Forced vital capacity (FVC) AUC_{0-12} and change from baseline by post-dose time point. AUC will be normalized by dividing by 12 so that the units of AUC will be L. Baseline is average of pre-dose FVC values across Visits 2 and 4.
- Change from baseline for mean morning trough IC (mean of -60 and -30 min pre-dose), where baseline is the average of pre-dose IC values across Visits 2 and 4.
- Change from baseline for mean evening trough IC (mean of 11.5 and 12 hours post-dose), where baseline is the average of IC pre-dose values across Visits 2 and 4.
- Mean number of puffs of rescue medication recorded in patient diaries, during each treatment period and by treatment and number of days treated.

9.2.2 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, Dry Mouth, 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. QTcF prolongation increase of >30 msec from test day baseline (QTc interval obtained from Treatment Day 1 pre-dose) and QTcF >450 msec for males and >470 msec for females at any time after taking study drug (Days 1 to 7) will be recorded.

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 combination treatment compared to GP MDI 36 µg ex-actuator and FF MDI 9.6 µg ex-actuator. Baseline (as defined in 9.2.1.1 above) 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 model will include Period effects.

For the primary efficacy objective, the family-wise Type I error will be controlled by hierarchical testing. For the primary objective, family-wise Type I error will be controlled as follows:

1) No efficacy claims will be advanced unless the GFF MDI 36/9.6 µg ex-actuator treatment is statistically significantly superior to both the GP MDI 36 µg ex-actuator and the FF MDI 9.6 µg ex-actuator treatments. Both comparisons with the individual components must be statistically significant before an improvement over the individual components is claimed for this combination therapy.

2) If an improvement over the individual components is detected for the GFF MDI 36/9.6 µg ex-actuator treatment, then the GFF MDI 36/7.2 µg ex-actuator treatments will be compared with the individual components. Both comparisons with the individual components must be statistically significant before an improvement over the individual components is claimed for this combination therapy

3) If an improvement over the individual components is detected for the GFF MDI 36/9.6 µg ex-actuator treatment, then the GFF MDI 18/9.6 µg ex-actuator treatments will be compared with the individual components. Both comparisons with the individual components must be statistically significant before an improvement over the individual components is claimed for this combination therapy.

4) If an improvement over the individual components is detected for the GFF MDI 18/9.6 µg ex-actuator treatment, then the GFF MDI 9/9.6 µg ex-actuator treatments will be compared with the individual components. Both comparisons with the individual components must be statistically significant before an improvement over the individual components is claimed for this combination therapy.

The use of a hierarchical testing strategy obviates the need for any multiplicity adjustment (Bauer *et al*, 1998; page 2135).

9.3.2 Secondary Efficacy Analysis

Secondary and exploratory efficacy analysis will involve the same comparisons on secondary efficacy endpoints. For endpoints other than time to onset and puffs of rescue medication from diary entries, these comparisons will be performed using the same mixed model and the same algorithms as for the primary efficacy objective. Hierarchical testing will not be imposed for secondary endpoints.

Analysis of time to onset of action for FEV_1 effect evaluated on Day 1 will use baseline defined as the average of observed pre-dose values from Visits 2 and 4. The "event" is a greater than or equal to 10% improvement from baseline for FEV_1 post-dose, excluding subjects with a ≥10% improvement from baseline at the start of dosing (defined as pre-dose average of 30 minute and 60 minute pre-dose assessments of FEV_1 for a treatment period).

Time to onset 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).

The number of puffs of rescue mediation will be summarized using descriptive statistics only.

9.3.3 Safety Analysis

9.3.3.1 Adverse Events

Adverse events during each treatment regime 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 most recent version of MedDRA will be used throughout the study. If a new version of MedDRA is released during the study, any existing coded events will be updated to conform to the new version. 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.

9.3.3.2 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.

9.3.3.3 Dry Mouth

The incidence of dry mouth 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.

9.3.3.4 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.

9.3.3.5 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 (> 11.1 mmol/L) will also be listed and tabulated by treatment.

9.3.3.6 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.

9.3.3.7 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.

The percentage and number of patients with 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 will be tabulated. No hypothesis tests will be performed, but a Clopper person confidence interval may be provided for each group.

9.4 Randomization

Patients will be randomly assigned to a sequence number using an IWRS. The treatment allocation for each sequence is shown in Table 8. Each of the 30 possible sequences of two treatments chosen from six occurs 5 times.

Table 8 Treatment Sequences

Seq.	P1	P2	Seq.	P1	P2	Seq.	P1	P2
1	GFF36/9.6	GFF36/7.2	51	GFF36/9.6	GFF18/9.6	101	GP36	GFF18/9.6
2	GFF18/9.6	GFF36/7.2	52	GFF36/9.6	GFF9/9.6	102	FF9.6	GFF18/9.6
3	GFF9/9.6	GFF36/7.2	53	GFF36/9.6	GP36	103	GP36	GFF9/9.6
4	GP36	GFF36/7.2	54	GFF36/9.6	FF9.6	104	FF9.6	GFF9/9.6
5	FF9.6	GFF36/7.2	55	GFF18/9.6	GFF9/9.6	105	FF9.6	GP36
6	GFF18/9.6	GFF36/9.6	56	GFF18/9.6	GP36	106	GFF36/7.2	GFF36/9.6
7	GFF9/9.6	GFF36/9.6	57	GFF18/9.6	FF9.6	107	GFF36/7.2	GFF18/9.6
8	GP36	GFF36/9.6	58	GFF9/9.6	GP36	108	GFF36/7.2	GFF9/9.6
9	FF9.6	GFF36/9.6	59	GFF9/9.6	FF9.6	109	GFF36/7.2	GP36
10	GFF9/9.6	GFF18/9.6	60	GP36	FF9.6	110	GFF36/7.2	FF9.6
11	GP36	GFF18/9.6	61	GFF36/9.6	GFF36/7.2	111	GFF36/9.6	GFF18/9.6
12	FF9.6	GFF18/9.6	62	GFF18/9.6	GFF36/7.2	112	GFF36/9.6	GFF9/9.6
13	GP36	GFF9/9.6	63	GFF9/9.6	GFF36/7.2	113	GFF36/9.6	GP36
14	FF9.6	GFF9/9.6	64	GP36	GFF36/7.2	114	GFF36/9.6	FF9.6
15	FF9.6	GP36	65	FF9.6	GFF36/7.2	115	GFF18/9.6	GFF9/9.6
16	GFF36/7.2	GFF36/9.6	66	GFF18/9.6	GFF36/9.6	116	GFF18/9.6	GP36
17	GFF36/7.2	GFF18/9.6	67	GFF9/9.6	GFF36/9.6	117	GFF18/9.6	FF9.6
18	GFF36/7.2	GFF9/9.6	68	GP36	GFF36/9.6	118	GFF9/9.6	GP36
19	GFF36/7.2	GP36	69	FF9.6	GFF36/9.6	119	GFF9/9.6	FF9.6
20	GFF36/7.2	FF9.6	70	GFF9/9.6	GFF18/9.6	120	GP36	FF9.6
21	GFF36/9.6	GFF18/9.6	71	GP36	GFF18/9.6	121	GFF36/9.6	GFF36/7.2
22	GFF36/9.6	GFF9/9.6	72	FF9.6	GFF18/9.6	122	GFF18/9.6	GFF36/7.2
23	GFF36/9.6	GP36	73	GP36	GFF9/9.6	123	GFF9/9.6	GFF36/7.2
24	GFF36/9.6	FF9.6	74	FF9.6	GFF9/9.6	124	GP36	GFF36/7.2
25	GFF18/9.6	GFF9/9.6	75	FF9.6	GP36	125	FF9.6	GFF36/7.2

26 GFF18/9.6	GP36	76 GFF36/7.2	GFF36/9.6	126 GFF18/9.6	GFF36/9.6
27 GFF18/9.6	FF9.6	77 GFF36/7.2	GFF18/9.6	127 GFF9/9.6	GFF36/9.6
28 GFF9/9.6	GP36	78 GFF36/7.2	GFF9/9.6	128 GP36	GFF36/9.6
29 GFF9/9.6	FF9.6	79 GFF36/7.2	GP36	129 FF9.6	GFF36/9.6
30 GP36	FF9.6	80 GFF36/7.2	FF9.6	130 GFF9/9.6	GFF18/9.6
31 GFF36/9.6	GFF36/7.2	81 GFF36/9.6	GFF18/9.6	131 GP36	GFF18/9.6
32 GFF18/9.6	GFF36/7.2	82 GFF36/9.6	GFF9/9.6	132 FF9.6	GFF18/9.6
33 GFF9/9.6	GFF36/7.2	83 GFF36/9.6	GP36	133 GP36	GFF9/9.6
34 GP36	GFF36/7.2	84 GFF36/9.6	FF9.6	134 FF9.6	GFF9/9.6
35 FF9.6	GFF36/7.2	85 GFF18/9.6	GFF9/9.6	135 FF9.6	GP36
36 GFF18/9.6	GFF36/9.6	86 GFF18/9.6	GP36	136 GFF36/7.2	GFF36/9.6
37 GFF9/9.6	GFF36/9.6	87 GFF18/9.6	FF9.6	137 GFF36/7.2	GFF18/9.6
38 GP36	GFF36/9.6	88 GFF9/9.6	GP36	138 GFF36/7.2	GFF9/9.6
39 FF9.6	GFF36/9.6	89 GFF9/9.6	FF9.6	139 GFF36/7.2	GP36
40 GFF9/9.6	GFF18/9.6	90 GP36	FF9.6	140 GFF36/7.2	FF9.6
41 GP36	GFF18/9.6	91 GFF36/9.6	GFF36/7.2	141 GFF36/9.6	GFF18/9.6
42 FF9.6	GFF18/9.6	92 GFF18/9.6	GFF36/7.2	142 GFF36/9.6	GFF9/9.6
43 GP36	GFF9/9.6	93 GFF9/9.6	GFF36/7.2	143 GFF36/9.6	GP36
44 FF9.6	GFF9/9.6	94 GP36	GFF36/7.2	144 GFF36/9.6	FF9.6
45 FF9.6	GP36	95 FF9.6	GFF36/7.2	145 GFF18/9.6	GFF9/9.6
46 GFF36/7.2	GFF36/9.6	96 GFF18/9.6	GFF36/9.6	146 GFF18/9.6	GP36
47 GFF36/7.2	GFF18/9.6	97 GFF9/9.6	GFF36/9.6	147 GFF18/9.6	FF9.6
48 GFF36/7.2	GFF9/9.6	98 GP36	GFF36/9.6	148 GFF9/9.6	GP36
49 GFF36/7.2	GP36	99 FF9.6	GFF36/9.6	149 GFF9/9.6	FF9.6
50 GFF36/7.2	FF9.6	100 GFF9/9.6	GFF18/9.6	150 GP36	FF9.6

The design is balanced for first order carry over effects and for period.

9.5 Sample Size Consideration

Power calculations were based on the primary endpoint, FEV_1 AUC_{0-12} on the last day of each dosing period following administration of the study drug.

Estimates of within subject standard deviation of FEV_1 AUC_{0-12} were obtained from published studies (D'Urzo et al, 2001; van Noord et al, 2005; Maesen et al 1995). A composite within-subjects variance component of 0.13 L was adopted. A between-subjects variance component of FEV_1 AUC_{0-12} was obtained from Dahl et al, 2001 and from Calverley et al, 2003. A composite value of 0.13 L was adopted. This represents a total standard deviation of 0.18 L. Note that variance components here are expressed as the standard deviation of the relevant random effect (not the variance).

For the efficacy comparisons, power was calculated as follows:

1. Between and within patients variance components were assumed to have standard deviations of 0.13 L.

2. The standard error of each contrast was calculated, assuming a generalized least squares analysis in which the ratio of between and within patient variance components was known. The generalized least squares estimates also assumed spherical errors. This is an approximation to the standard error of the REML estimates. It was assumed that there are no carryover effects.

3. The non-centrality parameter of the t-test was calculated, assuming the standard error from the generalized least squares analysis, and a difference of 0.1 L (the minimally clinically significant difference).

Power was calculated as the sample size was varied in sets of 15 patients (to ensure a completely balanced incomplete block design). The sample size required to achieve 91% power (assuming a significance test at the 5% level, with no multiplicity adjustment) is then 150 patients. Approximately 175 patients will be recruited in order to achieve approximately 150 completed patients at study termination.

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 signed before database lock.

9.7 Study Populations

The following analysis populations are defined in this study:

- The **Intent-To-Treat (ITT) Population** is defined as all subjects who are 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).

- A **Modified ITT (MITT) Population** will be used for analysis of efficacy variables, where subjects must have completed at least 1 treatment period, with minimally 2 hours post-dosing on Day 7 for that treatment period (i.e., no greater than one missing data-point from 15 minutes to 2 hours inclusive). Any evaluability criteria with a potential impact on efficacy results will be identified 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 time point within a treatment period. Protocol deviations for exclusion of data from the MITT Population will be agreed between the investigator, Pearl Therapeutics, and the biostatistician prior to data base lock and will be pre-specified in the Statistical Analysis Plan written prior to database lock.

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

Safety 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 ITT, MITT, PP, and Screen Failure 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 Populations, with the MITT Population being considered the primary population for these analyses. The ITT analyses on the primary parameter 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

Change from baseline in pre-dose FEV_1 on Day 7 is defined as the average of the 60 and 30 minute pre-dose values on Treatment Day 7 – baseline. In subjects missing either of these

pre-dose assessments, the value will be calculated from the single measurement. In subjects missing both pre-dose values, pre-dose FEV_1 on Day 7 will not be calculated, but other FEV_1 parameters will be calculated provided they meet the requirements below.

Peak change from baseline in FEV_1 will be included in analyses as long as there is complete FEV_1 data up to and including 2 hours (i.e., no greater than one missing data-point from 15 minutes to 2 hours, inclusive).

Missing data will not be imputed other than specified for the last-one-carried forward (last observation carried forward) as specified below for calculation of FEV_1 AUC_{0-12} as follows:

1. FEV_1 AUC_{0-12} will be calculated if the requirements for Peak FEV_1 are met and there are no 2 adjacent data-points missing at any time-point up to and including hour 12 post-dose and no more than 4 data points missing in the 0 - 12 hours post-dose time interval.

2. If the data obtained for a subject are deemed to be invalid by the study investigator, AUC will not be calculated for the visit;

3. If the final spirometry measurement (12 hours post-dose) is missing, (i.e., the values obtained at the 11.5-hour measurement will be carried forward. If the 11.5-hour measurement is also missing, AUC will not be calculated);

4. AUC will be calculated using last-one-carried forward;

5. Given the missing value rules specified above, AUC will be calculated using trapezoidal integration on the available time points.

AUC will be calculated similary for FVC AUC and PEFR AUC.

If either the 11.5 or 12-hour spirometry measurements is missing, but not both, trough values will be calculated using the other non-missing measurement (11.5 or 12 hour).

If both the 11.5 and 12-hour measurements are missing, trough values will be considered missing.

9.9 Statistical Software

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

10 ADMINISTRATIVE CONSIDERATIONS

10.1 Regulatory Authority Approval

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

10.2 Ethical Conduct of the Study and Institutional Review Board (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).
- United States (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 Laboratory Accreditation

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

10.5 Confidentiality

10.5.1 Confidentiality of Data

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

10.5.2 Confidentiality of Subject/Patient Records

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

10.6 Quality Control and Assurance

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

10.7 Data Management

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

10.8 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 10.9. The investigator will also permit inspection of the study files by Pearl Therapeutics's Quality Assurance auditors, and authorized representatives of the FDA or other applicable regulatory agencies.

10.9 Retention of Data

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

10.10 Financial Disclosure

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

10.11 Investigator's Final Report

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

10.12 Publication Policy

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

authorship will reflect the contribution made by Pearl Therapeutics personnel, the investigators and others involved, such as statisticians.

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

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

11 REFERENCE LIST

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

Akaike H. A new look at the statistical model identification. IEEE Transactions on Automatic Control. 1974;19(6):716–723.

Bauer, P., Röhmel, J., Maurer, W., and Hothorn, L. (1998). Testing strategies in multi- dose experiments including active control. Statistics in Medicine, 17(18):2133–2146.

Calverley P, Lee A, Towse L, et al. Effect of tiotropium bromide on circadian variation in airflow limitation in chronic obstructive pulmonary disease. Br Medical J. 2003;58(10):855–860.

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

Campbell SC, Criner GJ, Levine BE, et al. Cardiac safety of formoterol 12 µg twice daily in patients with chronic obstructive pulmonary disease. Pulm Pharmacol Ther 2007;20:571-579.

Casaburi R, Kukafka D, Cooper CB, Witek TJ Jr, Kesten S. Improvement in exercise tolerance with the combination of tiotropium and pulmonary rehabilitation in patients with COPD. Chest 2005;127:809–817.

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

Dahl R, Greefhorst LA, Nowak D, et al. Inhaled formoterol dry powder versus ipratropium bromide in chronic obstructive pulmonary disease. American Journal of Respiratory and Critical Care Medicine 2001; 164:778–84.

D'Urzo A, Salvo M D, Ramirez-Rivera A, et al. In patients with copd, treatment with a combination of formoterol and ipratropium is more effective than a combination of salbutamol and ipratropium a 3-week, randomized, double-blind, within-patient, multicenter study. Chest. 2001;119(5):1347–1356.

GOLD (Global Initiative for Chronic Obstructive Lung Disease). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. National Institutes of Health, updated 2008 (www.goldcopd.com). Accessed February 16, 2009.

Hansel TT, Barnes PJ. Tiotropium bromide: a novel once daily anticholinergic bronchodilator for the treatment of COPD. Drugs Today 2002; 38: 585–600.

Kuna P, Vinkler I, Overend T, Snape S, Tansley R. Efficacy and tolerability of NVA237 a once daily long acting muscarinic antagonist in COPD patients [abstract]. European Respiratory Journal 2007; P213.

MIMS Online Australia, 2008. CMPMedica Australia Pty Ltd.

Murray, S. (2001). Using Weighted Kaplan–Meier Statistics in Nonparametric Comparisons of Paired Censored Survival Outcomes. Biometrics, 57(2):361–368.

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

Noord JAV. Comparison of tiotropium once daily, formoterol twice daily and both combined once daily in patients with COPD. European Respiratory Journal. 2005;26(2):214–222.

Patterson H and Thompson R. Recovery of inter-block information when block sizes are unequal. Biometrika, 1971; 58:545–554.

Rossi A, Kristufek P, Levine BE, et al. Comparison of the efficacy, tolerability, and safety of formoterol dry powder and oral, slowrelease theophylline in the treatment of COPD. Chest 2002;121:1058-1069.

Sears MR. Adverse effects of beta-agonists. Journal of Allergy and Clinical Immunology 2002;110:S322–8.

Vogelmeier, C. Verkindre, C, Cheung D, Galdiz J. B., Guclu S. Z., Spangenthal S, Overend T, Henley M, Mizutani G, Zeldin R, Geba G. Safety and tolerability of NVA237, a once daily long-acting muscarinic antagonist, in patients with COPD[abstract]. European Respiratory Journal 2008; CP629S.

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 $\geq$15 s (longer times are recommended) and measuring volumes of $\geq$8 L (body temperature (i.e., 37°C), ambient pressure, saturated with water vapor, BTPS) with an accuracy of at least $\pm$3% of reading or $\pm$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 $\geq$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 $L\text{-}s^{-1}$ (with 3-L injection times of 6 s and 0.5 s). The volume at each flow should meet the accuracy requirement of ±3.5%. For devices using disposable flow sensors, a new sensor from the supply used for patient tests should be tested each day.

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

VC AND IC MANEUVERS

Equipment

For measurements of VC and IC, the spirometer or flow meter must comply with the requirements for FVC (as described previously) and be capable of accumulating volume for

≥30 s. Expiratory maneuvers or, ideally, both inspiratory and expiratory maneuvers should be included in the display of VC maneuver. Regardless of whether the inspiratory or expiratory maneuver is used for deriving measurements, a display of the entire recorded VC maneuver must be provided. The maximal expiratory volume must be assessed to determine whether the subject has obtained a plateau in the expiratory effort. For display of the slow VC, the time scale may be reduced to 5 mm-s^{-1}.

TECHNICAL CONSIDERATIONS

Minimal recommendations for spirometry systems

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

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

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

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

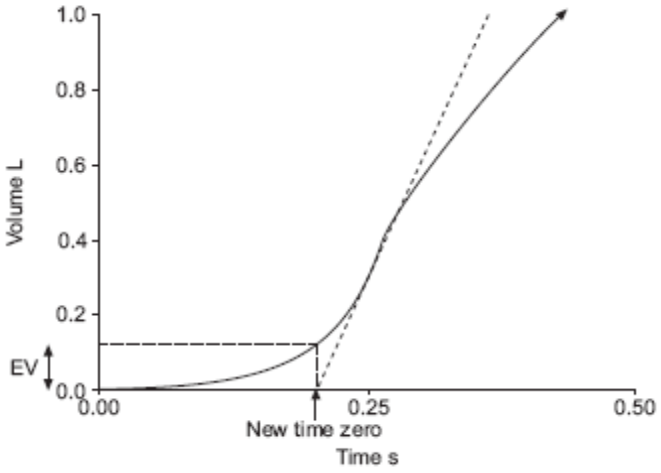
***Acceptable* Tests must meet the following 7 Criteria:**

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

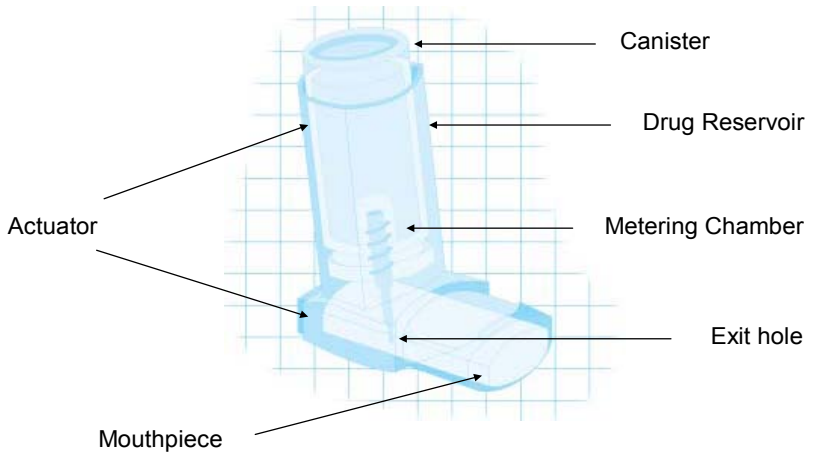
If these criteria are met, the spirometry testing for that time-point may conclude. The highest FEV_1 and the highest FVC obtained at each testing time-point (even if from different reproducible tracings), will be collected.

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 Patient Instructions for Use of GFF MDI, GP MDI, and FF MDI Devices

1. The inhaler should be stored at room temperature.
2. Take the cap off the mouthpiece of the actuator.
3. Inspect the front of the inhaler and make sure there is nothing inside the mouthpiece of the inhaler. Make sure the canister is fully and firmly inserted into the actuator.
4. All MDIs must be primed before the first use. Priming involves releasing a certain number of sprays (4) into the air before the first use of the inhaler. Shaking and priming the inhaler fills a chamber inside the canister with the correct dose and mix of medication so that it'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 7, 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 4 Instructions for Use of Ventolin HFA Inhaler

The Parts of Your VENTOLIN HFA Inhaler

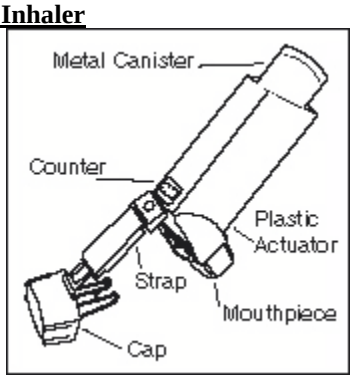


Figure 1

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:

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

Priming your VENTOLIN HFA:

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

Instructions for taking a dose from your VENTOLIN HFA:

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

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

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

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

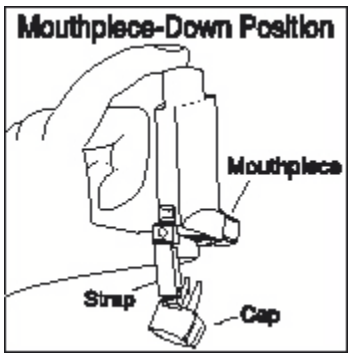


Figure 2

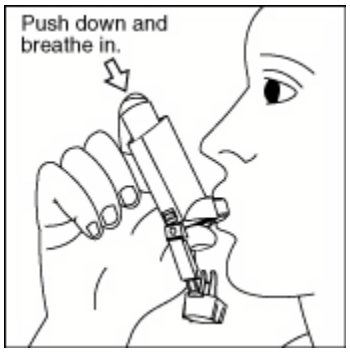


Figure 3

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

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

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

When to Replace Your VENTOLIN HFA

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

How to Clean Your VENTOLIN HFA

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

Wash the actuator at least once a week.

Cleaning instructions:

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

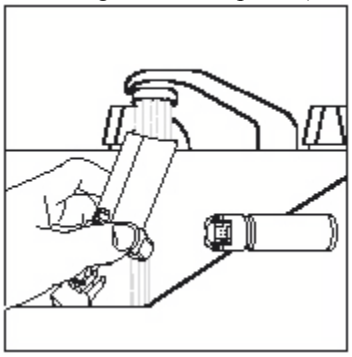


Figure 4

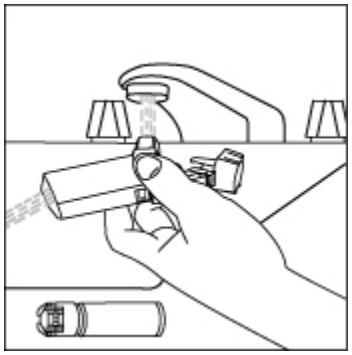


Figure 5

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

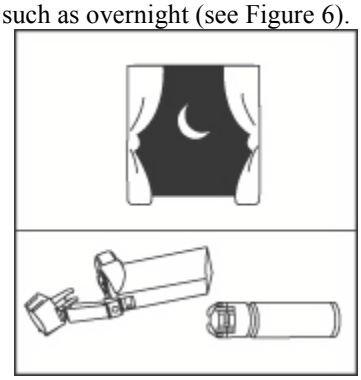


Figure 6

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

If your actuator becomes blocked:

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

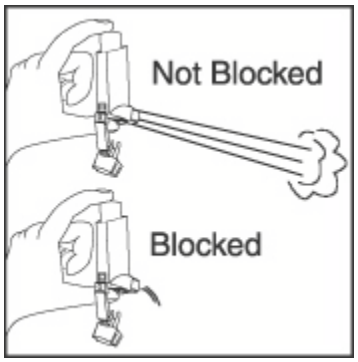


Figure 7

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 5 Sponsor Signatory

Study Title: A Randomized, Double-Blind, Chronic Dosing (7 Days), Two-Period, Six-Treatment, Incomplete Block, Cross-Over, Multi-Center Study to Assess Efficacy and Safety of Four Doses of GFF MDI in Patients With Moderate to Severe COPD, Compared With Its Individual Components (FF MDI and GP MDI) as Active Controls

Study Number: PT003004-00

Final Date: [redacted]

Amendment 1 Date: [redacted]

Signature: [redacted] Date: [redacted]

Name: [redacted]

Title: [redacted] Pearl Therapeutics, Inc

Appendix 6 Investigator's Agreement and Signature Page

Study Title: A Randomized, Double-Blind, Chronic Dosing (7 Days), Two-Period, Six-Treatment, Incomplete Block, Cross-Over, Multi-Center Study to Assess Efficacy and Safety of Four Doses of GFF MDI in Patients With Moderate to Severe COPD, Compared With Its Individual Components (FF MDI and GP MDI) as Active Controls

Study Number: PT003004-00

Final Date: [redacted]

I agree:

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

Signature:_____ Date:_____

Name:_____

Affiliation: _____

_____

Clinical Trial Protocol: PT003004-01

Study Title:	A Randomized, Double-Blind, Chronic Dosing (7 Days), Two-Period, Six-Treatment, Incomplete Block, Cross-Over, Multi-Center Study to Assess Efficacy and Safety of Four Doses of GFF MDI in Patients With Moderate to Severe COPD, Compared With Its Individual Components (FF MDI and GP MDI) as Active Controls
Study Number:	PT003004-01
Study Phase:	IIb
Product Name:	Glycopyrrolate and Formoterol Fumarate Inhalation Aerosol; PT003
IND Number:	107739
Indication:	COPD
Investigators:	Multicenter
Sponsor:	Pearl Therapeutics, Inc. [redacted]
Sponsor Contact:	[redacted]

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

SUMMARY OF CHANGES TO ORIGINAL PROTOCOL VERSION 1.0, DATED [redacted]

The protocol is amended to clarify the following:

Note: Text that has been added is shown in **bold font**, while text that has been deleted is shown in ~~strikethrough font~~.

- In Section 5.2 Exclusion Criteria, the following text was added for exclusion criteria #11 to clarify the exclusion of subjects with glaucoma.

  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, **uncontrolled** glaucoma **(subjects with previously diagnosed glaucoma who have intraocular pressure controlled with medication(s) are eligible. All medications approved for control of intraocular pressures are allowed, including topical ophthalmic nonselective beta-blockers such as timolol, levobunolol, metipranolol, carteolol)**, symptomatic prostatic hypertrophy (if treated and asymptomatic, the patient is eligible for enrollment), endocrine (including uncontrolled diabetes or thyroid disease), hematological medical problems, and urinary retention problems [including bladder-neck obstruction (e.g., difficulty passing urine, painful urination)].

- In Section 5.2 Exclusion Criteria, the following text was added for exclusion criteria #11 to clarify other exclusionary diseases.

  Note: Patients with a recent history of acute coronary syndrome, or who have undergone percutaneous coronary intervention or coronary artery bypass graft within the past three months are to be excluded. Patients with documented myocardial infarction are to be excluded for one year from the event.

- In Section 5.2 Exclusion Criteria, the following change was made to text for exclusion criteria #28 to clarify the exclusion of subjects previously enrolled in a Pearl Therapeutics Study.

  Patients who were previously enrolled in a Pearl Therapeutics PT001 ~~(Glycopyrrolate MDI)~~ (GP MDI), PT005 ~~(Formoterol Fumarate MDI)~~ (FF MDI), or PT003 (GFF MDI) study. ~~or Part B of Study PT0031002.~~

In addition, minor inconsistencies are addressed and further clarification is provided within the protocol as follows:

- In Section 6.4 the following typographical error was corrected as there is no placebo group in this study.

  Secondary Packaging and Labeling Information (Box): Investigational ~~or placebo~~ drug supplies for Visit 2 and 4 will be packaged in boxes as outlined in Table 3.

- In Section 8 Study Activities, a typographical error was corrected in Table 5 to fix an incorrect footnote symbol for the -1 hour pre-dose timepoint for the 12-Lead ECG.

- In Section 8 Study Activities, in Table 6, dry mouth and tremor assessments were removed for the -1 hour pre-dose timepoint.

- In Section 8.4 Visit 4 (Day 1 of Rx 2), the step to collect and review patient diary was deleted.

SYNOPSIS

Sponsor:
Pearl Therapeutics

Names of Finished Products:
Glycopyrrolate and Formoterol Fumarate Inhalation Aerosol; Glycopyrrolate and Formoterol Fumarate Metered Dose Inhaler; GFF MDI; PT003
Glycopyrrolate Inhalation Aerosol; Glycopyrrolate Metered Dose Inhaler; GP MDI; PT001
Formoterol Fumrate Inhalation Aerosol; Formoterol Fumarate Metered Dose Inhaler; FF MDI; PT005

Name of Active Ingredients:
Glycopyrrolate and Formoterol Fumarate
Glycopyrrolate
Formoterol Fumarate

Study Title:
A Randomized, Double-Blind, Chronic Dosing (7 Days), Two-Period, Six-Treatment, Incomplete Block, Cross-Over, Multi-Center Study to Assess Efficacy and Safety of Four Doses of GFF MDI in Patients With Moderate to Severe COPD, Compared With Its Individual Components (FF MDI and GP MDI) as Active Controls

Study Number: PT003004-01

Study Phase: IIb

Study Objective(s):

Primary objective:
The primary objective of this study is to demonstrate efficacy of GFF MDI relative to its individual components (GP MDI and FF MDI) in patients with moderate to severe COPD within the range of doses evaluated in this protocol. To this end, the primary efficacy endpoint, FEV_1 AUC_{0-12}, will be compared for each dose of GFF MDI relative to its individual components Glycopyrrolate Metered Dose Inhaler (GP MDI 36µg ex-actuator, BID) and Formoterol Fumarate Metered Dose Inhaler (FF MDI 9.6 µg ex-actuator, BID).

Secondary Objectives:
The secondary objective of the study is to characterize the dose-response curve for GFF MDI. The primary and secondary endpoints identified in Section 3.1 will be assessed for GFF MDI given as a twice-daily administration as compared to GP MDI and FF MDI.

Safety Objective:
The safety objective is to evaluate the safety of GFF MDI (36/7.2, 36/9.6, 18/9.6, and 9/9.6 µg ex-actuator, BID) in patients with moderate to severe COPD compared with GP MDI (36 µg ex-actuator, BID) and FF MDI (9.6 µg ex-actuator, BID). Safety will be assessed by adverse events (AEs), physical examination findings, assessments of dry mouth and tremor, monitoring for paradoxical bronchospasm, vital signs, electrocardiograms (ECGs), and laboratory assessments.

Study Design:

This is a randomized, double-blind, chronic dosing (7 days), two-period, six-treatment, balanced incomplete block, cross-over, multi-center study to assess efficacy and safety of four doses of GFF MDI (36/7.2, 36/9.6, 18/9.6, and 9/9.6 µg ex-actuator, BID) in patients with moderate to severe COPD, compared with its individual components, GP MDI (36 µg ex-actuator, BID) and FF MDI (9.6 µg ex-actuator, BID), as active controls.

This multi-center study will be conducted at approximately 10-15 sites, contributing approximately 10 to 15 patients per site in the United States. Across these sites, it is planned that approximately 175 patients with moderate to severe COPD will be randomized into the study to provide approximately 150 patients to complete the study. The entire study period is scheduled to take a maximum of 9 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 175 patients with moderate to severe COPD will be enrolled to provide approximately 150 patients to complete the study.

Test Product, Dose, and Mode of Administration:
Investigational materials will be provided by Pearl Therapeutics as summarized in the table below.

Product Name and Potency	Product Strength	Dosage Form	Comments
GFF MDI 36/7.2 µg ex-actuator	GFF MDI 18/ 3.6 µg per actuation	MDI	Taken as 2 inhalations.
GFF MDI 36/9.6 µg ex-actuator	GFF MDI 18/ 4.8 µg per actuation	MDI	Taken as 2 inhalations.
GFF MDI 18/9.6 µg ex-actuator	GFF MDI 9/4.8 µg per actuation	MDI	Taken as 2 inhalations.
GFF MDI 9/9.6 µg ex-actuator	GFF MDI 4.5/4.8 µg per actuation	MDI	Taken as 2 inhalations.
GP MDI 36 µg ex-actuator†	GP MDI 18 µg per actuation	MDI	Taken as 2 inhalations.
FF MDI 9.6 µg ex-actuator†	FF MDI 4.8 µg per actuation	MDI	Taken as 2 inhalations.
Albuterol Sulfate inhalation aerosol 90 µg ex-actuator§	US source: (Ventolin HFA) Each inhalation contains 108 µg corresponding to 90 µg albuterol base per actuation	MDI	Supplies are open-label.

FF MDI = Formoterol Fumarate Metered Dose Inhaler; GFF MDI = Glycopyrrolate and Formoterol Fumarate Metered Dose Inhaler; GP MDI = Glycopyrrolate Metered Dose Inhaler; MDI = Metered Dose Inhaler.
† Active control
§ Rescue medication during treatment periods.
Note: All study test medications will be administered by oral inhalation.

Duration of Treatment:
Each patient will receive 7 days of study treatment with each of their assigned treatments for a total of 2 separate treatment periods. A washout period of at least 7 days (up to 21 days) will occur between each treatment period. The entire study is scheduled to take a maximum of 9 weeks for each individual patient from the time of screening (see Figure 1).

Efficacy Assessments:
All efficacy assessments are relative to baseline, and will be compared with the individual components as active controls. Since pre-dose values are known to be variable, and an isolated time-point may not accurately reflect the true baseline, the following baseline will be used for statistical analyses unless otherwise specified for exploratory endpoints: the mean of available pre-dose values on the first day of each treatment cycle, i.e., the mean of pre-dose values at Visits 2 and 4, where the mean of the -60 and -30 minute value for each visit day is averaged and then both visit means are averaged. Previous studies showed that this average baseline was a more effective covariate than with the mean of pre-dose values on the current day, or the mean of pre-dose values during Visit 2 alone.

Primary Efficacy Endpoint Evaluated on Treatment Day 7 (Visits 3 and 5, following chronic dosing):

- Forced expiratory volume in 1 second area under the curve (FEV_1 AUC_{0-12}) relative to baseline following chronic dosing (1 week). 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:
Secondary Endpoints Evaluated on Treatment Day 1 (Visits 2 and 4) Relative to Baseline Defined as Average of Pre-Dose Values Across Visits 2 and 4*:*

- Peak change from baseline in FEV_1 (defined as change at highest value of FEV_1 post-dose)
- Time to onset of action (≥10% improvement in FEV_1 relative to baseline)
- Proportion of patients achieving ≥ 12% improvement in FEV_1 relative to baseline
- Peak change in Inspiratory Capacity (IC) (mean of 1 and 2 hour post-dose)

Secondary Endpoints Evaluated on Treatment Day 7 (Visits 3 and 5, following chronic dosing):

- Change from baseline in morning pre-dose FEV_1, defined as the average of the 60 and 30 minute pre-dose values on Treatment Day 7 – Baseline, defined as the average across Visits 2 and 4.
- Peak change from baseline in FEV_1 (defined as highest value of FEV_1 post-dose) where baseline is defined as the average of pre-dose values across Visits 2 and 4.

- Peak change from baseline in IC (mean of 1 and 2 hours post-dose assessments) where baseline is defined as the average IC pre-dose values across Visits 2 and 4.
- 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), where baseline is defined as the average of FEV_1 pre-dose values across Visits 2 and 4.
- Change from baseline morning (A.M.) pre-dose daily peak flow readings taken by subjects, during each treatment period (excluding reading taken pre-dose on Visit 2 (Treatment 1 Day 1), where baseline is defined as the pre-dose measurement on Treatment Day 1. Baseline is taken with the home instrument.
- Change from baseline morning (A.M.) post-dose daily peak flow readings taken by subjects, during each treatment period (excluding reading taken pre-dose on Visit 2 (Treatment 1 Day 1), where baseline is defined as the pre-dose measurement on Treatment Day 1. Baseline is taken with the home instrument.
- Change from baseline evening (P.M.) pre-dose daily peak flow readings taken by subjects, during each treatment period, where baseline is defined as the pre-dose measurement on Treatment Day 1. Baseline is taken with the home instrument.
- Change from baseline evening (P.M.) post-dose daily peak flow readings taken by subjects, during each treatment period, where baseline is defined as the pre-dose measurement on Treatment Day 1. Baseline is taken with the home instrument.

Exploratory Endpoints Evaluated on Treatment Day 7 (Visits 3 and 5, following chronic dosing):

- Peak expiratory flow rate (PEFR) AUC_{0-12} and change from baseline by post-dose time point. AUC will be normalized by dividing by time so that the units of AUC will be L. Baseline is average of PEFR pre-dose values across Visits 2 and 4.
- Forced vital capacity (FVC) AUC_{0-12} and change from baseline by post-dose time point. AUC will be normalized by dividing by 12 so that the units of AUC will be L. Baseline is average of pre-dose FVC values across Visits 2 and 4.
- Change from baseline for mean morning trough IC (mean of -60 and -30 min pre-dose), where baseline is the average of pre-dose IC values across Visits 2 and 4.
- Change from baseline for mean evening trough IC (mean of 11.5 and 12 hours post-dose), where baseline is the average of IC pre-dose values across Visits 2 and 4.
- Mean number of puffs of rescue medication recorded in patient diaries, during each treatment period and by treatment and number of days treated.

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

Statistical Methods:

Sample Size Determination: Power calculations were based on the properties of the primary endpoint, FEV_1 $AUC_{0-12,}$ on the last day of each dosing period following administration of the study drug. Estimates of within subject standard deviation of FEV_1 AUC_{0-12} were obtained from published studies (D'Urzo et al, 2001; van Noord et al, 2005; Maesen et al 1995). A composite within-subjects variance component of 0.13L was adopted. A between-subjects variance component of FEV_1 AUC_{0-12} was obtained from Dahl et al, 2001 and from Calverley et al, 2003. A composite value of 0.13 L was adopted. This represents a total standard deviation of 0.18 L. Note that variance components here are expressed as the standard deviation of the relevant random effect (not the variance). Between and within patients variance components were assumed to have standard deviations of 0.13 L.

The standard error of each contrast was calculated, assuming a generalized least squares analysis in which the ratio of between and within patient variance components was known. The generalized least squares estimates also assumed spherical errors. This is an approximation to the standard error of the REML estimates. It was assumed that there are no carryover effects. The non-centrality parameter of the t-test was calculated, assuming the standard error from the generalized least squares analysis, and a difference of 0.1 L (the minimally clinically significant difference). A sample size of 150 patients achieves 91% power (assuming a significance test at the 5% level, with no multiplicity adjustment. Approximately 175 patients will be recruited in order to achieve 150 patients completing.

Efficacy Analyses: The primary efficacy analysis involves the comparison of the mean primary efficacy endpoint (FEV_1 AUC_{0-12} relative to baseline) for each combination treatment compared to GP MDI 36 µg ex-actuator and FF MDI 9.6 µg ex-actuator. Baseline 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.

For the primary objective, family-wise Type I error will be controlled as follows:

1. No efficacy or non-inferiority claims will be advanced unless the GFF MDI 36/9.6 µg ex-actuator treatment is statistically significantly superior to both the GP MDI 36 µg ex-actuator and the FF MDI 9.6 µg ex-actuator treatments. Both comparisons must be statistically significant before an improvement over the individual components is claimed for this combination therapy.

2. If an improvement over the individual components is detected for the GFF MDI 36/9.6 µg ex-actuator treatment, then the GFF MDI 36/7.2 µg ex-actuator treatments will be compared with the individual components. Both comparisons with the individual components must be statistically significant before an improvement over the individual components is claimed for

this combination therapy.

3. If an improvement over the individual components is detected for the GFF MDI 36/9.6 µg ex-actuator treatment, then the GFF MDI 18/9.6 µg ex-actuator treatments will be compared with the individual components. Both comparisons with the individual components must be statistically significant before an improvement over the individual components is claimed for this combination therapy.

4. If an improvement over the individual components is detected for the GFF MDI 18/9.6 µg ex-actuator treatment, then the GFF MDI 9/9.6 µg ex-actuator treatments will be compared with the individual components. Both comparisons with the individual components must be statistically significant before an improvement over the individual components is claimed for this combination therapy.

Secondary and exploratory efficacy analysis will involve the same comparisons on secondary efficacy endpoints. For endpoints other than time to onset and puffs of rescue medication from diary entries, these comparisons will be performed using the same mixed model and the same algorithms as for the primary efficacy objective. Hierarchical testing will not be imposed for secondary endpoints. For time to onset, comparisons will be based on Murray's method for weighted Kaplan-Meier statistics for paired data (Murray, 2001). The number of puffs of rescue mediation will be summarized using descriptive statistics only.

Safety analyses: Safety analyses will be based on descriptive statistics for ECG, vital sign and laboratory measurements as appropriate, and also on frequencies of adverse events and the number of patients reporting an adverse event.

Statistical Analysis Plans: All statistical analyses will be documented 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 [redacted]

Date of Original Approved Protocol: [redacted]

Date of Most Recent Protocol Amendment (if applicable): [redacted]

Prepared in: [redacted]

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

LIST OF APPENDICES

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
BID	bis in die, twice daily
BMP	Basic Metabolic Panel
BP	Blood Pressure
BPM	Beats per minute
BTPS	Body Temperature and Pressure Saturated
BUN	Blood urea nitrogen
$CaCl_2$	Calcium chloride
CFR	Code of Federal Regulations
CIR	Cumulative incidence ratio
CMP	Comprehensive Metabolic Panel
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case report form
CRO	Contract Research Organization
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
IC	Inspiratory Capacity
ICF	Informed consent form
ICH	International Conference on Harmonization
ICMJE	International Committee of Medical Journal Editors
ICS	Inhaled Corticosteroid
IEC	Independent Ethics Committee
IM	Intramuscular
IRB	Institutional Review Board
ITT	Intention-to-treat
IUD	Intrauterine device
IV	Intravenous
IWRS	Interactive Web Response System
L	Liter
LABA	Long-acting beta agonist
LAMA	Long-acting antimuscarinic agents
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
PFT	Pulmonary function test
PP	Per protocol
PRN	pro re nata
REML	Residual or restricted maximum likelihood
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
SVC	Slow Vital Capacity
TLC	Total Lung Capacity
TNFα	Tumor necrosis factor α
US	United States

TRADEMARK INFORMATION

Trademarks Not Owned By Pearl Therapeutics

Aerolizer

Atrovent

Dulera

Foradil

Handihaler

PulmoSphere

Robinul

Robinul Forte

Spiriva

Symbicort

Ventolin

1 INTRODUCTION

Pearl Therapeutics is developing a combination product comprising the long acting β_2-agonist (LABA) formoterol fumarate and the long acting muscarcinic antagonist (LAMA) glycopyrrolate (Glycopyrrolate and Formoterol Fumarate Inhalation Aerosol [hereafter referred to as Glycopyrrolate and Formoterol Fumarate Metered Dose Inhaler [MDI] or GFF MDI) for the maintenance treatment of bronchospasm associated with Chronic Obstructive Pulmonary Disease (COPD), including chronic bronchitis and emphysema.

COPD is a disease state characterized by airflow limitation that is not fully reversible. The airflow limitation is usually both progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases (GOLD, 2008). None of the existing medications for COPD have been shown to modify the long-term decline in lung function that is the hallmark of this disease. Therefore, pharmacotherapy for COPD is used to decrease symptoms and/or complications (GOLD, 2008).

Bronchodilator medications are central to the symptomatic management of COPD. The principal bronchodilator treatments are β_2-agonists, anticholinergics, and methylxanthines used as single agents or in combination. Regular treatment with long-acting bronchodilators is more effective and convenient than treatment with short-acting bronchodilators (GOLD, 2008). Combining bronchodilators may improve efficacy and decrease the risk of side effects compared to increasing the dose of a single bronchodilator (GOLD, 2008). Anticholinergics and β_2-agonists reduce bronchoconstriction through different mechanisms and there is a long history of combination therapy for COPD with short-acting agents in these classes.

Formoterol is a potent and selective β_2-agonist approved in many countries worldwide for use in asthma and COPD. In patients with COPD, formoterol is typically administered at an orally inhaled dose of 12 µg twice daily with doses up to 24 µg twice daily approved in some countries. Formoterol is classified as a LABA, although it has a rapid onset of action similar to SABAs. Formoterol is also approved in the United States (US) as part of two combination products, Symbicort® (budesonide and formoterol fumarate dihydrate) and Dulera® (mometasone furoate and formoterol fumarate), for the treatment of COPD and asthma, respectively.

Five large, placebo controlled clinical studies of up to 12 months in duration in nearly 2,500 patients demonstrated that formoterol fumarate is effective and well tolerated in patients with COPD (Dahl, 2001; Rossi, 2002; Aalbers, 2002; Campbell, 2005; Campbell, 2007). Many of the adverse events (AEs) associated with β_2-agonists are pharmacologically predictable (Sears, 2002). Treatment with LABAs can result in tachycardia, arrhythmia, other cardiac AEs (e.g. ischemia, heart failure, cardiomyopathy), tremor, and metabolic imbalances, such as decreased serum potassium levels or increased glucose levels. Formoterol fumarate has been well tolerated in placebo-controlled studies, demonstrating a safety profile similar to placebo (Aalbers, 2002; Dahl, 2001; Campbell, 2005; and Rossi, 2002). In addition, a placebo-controlled cardiovascular safety study in over 200 patients with COPD demonstrated that formoterol fumarate had a good cardiovascular safety profile (Campbell, 2007).

Glycopyrrolate (Robinul® and Robinul Forte®) is an anticholinergic drug that is marketed in Australia and New Zealand as a parenteral formulation and in the US in both oral and parenteral formulations. Glycopyrrolate is a quaternary ammonium derivative that when inhaled results in minimal mucosal absorption and systemic side effects. Glycopyrrolate is not approved for respiratory inhalation. However, another anticholinergic drug, tiotropium bromide (Spiriva®), is licensed in the US, Europe (Hansel, 2002) and Australia (eMIMS 2008) as a powder for inhalation. It has been shown to reduce the rate of COPD exacerbations and to improve the effectiveness of pulmonary rehabilitation (Niewoehner, 2005; Casaburi, 2005).

Although glycopyrrolate is not approved for administration via inhalation, there is a large body of published data evaluating the safety and efficacy of inhaled glycopyrrolate in healthy volunteers, patients with COPD, and patients with asthma that support its safety. Inhaled glycopyrrolate has been safely administered to over 550 patients with COPD. The safety and efficacy of chronic daily administration are supported by two large, well-conducted, dose-ranging studies of 28 days duration that evaluated doses up to 240 µg administered via a dry powder inhaler (Kuna, 2007; Vogelmeier, 2008).

Pearl Therapeutics has recently completed clinical studies with its LABA/LAMA formulation (GFF MDI; Studies PT0030901 and PT0031002) as well as Phase IIa dose-ranging studies in patients with COPD with each of the individual component products (Formoterol Fumarate MDI [FF MDI] and Glycopyrrolate MDI [GP MDI]; Studies PT0050801 and PT0010801).

Study PT0030901 was a single center, randomized, double-blind, 4-period cross over study evaluating 4 single-dose inhaled treatments (GP MDI 72 µg, FF MDI 9.6 µg, and GFF MDI 72/9.6 µg delivered individually and GP MDI 72 µg and FF MDI 9.6 µg delivered together in separate inhalers) in healthy subjects. The objectives of this study were to evaluate safety and pharmacokinetics (PK) following each treatment. A total of 16 subjects were enrolled, 13 of whom completed the study. All 4 treatments were safe and well-tolerated in this study. Overall, the most frequently reported AEs were headache and dry mouth. No serious adverse events (SAEs) or AEs leading to withdrawal occurred following any treatment, and no clinically significant changes were noted in QTc values, vital signs, laboratory values, or serum potassium values.

Study PT0031002 was a randomized, double-blind, chronic dosing (7 days), four-period, eight-treatment, placebo and active-controlled, customized, unbalanced, incomplete block crossover multi-center study that evaluated the efficacy, safety and PK of two doses of GFF MDI (72 µg/9.6 µg and 36 µg/9.6 µg twice daily), two doses of FF MDI (9.6 µg and 7.2 µg twice daily) and one dose of GP MDI (36 µg twice daily) in patients with moderate to very severe COPD, compared to placebo, Foradil® Aerolizer® (12 µg twice daily, open label) and Spiriva® Handihaler® (18 µg once daily, open label) as active controls. No substantial differences were noted between any of the active treatments and placebo in terms of common AEs, SAEs, and AEs leading to withdrawal. The most commonly reported AEs (≥ 5% of subjects) overall were dry mouth, headache, COPD worsening, cough, and tremor. No deaths were reported in the study. Five subjects reported a total of 6 SAEs, none of which

were attributed to study treatment: inhaled foreign body, COPD exacerbation (for which the subject was withdrawn), ruptured appendix, atypical chest pain (for which the subject was withdrawn), and gastritis and abdominal aortic aneurysm reported in one subject. A total of 11 subjects were withdrawn from the study due to AEs: 8 subjects experienced COPD (increase/exacerbation); 2 subjects experienced lower respiratory tract infection (chest infection); and 1 subject experienced chest pain. All AEs leading to subject discontinuation from the study were considered unrelated to study treatment with the exception of one event of lower respiratory tract infection reported in 1 subject considered possibly due to treatment with FF MDI 9.6 µg. No clinically significant changes were noted in QTc values, vital signs, laboratory values, or serum potassium values.

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. The primary objective was to evaluate the safety and tolerability of FF MDI at doses of 2.4, 4.8, and 9.6 µg compared to placebo MDI and Foradil Aerolizer 12 µg. A total of 34 patients were enrolled, 29 of whom received all 5 treatments. 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. Changes in laboratory values and vital signs were generally small, and no important trends were noted for FF MDI at any dose. Headache was the most frequently reported AE with FF MDI treatment (5 events following 2.4 µg, 1 following 9.6 µg, 2 following Foradil Aerolizer, and 2 following placebo) followed by dyspnea (1 event following 2.4 µg, 1 following 4.8 µg, 1 following Foradil Aerolizer, and 2 following placebo). Two cases of migraine were reported in 1 patient following treatment with FF MDI 9.6 µg; however, this patient also reported a case of migraine at Screening prior to receiving any treatment. Two SAEs were reported, one following placebo (small intestinal obstruction) and one following FF MDI 4.8 µg (exacerbation of COPD); neither were deemed related to study drug by the Investigator. Two additional AEs resulted in withdrawal of the patient from the study: moderate dyspnea following treatment with Foradil Aerolizer 12 µg, and mild atrial fibrillation following treatment with placebo; both of these events were considered not related or unlikely related to study drug by the investigator. One patient experienced mild tremor following FF MDI 9.6 µg treatment.

Study PT0010801 was a randomized, double-blind, single ascending dose, four-period, six-treatment, balanced, incomplete block, cross-over, placebo and active-controlled, multi-center study that was conducted in patients with mild to severe COPD deemed clinically stable by their physician. The primary objective was to evaluate the efficacy and safety of four doses of GP MDI (18, 36, 72, and 144 µg) compared to placebo MDI and Spiriva Handihaler 18 µg. A total of 33 patients were enrolled, 30 of whom completed the study per protocol. No substantial differences were noted between the GP MDI treatment groups and placebo or Spiriva on any other safety parameter. Dry mouth was the most frequently reported AE with GP MDI treatment, although a clear dose relationship was not observed. Oropharyngeal pain was reported in 2 patients following Glycopyrrolate MDI treatment (18 µg and 144 µg). Changes in laboratory values, vital signs, and ECG parameters were generally small, and no important trends were noted for GP MDI at any dose compared to

placebo or Spiriva. No deaths, SAEs or AEs leading to withdrawal occurred during the study. One death due to complications of COPD occurred outside of the protocol specified reporting period (>30 days from last dose) and was deemed not related to study drug by the investigator.

Note: Unless otherwise indicated, throughout this document all references to doses of GFF MDI will be to the ex-actuator or "delivered" doses (36/7.2, 36/9.6, 18/9.6, and 9/9.6 µg); all references to the FF MDI dose will be to the ex-actuator or "delivered" doses (9.6 µg); all references to the GP MDI dose will be to the ex-actuator or "delivered" doses (36 µg); all references to doses of Ventolin HFA (albuterol sulfate inhalation aerosol) will be to the ex-actuator or "delivered" doses (90 µg).

1.1 Study Rationale

The GOLD guidelines and published literature support the rationale for developing a combination product containing a long-acting β_2-agonist and an anticholinergic in a single device.

Formoterol is a well-established and extensively tested LABA that is clinically indicated for the management of COPD. Glycopyrrolate is under clinical investigation for patients with asthma and patients with COPD. Pearl Therapeutics's clinical studies with the combination of formoterol fumarate and glycopyrrolate (GFF MDI) demonstrated superior efficacy to the individual components (GP MDI and FF MDI), Spiriva, and Foradil for change in FEV_1 AUC_{0-12} after 1 week of dosing. GFF MDI was safe and well-tolerated with a safety profile comparable to Spiriva and Foradil. These data support the further evaluation of GFF MDI in the management of patients with COPD.

Novel technology based on spray-dried porous particles comprised of distearoylphophatidylcholine (DSPC) and $CaCl_2$ that are cosuspended with crystalline active drug substances and formulated into suspension-based hydrofluoroalkane (HFA) MDIs has enabled the development of Glycopyrrolate and Formoterol Fumarate either alone or as fixed combination MDI products, 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 Glycopyrrolate and Formoterol Fumarate either alone or as fixed combination MDI products in this porous particle platform for the long-term, twice daily, maintenance treatment of bronchospasm associated with COPD, including chronic bronchitis and emphysema.

In the development of a combination product, the optimal dose of the individual components needs to be established and then the combination product is compared to the individual components in order to meet the combination rule as outlined in Title 21 CFR Part 300.50. However, in parallel to the dose ranging studies for the individual components, data with the combination product can also provide useful information to aid in dose selection and in the evaluation of efficacy and safety in further studies.

To this end, this study will dose range glycopyrrolate on a fixed background of formoterol fumarate 9.6 µg (GFF MDI 9/9.6, 18/9.6, and 36/9.6 µg versus FF MDI 9.6 µg) to assess the incremental benefit offered by each successive dose. Similarly, this study will assess the incremental benefit of formoterol fumarate on a fixed background of glycopyrrolate 36 µg (GFF MDI 36/7.2 and 36/9.6 µg versus GP MDI 36 µg).

In Study PT0031002, comparable efficacy results were demonstrated for GFF MDI 36/9.6 µg and GFF MDI 72/9.6 µg administered twice daily, thus GFF MDI 36/9.6 µg and lower doses (GFF MDI 18/9.6 and 9/9.6 µg) administered twice daily will be further evaluated in this study. The results from Study PT0031002 also demonstrated that both FF MDI doses (7.2 and 9.6 µg) were non-inferior to Foradil Aerolizer 12 µg for the primary endpoint, FEV_1 AUC_{0-12} at Day 7, (mean difference = -24mL, 90% CI: -62, +15 mL and mean difference = -16 mL, 95% CI: -54, +22 mL, respectively) with only FF MDI 9.6 µg demonstrating bioequivalence from a PK perspective with Foradil Aerolizer 12 µg. These data further support the inclusion of 9.6 µg of formoterol fumarate in the combination product, GFF MDI, and also support the inclusion of 7.2 µg of formoterol fumarate in the combination product to evaluate whether the addition of 7.2 µg of formoterol fumarate to 36 µg of glycopyrrolate (GFF MDI 36/7.2 µg) provides benefit.

Since the mean half-life of GP MDI, FF MDI and GFF MDI is less than 12 hours, a 1-week treatment period should ensure that steady state conditions are achieved. Similarly, a minimum of a 1-week (i.e., more than 10 half-lives) washout period between treatments should ensure that there is no residual carry over effect from one treatment period to another.

The duration of exposure to GFF, GP, and FF MDIs in this study is supported by 14-day toxicology studies in rats and dogs conducted in compliance with Good Laboratory Practices regulations that include a full range of safety assessments including recovery groups, toxicokinetics and abbreviated safety pharmacology. In addition, weekly exposure to PulmoSpheres® in rats and dogs for up to 6 months has demonstrated the safety of the porous particle platform (summarized in the Investigator's Brochure).

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of this study is to demonstrate efficacy of GFF MDI relative to its individual components (GP MDI and FF MDI) in patients with moderate to severe COPD within the range of doses evaluated in this protocol. To this end, the primary efficacy endpoint, FEV_1 AUC_{0-12}, will be compared for each dose of GFF MDI relative to its individual components Glycopyrrolate Metered Dose Inhaler (GP MDI 36 µg ex-actuator, BID) and Formoterol Fumarate Metered Dose Inhaler (FF MDI 9.6 µg ex-actuator, BID).

2.2 Secondary Objectives

The secondary objective of the study is to characterize the dose-response curve for GFF MDI. The primary and secondary endpoints identified in Section 3.1 will be assessed for GFF MDI given as a twice-daily administration as compared to GP MDI and FF MDI.

2.3 Safety Objective

The safety objective is to evaluate the safety of GFF MDI (36/7.2, 36/9.6, 18/9.6, and 9/9.6 µg ex-actuator, BID) in patients with moderate to severe COPD compared with GP MDI (36 µg ex-actuator, BID) and FF MDI (9.6 µg ex-actuator, BID). Safety will be assessed by adverse events (AEs), physical examination findings, assessments of dry mouth and tremor, monitoring for paradoxical bronchospasm, vital signs, electrocardiograms (ECGs), and laboratory assessments.

3 STUDY ENDPOINTS

3.1 Efficacy Endpoints

All efficacy assessments are relative to baseline, and will be compared with the individual components as active controls. Since pre-dose values are known to be variable, and an isolated time-point may not accurately reflect the true baseline, the following baseline will be used for statistical analyses unless otherwise specified for exploratory endpoints: the mean of available pre-dose values on the first day of each treatment cycle, i.e., the mean of pre-dose values at Visits 2 and 4, where the mean of the -60 and -30 minute value for each visit day is averaged and then both visit means are averaged. Previous studies showed that this average baseline was a more effective covariate than with the mean of pre-dose values on the current day, or the mean of pre-dose values during Visit 2 alone.

3.1.1 Primary Efficacy Endpoint

Primary Efficacy Endpoint Evaluated on Treatment Day 7 (Visits 3 and 5, following chronic dosing):

- Forced expiratory volume in 1 second area under the curve (FEV_1 AUC_{0-12}) relative to baseline following chronic dosing (1 week). 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 Efficacy Endpoints

Secondary Endpoints Evaluated on Treatment Day 1 (Visits 2 and 4) Relative to Baseline Defined as Average of Pre-Dose Values Across Visits 2 and 4:

- Peak change from baseline in FEV_1 (defined as change at the highest value of FEV_1 post-dose)
- Time to onset of action (≥10% improvement in FEV_1 relative to baseline)
- Proportion of patients achieving ≥ 12% improvement in FEV_1 relative to baseline
- Peak change in Inspiratory Capacity (IC) (mean of 1 and 2 hour post-dose)

Secondary Endpoints Evaluated on Treatment Day 7 (Visits 3 and 5, following chronic dosing):

- Change from baseline in morning pre-dose FEV_1 , defined as the average of the 60 and 30 minute pre-dose values on Treatment Day 7 – Baseline, defined as the average across Visits 2 and 4.
- Peak change from baseline in FEV_1 (defined as highest value of FEV_1 post-dose) where baseline is defined as the average of pre-dose values across Visits 2 and 4.

- Peak change from baseline in IC (mean of 1 and 2 hours post-dose assessments) where baseline is defined as the average IC pre-dose values across Visits 2 and 4.
- 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), where baseline is defined as the average of FEV1 pre-dose values across Visits 2 and 4.
- Change from baseline morning (A.M.) pre-dose daily peak flow readings taken by subjects, during each treatment period (excluding reading taken pre-dose on Visit 2 (Treatment 1 Day 1), where baseline is defined as the pre-dose measurement on Treatment Day 1. Baseline is taken with the home instrument.
- Change from baseline morning (A.M.) post-dose daily peak flow readings taken by subjects, during each treatment period (excluding reading taken pre-dose on Visit 2 (Treatment 1 Day 1), where baseline is defined as the pre-dose measurement on Treatment Day 1. Baseline is taken with the home instrument.
- Change from baseline evening (P.M.) pre-dose daily peak flow readings taken by subjects, during each treatment period, where baseline is defined as the pre-dose measurement on Treatment Day 1. Baseline is taken with the home instrument.
- Change from baseline evening (P.M.) post-dose daily peak flow readings taken by subjects, during each treatment period, where baseline is defined as the pre-dose measurement on Treatment Day 1. Baseline is taken with the home instrument.

3.1.3 Other/Exploratory Endpoints

Exploratory Endpoints Evaluated on Treatment Day 7 (Visits 3 and 5, following chronic dosing):

- Peak expiratory flow rate (PEFR) AUC_{0-12} and change from baseline by post-dose time point. AUC will be normalized by dividing by time so that the units of AUC will be L. Baseline is average of PEFR pre-dose values across Visits 2 and 4.
- Forced vital capacity (FVC) AUC_{0-12} and change from baseline by post-dose time point. AUC will be normalized by dividing by 12 so that the units of AUC will be L. Baseline is average of pre-dose FVC values across Visits 2 and 4.
- Change from baseline for mean morning trough IC (mean of -60 and -30 min pre-dose), where baseline is the average of pre-dose IC values across Visits 2 and 4.
- Change from baseline for mean evening trough IC (mean of 11.5 and 12 hours post-dose), where baseline is the average of IC pre-dose values across Visits 2 and 4.
- Mean number of puffs of rescue medication recorded in patient diaries, during each treatment period and by treatment and number of days treated.

3.2 Safety Endpoints

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

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

This is a randomized, double-blind, chronic dosing (7 days), two-period, six-treatment, balanced incomplete block, cross-over, multi-center study to assess efficacy and safety of four doses of GFF MDI (36/7.2, 36/9.6, 18/9.6, and 9/9.6 µg ex-actuator, BID) in patients with moderate to severe COPD, compared with its individual components, GP MDI (36 µg ex-actuator, BID) and FF MDI (9.6 µg ex-actuator, BID), as active controls.

This multi-center study will be conducted at approximately 10-15 sites, contributing approximately 10 to 15 patients per site in the United States. Across these sites, it is planned that approximately 175 patients with moderate to severe COPD will be randomized into the study to provide approximately 150 patients to complete the study (see Study Flow Diagram). The entire study period is scheduled to take a maximum of 9 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 Inhalation Aerosol (Ventolin HFA) will be assessed at Screening to characterize the patient population but will not be used to determine eligibility to participate in the study. Patients who are not using a prohibited medication and meet all other entry criteria will return to the clinic at least 7 days (≥2 weeks if taking tiotropium) after screening for Visit 2 (Randomization).

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 1 week (at least 2 weeks if taking tiotropium or phosphodiesterase inhibitors), but not greater than 28 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 (e.g. follow-up on missing chest x-ray or CT scan) at a second Screening visit (Visit 1b) at the investigator's discretion.

At Visit 2 (Randomization Visit; Treatment [Rx] 1, Day 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 30 sequences. Each sequence will include exactly 2 of the 6 treatment groups included in this study. On every treatment day the patient, clinical site personnel and Pearl Therapeutics will be unaware of the treatment to be assigned that day.

Randomization will be centralized, through the use of an IWRS (Interactive Web Response System). All study test medications will be administered twice daily. Each of the 2 treatments will be administered for 7 days with a washout period of at least 7 days (up to 21 days) in between treatments.

During Visit 2 (Rx 1, Day 1), patients will be dispensed study medication and will administer their first 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). Patients will then be discharged from the clinic and will continue to administer study medication for 1 week at home.

Patients will return to the clinic following 1 week of treatment for Visit 3 (Rx 1, Day 7) at approximately the same time as Visit 2 (± 2 hours). Patients will receive their last dose of Rx 1 study medication that morning under supervision and will be required to remain at the clinic until completion of all protocol-defined assessments (see Table 6). Following discharge, patients will undergo a study medication washout period of at least 1 week but no more than 3 weeks duration 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 next treatment in their assigned sequence, as follows:

Visit 4 (Rx 2, Day 1): Administer first dose of Rx 2 study medication and remain at the clinic until completion of all protocol-defined assessments (see Table 5). Following discharge, patients will continue daily administration for 1 week.

Visit 5 (Rx 2, Day 7): Administer last dose of Rx 2 study medication and remain at the clinic until completion of all protocol-defined assessments (see Table 6). Following completion of Visit 5, patients should be returned to pre-study or appropriate COPD maintenance medications and return for the final/follow-up visit after at least 7 days but not greater than 14 days.

Visit 6 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.

Every effort must be made to ensure that patients return to the clinic on Day 7 (1 week) following initiation of each treatment arm. To accommodate scheduling conflicts a window of 7 ± 2 days is permitted (i.e., Treatment Day 7 procedures must be done within a minimum of 5 days and a maximum of 9 days from Treatment Day 1). If any patient exceeds 9 days of

treatment for any treatment, Pearl Therapeutics should be notified and the patient may be withdrawn from the study.

A sponsor-provided peak flow meter and appropriate training on the proper use of the device will be provided to the patient at the Screening Visit. Starting at the Screening Visit, patients will receive a diary in which they will be asked to maintain a daily record of their study medication dosing, rescue medication use, and collection of daily peak flow rates using a sponsor-provided portable peak flow meter.

During the treatment periods (between Visits 2 and 3, and Visits 4 and 5), patients will be permitted to use sponsor-provided Ventolin HFA on an as needed basis for relief of COPD symptoms.

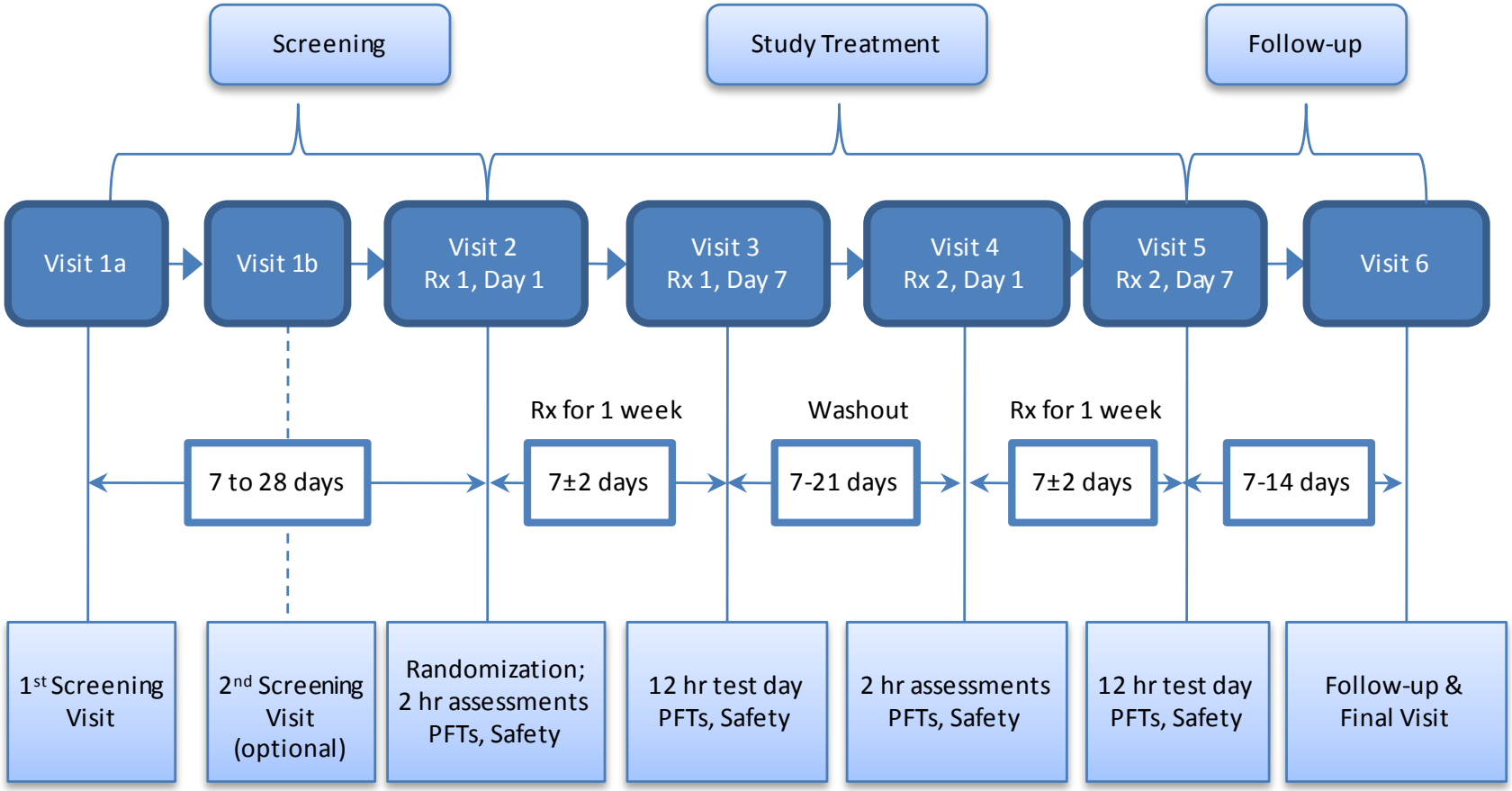
During the washout period when subjects are not taking study drug (between Visits 3 and 4), patients will be permitted to use short-acting bronchodilators (albuterol MDI, Atrovent HFA, or albuterol/ipratropium combination MDI) per the investigator's discretion.

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



PFT = pulmonary function test, Rx = treatment

5 STUDY POPULATION SELECTION AND WITHDRAWAL CRITERIA

5.1 Inclusion Criteria

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

1. Give their signed written informed consent to participate.
2. Are 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 2 years 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 until 2 weeks after Visit 6):
     - Complete abstinence from intercourse from screening until 2 weeks after Visit 6 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. 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 relief of COPD symptoms for at least 1 week prior to randomization and for the duration of the study.
8. 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.
9. Compliance: Patients must be willing to remain at the study center as required per protocol to complete all visit assessments.

5.2 Exclusion Criteria

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

1. 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, uncontrolled glaucoma (subjects previously diagnosed with glaucoma who have intraocular pressure controlled with medication(s) are eligible. All medications approved for control of intraocular pressures are allowed, including topical ophthalmic nonselective beta-blockers such as timolol, levobunolol, metipranolol, carteolol), symptomatic prostatic hypertrophy (if treated and asymptomatic, the patient is eligible for enrollment), uncontrolled diabetes (random blood glucose > 200 mg/dL at screening), uncontrolled thyroid disease or other endocrine disorders, hematological medical problems, and urinary retention problems [including bladder-neck obstruction (e.g., difficulty passing urine, painful urination)]. Note: Patients with a recent history of acute coronary syndrome, or who have undergone percutaneous coronary intervention or coronary artery bypass graft within the past three months are to be excluded. Patients with documented myocardial infarction are to be excluded for one year from the event.
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 basal cell carcinoma of the

skin and 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, glycopyrrolate or other muscarinic anticholinergics, or any component of the MDI.
17. Substance Abuse: Patients with a known or suspected history of alcohol or drug abuse within the last 2-year period prior to Screening.
18. 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.
19. 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
20. 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.
21. 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.
22. 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.
23. 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.

24. 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.
25. 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.
26. 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.
27. A patient who requires the use of a spacer device to compensate for poor hand-to-breath coordination with a MDI.
28. Patients who were previously enrolled in a Pearl Therapeutics PT001 (GP MDI), PT005 (FF MDI), or PT003 (GFF MDI) study.

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*
- phosphodiesterase 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 corticosteroids 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, Atrovent HFA, 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 formoterol and budesonide will be switched to the corresponding dose of fluticasone, mometasone or budesonide administered as a single agent, with short-acting bronchodilators (albuterol MDI, Atrovent HFA, 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 LAMA (tiotropium) administered alone or as a loose combination will have these medications discontinued and replaced with short-acting bronchodilators (albuterol MDI, Atrovent HFA, or albuterol/ipratropium combination MDI) per the investigator's discretion.

Note: During study treatment (i.e., between Visits 2 and 3, and Visits 4 and 5), patients will receive study drug to be administered twice daily and are only allowed sponsor-provided Ventolin HFA to be used as needed for relief of symptoms. Patients are permitted to resume other short-acting bronchodilators during washout period.

Note: During the screening phase and washout period (i.e., between Visit 3 and 4), Albuterol, Atrovent HFA, or ipratropium/albuterol combination drugs 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 6 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 Interactive Web Response System (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 the Sponsor. 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 and Potency	Product Strength	Dosage Form	Comments
GFF MDI 36/7.2 µg ex-actuator	GFF MDI 18/ 3.6 µg per actuation	MDI	Taken as 2 inhalations.
GFF MDI 36/9.6 µg ex-actuator	GFF MDI 18/ 4.8 µg per actuation	MDI	Taken as 2 inhalations.
GFF MDI 18/9.6 µg ex-actuator	GFF MDI 9/4.8 µg per actuation	MDI	Taken as 2 inhalations.
GFF MDI 9/9.6 µg ex-actuator	GFF MDI 4.5/4.8 µg per actuation	MDI	Taken as 2 inhalations.
GP MDI 36 µg ex-actuator†	GP MDI 18 µg per actuation	MDI	Taken as 2 inhalations.
FF MDI 9.6 µg ex-actuator†	FF MDI 4.8 µg per actuation	MDI	Taken as 2 inhalations.
Albuterol Sulfate inhalation aerosol 90 µg ex-actuator§	US source: (Ventolin HFA) Each inhalation contains 108 µg corresponding to 90 µg albuterol base per actuation	MDI	Supplies are open-label.

FF MDI = Formoterol Fumarate Metered Dose Inhaler; GFF MDI = Glycopyrrolate and Formoterol Fumarate Metered Dose Inhaler; GP MDI = Glycopyrrolate Metered Dose Inhaler; MDI = Metered Dose Inhaler.
† Active control
§ Rescue medication during treatment periods.
Note: All study test medications will be administered by oral inhalation.

For 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 Sponsor as summarized in Table 2. Ventolin HFA supplies will be supplied as open-label MDIs.

Table 2. Packaging of Clinical Supplies

Product Name and Potency	Product Strength	Fill Count	Dosing Instructions
GFF MDI 36/7.2 µg ex-actuator	GFF MDI 18/ 3.6 µg per actuation	1 MDI 120 actuations	Take as directed in the morning and evening.
GFF MDI 36/9.6 µg ex-actuator	GFF MDI 18/ 4.8 µg per actuation	1 MDI 120 actuations	Take as directed in the morning and evening.
GFF MDI 18/9.6 µg ex-actuator	GFF MDI 9/4.8 µg per actuation	1 MDI 120 actuations	Take as directed in the morning and evening.
GFF MDI 9/9.6 µg ex-actuator	GFF MDI 4.5/4.8 µg per actuation	1 MDI 120 actuations	Take as directed in the morning and evening
GP MDI 36 µg ex-actuator[§]	GP MDI 18 µg per actuation	1 MDI 120 actuations	Take as directed in the morning and evening
FF MDI 9.6 µg ex-actuator[§]	FF MDI 4.8 µg per actuation	1 MDI 120 actuations	Take as directed in the morning and evening
Albuterol Sulfate inhalation aerosol 90 µg[†]	US source: (Ventolin HFA) Each inhalation contains 108 µg corresponding to 90 µg albuterol base per actuation	1 MDI 60 or 120 actuations	Use only as directed

[§] Active control
[†] Rescue medication during treatment periods.

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 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 supplies for Visit 2 and 4 will be packaged in boxes as outlined in Table 3. Open-label Ventolin HFA supplies will be provided 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 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)
- 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.

Ventolin HFA supplies:

Store at room temperature, 59-77°F (15-25°C), with mouthpiece down. 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

GFF MDI, GP MDI, and FF MDI

Individual GFF, GP, and FF 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 a 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.

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. Patients will be dispensed the MDI and instructed to continue taking study medication twice daily, 2 puffs in the morning and 2 puffs in the evening approximately 12 hours apart, for 7 days at home. The MDI should be stored at room temperature by the patient, avoiding temperature extremes and storage in direct sunlight. See Appendix 3 for instructions on the administration of GFF MDI, GP MDI, and FF MDI.

Ventolin HFA (albuterol sulfate inhalation aerosol)

Bulk supplies of open-label Ventolin HFA will be provided by the sponsor and stored in a secured location within the clinic or pharmacy facilities. Patients will be dispensed Ventolin HFA MDI to take as rescue medication between Visits 2 and 3 and Visits 4 and 5. Ventolin HFA should be stored at room temperature by the patient. Ventolin HFA should be primed per manufacturer's instructions prior to dispensing to patient. See Appendix 4 for the manufacturer's instructions on the administration of Ventolin HFA. Study personnel will record number on the dose counter at the time of dispensing (following priming) and upon return.

6.8 Drug Accountability/Return of Clinical Supplies

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

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

Sites should check with the Pearl Therapeutic 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 on Day 1 (Visits 2 and 4) and Day 7 (Visits 3 and 5) of each treatment period are provided in Table 5 and Table 6, respectively.

All assessments during Visits 2 through 5 will be conducted in the following order: dry mouth and tremor assessments, vital signs, ECGs, clinical laboratory assessments, and spirometry (IC, when conducted should be obtained prior to all other spirometry assessments).

7.1 Efficacy Assessments

Both forced expiratory spirometry for derivation of FEV_1, FVC and PEFR, and Slow Vital Capacity (SVC) maneuvers for IC determination will be assessed using a spirometer that meets or exceeds minimum performance recommendations of the 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., 3.09 L to 2.91 L (ATS/ERS). The results will be printed and maintained in a calibration log, which will be monitored for compliance during the monitoring visits (Refer to Appendix 2, Spirometry Assessment Criteria).

On Day 1 of each treatment period (Visits 2 and 4), spirometry will be conducted 60 minutes and 30 minutes prior to study drug administration. The average of these two assessments will be used to establish test-day baseline FEV_1, FVC and PEFR. **The baseline FEV_1 at Visits 4 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 within 20% of the baseline FEV_1 obtained at Randomization, 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 <u>not</u> 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 investigator's 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 and 2 hours post-dosing of study drug.

On Day 7 of each treatment period (Visits 3 and 5), spirometry will be conducted 60 and 30 minutes prior to study drug administration. The average of these two assessments will be used to establish Day 7 pre-dose FEV_1, FVC, and PEFR. 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. Specifically, FEV_1, FVC and PEFR data will be analyzed for primary and secondary assessments.

On Day 1 of each treatment period (Visits 2 and 4), IC assessments will be obtained at 60 and 30 minutes prior to study drug and at 1 and 2 hours after study drug

On Day 7 of each treatment period (Visits 3 and 5), IC assessments will be obtained at 60 and 30 minutes prior to study drug and at 1, 2, 11.5, and 12 hours after study drug. IC assessments are to precede spirometry assessments.

All patients will be instructed on the performance of the IC maneuver. Subjects must be tested in the seated position wearing a nose clip with no air leaks between the mouth and mouthpiece. Subjects should be relaxed with shoulders down and asked to breathe regularly for several breaths until the end-expiratory lung volume (FRC) is stable (this usually requires at least five tidal maneuvers). They are then urged to take a deep breath to total lung capacity (TLC) with no hesitation. From at least three acceptable trials, the two largest IC measurements should agree within 5% or 100 mL, both of these IC values will be captured and analyzed. Change in peak IC is a secondary endpoint.

7.1.1 Pulmonary Function Tests

All pulmonary function tests including FEV_1, FVC, PEFR, SVC and IC 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 standardized training at the investigator meetings. All technicians are required to demonstrate proficiency in the use of the equipment and the ability to perform technically acceptable 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 7.3 for specific FEV_1 criteria that prompt patients to be discontinued from the study.

7.1.2 Patient Diary

The study coordinator will be responsible for explaining to the patient the proper methods for completing the diary. The diary contains questions concerning actual time of dosing, rescue Ventolin HFA use, and collection of home peak flow measurements using a sponsor-provided home peak flow meter.

Beginning with the Screening Visit (Visit 1) and at Visits 2 and 4, the patient will be given a diary to be completed daily and returned at the next visit. The patient diary will not be dispensed at Visits 3 and 5. Before giving the diary to the patient, the study coordinator will be responsible for entering the patient's identification (screening number [Visit 1] and randomization number [Visits 2 and 4]), and dates of the week(s) the diary is to be completed.

The diary should be completed on the designated dates prefilled by the study site personnel. Upon arriving at the site for Visits 3 and 5, patients will return the diary provided at the previous visit. For example, patients returning for Visit 5 will return the diary given to them at Visit 4.

At or prior to Visit 2 only, patients must demonstrate acceptable use of the diary to be eligible for randomization. Diary data is considered acceptable if the requisite data is completed on at least 4 of 7 consecutive days and patient data would qualify for chronic dosing assessments. Patients who fail their first demonstration of proper diary use may at the investigator's discretion be retrained and Visit 2 rescheduled. Patients who fail to demonstrate proper diary use ≥2 times will be excluded from the study.

The patient is to return the completed diary at each scheduled visit. The study coordinator will be responsible for reviewing the diary for completeness and accuracy with the patient. All data fields should be completed by the patient. The patient will sign (initial) and date each page of the diary on the day it was completed and the study coordinator will initial and date each diary page at the site visit when the diary is returned to validate the authenticity of the entries. If discrepancies or *omissions of data are observed at this review, **the patient**, not the study coordinator, should make the corrections. The patient should draw a single line through the error and initial and date all corrections. The patient should make all entries on the diary card in blue or black ink—**correction fluid or pencil should never be used**. The diary card is considered a source document and should be retained in the appropriate section of the patient binder*.

Furthermore, in conjunction with review of the diary, the patient will be prompted for missed doses of study medication and additional COPD medication. The patient should be instructed to record this information in the diary card. Missing data from >24 hours prior to the site visit should be left blank. Subjects should be instructed to record the time of measurements and doses of study medication and rescue medication in hours and minutes a.m. or p.m., not in 24-hour clock time. P.M. medications taken after midnight but before 6 a.m. on a diary day should be noted as taken on the previous diary day.

7.1.3 Rescue Ventolin HFA Use

The patient will record the total number of "puffs" of rescue Ventolin HFA used on a daily basis. The number of "puffs" of rescue Ventolin HFA to be recorded is the number of actuations of the canister. For example, when rescue Ventolin HFA is required and 2 actuations are inhaled, this should be recorded as 2 "puffs." In the event the patient requires 4

actuations this should be recorded as 4 "puffs." Patients requiring more than 8 puffs per day on 3 or more consecutive days with worsening symptoms should contact the site.

7.1.4 Home Peak Expiratory Flow Rate

The peak flow meter will be provided to all study patients for measurement of PEFR at home. Under supervision and with coaching from the site staff, the patient will be instructed to perform peak expiratory flow efforts using the peak flow meter at Visit 1.

The peak flow meter will be used by all patients for home measurements of pre- and post-dose morning and evening assessments. At each study visit, the site will download data from the home peak flow meter onto a laptop provided by [redacted]. The investigator or designee will print a copy of the PEFR readings and review. Any findings will be discussed with the patient and clinical relevance determined. Patients will bring their peak flow meter to the clinic at each visit.

On each day starting with Day 1 of each treatment, the patient will measure PEFR immediately before and 30 minutes after dosing with study medication. Note: The 30 minute post-dose PEFR on Day 1 should be obtained after spirometry assessments allowing enough time for the patient to recover from the pulmonary function test maneuvers. The patient will be instructed to forcefully exhale from total lung capacity 3 times into the peak flow meter and confirm the collection of PEFR measurements on the diary card.

7.1.5 Medication Compliance

Time of dosing with study medication will be recorded in the patient diary for each day of treatment. Study medication compliance will be checked at all visits and any issues identified will be noted in the appropriate study files.

7.2 Safety Assessments

The safety assessments include ECGs, vital signs, physical examination findings, clinical laboratory tests, monitoring for paradoxical bronchospasm, and assessment of symptoms of dry mouth and 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 6). 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 7.3 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 and 2 hours after study drug [Visits 2 and 4]; 15 and 30 minutes, and 1, 2, 4, 6, 8, 10, 11.5, and 12 hours after study drug on Day 7 of each treatment period [Visits 3 and 5]) 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. On Day 1 of each treatment period (Visits 2 and 4), 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, and 2 hours after study drug. On Day 7 of each treatment period (Visits 3 and 5), 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. Original ECGs with interval printouts and rhythm strip run at 25 mm/sec must be attached to the appropriate CRF.

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. Refer to Section 7.3 for specific criteria for QTcF that prompt patients to be discontinued from 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.

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.

On Day 1 of each treatment period (Visits 2 and 4), hematology (Complete Blood Count) and chemistry (Comprehensive Metabolic Panel) will be obtained within 60 minutes prior to dosing. A basic metabolic panel (BMP) with focus on potassium and glucose parameters will be obtained at 2 hours post-dosing on all patients (see Table 5).

On Day 7 of each treatment period (Visits 3 and 5), hematology (Complete Blood Count) and chemistry (Comprehensive Metabolic Panel) will be obtained within 60 minutes prior to dosing and collect a BMP at 30 minutes and a CMP at 2 hours post-dosing (see Table 6).

Serum pregnancy testing will be performed at Screening and at the Final Visit (Visit 6) with Urine HCG testing occurring prior to the start of each treatment sequence (Visits 2 and 4) 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.

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 an SAE as defined below.

7.2.5.4 Severity

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

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

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

Severe: Associated with inability of 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 7.2.5.10.

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

7.2.5.8 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 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 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 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 may occur following inhalation from an MDI. Dry Mouth is a known side effect following administration of a LAMA. 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 specifically asked about the presence of dry mouth at baseline and at specified intervals (pre-dose and at 1 and 2 hours post-dose on Day 1 and on Day 7). On Day 7 if dry mouth persists at 2 hours additional assessments will be conducted every 2 hours until resolution of symptoms or completion of the test day (see Table 5 and Table 6) and if present, the severity (mild, moderate, and severe) of dry mouth symptoms will be assessed. If dry mouth is not noted at 2 hours post study drug administration, further dry mouth assessments do not need to be collected. All reports of dry mouth exceeding baseline will be recorded as AEs.

Instructions for Recording Dry Mouth AE:

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

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

    a. Patient has a history of dry mouth at Screening, and the event is considered a worsening of pre-existing dry mouth.

    b. Patient has no history of dry mouth at Screening.

3) The investigator should follow all AEs of dry mouth to resolution. An AE of dry mouth 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).

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, severe and very 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 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 document may include, but not be limited to the investigators brochure and approved product labeling for GFF MDI, GP MDI, and FF MDI.

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 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 8.6 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.

7.4 Termination of the Study

The study may be terminated prematurely with sufficient notice in advance by the investigator for any reason as per the terms of the contract with Pearl 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 on Day 1 (Visits 2 and 4) and Day 7 (Visits 3 and 5) of each treatment period are provided in Table 5 and Table 6, respectively.

Table 4. Schedule of Events

Procedures	Screening[a]		Treatment Period 1[a]		Treatment Period 2[a]		Follow-Up/ Final
	Visit 1a	Visit 1b (optional)	Visit 2 Randomization (Rx 1, Day 1)	Visit 3 (Rx 1, Day 7)	Visit 4 (Rx 2, Day 1)	Visit 5 (Rx 2, Day 7)	Visit 6 Final Visit
Informed Consent	X						
Eligibility Criteria	X	X	X				
Verify Continued Eligibility				X	X	X	
Dispense Peak Flow Meter	X						
Reversibility to Ventolin HFA[b]	X						
Demographics & Medical/Surgical History	X	X					
Concomitant Medications[c]	X	X	X	X	X	X	X
Spirometry[d]	X	X	X	X	X	X	
Physical Examination[e]	X						X
Vital Signs[f]	X		X	X	X	X	X
12-Lead ECG[g]	X		X	X	X	X	X
Pregnancy Test[h]	X		X	X	X	X	X
Clinical Laboratory Testing[h]	X		X	X	X	X	X
Adjust COPD Medications[i]	X					X	X
Adverse Events	X	X	X	X	X	X	X
Inhalation Device Training	X		X				
Study Drug Administration			X	X	X	X	
Dispense Patient Diary	X		X		X		
Collect/Review Patient Diary			X	X		X	
Download Peak Flow Meter Data and Review				X		X	
Study Drug Dispensing			X		X		
Study Drug Collection				X		X	
Dry Mouth/Tremor Assessment	X		X	X	X	X	
Paradoxical Bronchospasm[j]			X	X	X	X	

Table 4. Schedule of Events (continued)

a. Screening period of at least 7 days and up to 28 days. Patients are to return to the clinic within 7 days following initiation of each treatment arm. If any patient exceeds 9 days of treatment for any treatment, the Sponsor should be notified and the patient may be withdrawn. There must also be at least 7 days (not to exceed 21 days) between Visits 3 and 4 to allow for appropriate washout of study drug.

b. Assess reversibility of FEV_1 at 30 minutes following 4 puffs Ventolin HFA (to characterize the patient population only; not to be used to determine eligibility to participate in the study).

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 and 4. See Table 6 for spirometry assessments and specific time points to be performed at Visits 3 and 5.

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 hours 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 and 4. See Table 6 for SBP, DBP, and HR assessments and specific time points to be performed at Visits 3 and 5. At Visits 2-5, oral and/or tympanic 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 and 4. See Table 6 for ECG assessments and specific time points to be performed at Visits 3 and 5.

h. All clinical laboratory tests will be obtained at Screening and Follow-up. At Visits 2 through 5, hematology (Complete Blood Count) and chemistry (Comprehensive Metabolic Panel) will be obtained within 60 minutes prior to dosing. At Visits 2 and 4 (Treatment Day 1), BMP with focus on potassium and glucose parameters will be obtained at 2 hour post-dose on all patients (see Table 5). On Treatment Day 7 (Visits 3 and 5), BMP with focus on potassium and glucose parameters will be obtained at 30 minutes and a CMP at 2 hour post-dose (see Table 6). 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). At the end of the Visit 5, return patient to pre-study or other appropriate inhaled maintenance COPD medications.

j. Please refer to Section 7.2.6 for definition of paradoxical bronchospasm.

Table 5. Visit Procedures on Day 1 of Each Treatment Period (Visits 2 and 4)

	Pre-dosing		Post-dosing			
Clinical Variable[a]	**-1 hour**	**-30 minutes**	**15 minutes**	**30 minutes**	**1 hour**	**2 hours**
Dry Mouth and Tremor Assessment		X			X	X[b]
Vital Signs[c]	X	X	X	X	X	X
12- Lead ECG	X[d]	X[d]	X	X	X	X
Clinical Laboratory Testing[e]	X					X
Spirometry (FEV_1, FVC, PEFR)[g]	X[f]	X	X	X	X	X
Paradoxical Bronchospasm[h]			X	X		
Inspiratory Capacity	X	X			X	X
Peak Flow Meter Assessment		X		X		

a. Safety assessments (dry mouth and tremor assessments, vital signs, and ECG) 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 dry mouth or tremor is noted at the 2-hour time point, no further assessment is required. If dry mouth or tremor persists at 2 hours additional assessments will be conducted every 2 hours until resolution of symptoms or completion of the test day.

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

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

e. All clinical laboratory parameters will be obtained within 60 minutes prior to study drug administration; BMP with focus on potassium and glucose parameters will be obtained at 2 hours post-dose **on all patients**.

f. The baseline FEV_1 at Visits 4 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 within 20% of the baseline FEV_1 obtained at Randomization, 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 investigator's discretion (e.g., within one week), or the patient discontinued.

g. The 30 minute post-dose PEFR on Day 1 should be obtained after spirometry assessments allowing enough time for the patient to recover from the pulmonary function test maneuvers.

h. Please refer to Section 7.2.6 for definition of paradoxical bronchospasm.

Note: Where data collection time-points are concurrent, variables must be collected in the following order: Dry mouth and tremor assessment, vital signs, ECG, clinical laboratory assessments, and spirometry (IC when conducted, should be done prior to all other spirometry assessments).

Table 6. Visit Procedures on Day 7 of Each Treatment Period (Visits 3 and 5)

	Pre-dosing		Post-dosing									
Clinical Variable[a]	**-1 hr**	**-30 min**	**15 min**	**30 min**	**1 hr**	**2 hr**	**4 hr**	**6 hr**	**8 hr**	**10 hr**	**11.5 hr**	**12 hr**
Dry Mouth and Tremor Assessment[b]		X	X		X	X						
Vital Signs[c]	X	X	X	X	X	X	X	X	X	X	X	X
12- Lead ECG	X[d]	X[d]	X	X	X	X	X					X
Clinical Laboratory Testing[e]	X			X		X						
Spirometry (FEV_1, FVC, PEFR)[f]	X	X	X	X	X	X	X	X	X	X	X	X
Paradoxical Bronchospasm			X	X								
Inspiratory Capacity	X	X			X	X					X	X
Peak Flow Meter Assessment		X		X								

a. Safety assessments (dry mouth and tremor assessment, vital signs, and ECG) 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 dry mouth or tremor is noted at the 2-hour time point, no further assessment is required. If dry mouth or tremor persists at 2 hours additional assessments will be conducted every 2 hours until resolution of symptoms or completion of the test day.

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

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

e. All specified clinical laboratory parameters will be obtained within 60 minutes prior to study drug administration. A BMP with focus on potassium and glucose parameters will be obtained at 30 minutesand a CMP at 2 hours post-dose.

f. The 30 minute post-dose PEFR on Day 1 should be obtained after spirometry assessments allowing enough time for the patient to recover from the pulmonary function test maneuvers

Note: Where data collection time-points are concurrent, variables must be collected in the following order: Dry mouth and tremor assessment, vital signs, ECG, clinical laboratory assessments, and spirometry (IC when conducted, should be done prior to all other spirometry assessments).

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 dry mouth, glaucoma 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 (to characterize the patient population only; not to be used to determine eligibility to participate in the study).

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.
- Dispense patient diary, peak flow meter and provide instructions on use of peak flow meter and diary completion.

8.2 Randomization Visit (Visit 2; Rx 1, Day 1)

- Collect and review patient diary (if diary is not completed, re-train patient and Visit 2 must be rescheduled).
- Review inclusion/exclusion criteria to confirm patient eligibility.
- Obtain patient treatment assignment information from IWRS.
- 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).
- Dispense patient diary and provide instructions on diary completion if appropriate.
- 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 first dose of newly assigned study drug at the clinic.
    - The patient is to be considered randomized after receiving study medication.
- Perform all post-dosing assessments (refer to Table 5).
- Schedule Visit 3 and ensure patient has adequate supply of study drug and rescue Ventolin HFA.

8.3 Visit 3 (Rx 1, Day 7)

- Collect and review patient diary.
- Note time of last dose of short-acting bronchodilator and other COPD medications on CRF (if <6 hours, reschedule visit).
- Download and review data from Peak Flow Meter
- Confirm patient eligibility to continue.
- Record adverse events (if any).
- Perform urine pregnancy test (women of child-bearing potential only).
- Perform all pre-dose assessments (refer to Table 6).
- Patient will administer final dose of previously dispensed study drug at the clinic under supervision.
- Perform all post-dosing assessments (refer to Table 6).
- Collect previously dispensed study drug.
- Schedule next visit (following a washout period of at least 1 week but no longer than 3 weeks) and ensure patient has adequate supply of COPD medication.

8.4 Visit 4 (Day 1 of Rx 2)

- Review inclusion/exclusion criteria to confirm patient eligibility to continue.
- Download and review data from Peak Flow Meter
- Review of clinical laboratory results from previous visit. Please note whether the results are clinically significant and include comments where applicable.
- Record adverse events (if any).

- Review concomitant medications and ensure adherence to COPD regimen.
- Note time of last dose of short-acting bronchodilator and other COPD medications on CRF (if <6 hours, reschedule visit).
- Perform urine pregnancy test (women of child-bearing potential only).
- Perform all pre-dose assessments (refer to Table 5).
- Dispense patient diary and provide instructions on diary completion if appropriate.
- 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 first dose of newly assigned study drug at the clinic.
- Perform all post-dosing assessments (refer to Table 5).
- Schedule next visit and ensure patient has adequate supply of study drug and rescue Ventolin HFA.

8.5 Visit 5 (Day 7 of Rx 2)

- Collect and review patient diary.
- Note time of last dose of short-acting bronchodilator and other COPD medications on CRF (if <6 hours, reschedule visit).
- Download and review data from Peak Flow Meter
- Review concomitant medications and ensure adherence to COPD regimen.
- Confirm patient eligibility to continue.
- Record adverse events (if any).
- Perform urine pregnancy test (women of child-bearing potential only).
- Perform all pre-dose assessments (refer to Table 6).

- Patient will administer final dose of previously dispensed study drug at the clinic.
- Perform all post-dosing assessments (refer to Table 6).
- Collect previously dispensed study drug.
- Schedule the final/follow-up visit at least 1 week but no longer than 2 weeks from Visit 5. At completion of all Visit 5 assessments, return patient to pre-study or appropriate inhaled maintenance COPD medications.

8.6 Follow-Up (Final) Visit/Premature Discontinuation (Visit 6)

- 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 5, return patient to pre-study or appropriate inhaled maintenance COPD medications.
- Complete study completion page.

8.7 Completion of the Study

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

- 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 7.3).

9 PLANNED STATISTICAL METHODS

9.1 Introduction

This study will be conducted as a 2-period, 6-treatment, balanced incomplete block cross-over design evaluating the following treatments in approximately 175 patients (it is anticipated that 175 patients will be randomized to obtain complete data on 150 patients):

- GFF MDI 36/7.2 µg ex-actuator
- GFF MDI 36/9.6 µg ex-actuator
- GFF MDI 18/9.6 µg ex-actuator
- GFF MDI 9/9.6 µg ex-actuator
- GP MDI 36 µg ex-actuator
- FF MDI 9.6 µg ex-actuator

The overall objectives of this study are to determine the efficacy of the combination GFF MDI therapy, relative to its individual components (GP MDI 36 µg ex-actuator and FF MDI 9.6 µg ex-actuator), and to characterize the dose response of GFF MDI. To this end, each dose of GFF MDI will be compared to both GP MDI 36 µg ex-actuator and FF MDI 9.6 µg ex-actuator, with respect to the primary efficacy endpoint, FEV_1 $AUC_{0\text{-}12}$, relative to baseline.

A balanced incomplete block design will be adopted, in which each of the fifteen pairs of treatments (i.e., in Period 1 and Period 2 of the crossover) is expected to be administered to 10 patients (N=150 patients in total to receive a pair of treatments). The fifteen treatment selections (ignoring order) are shown in Table 7. Each pair of treatments will be used to generate five replicates of a Williams design. Let the treatments be numbered 1…6, then for each pair of treatments i,j (i,j,$\in$ 1, 6), there are 5 subjects receiving i in Period 1 and j in Period 2, and a further 5 subjects receiving j in Period 1 and i in Period 2.

Table 7. Treatment Selections (Ignoring Order)

Selection	Treatments	
1	GFF MDI 36/7.2	GFF MDI 36/9.6
2	GFF MDI 36/7.2	GFF MDI 18/9.6
3	GFF MDI 36/7.2	GFF MDI 9/9.6
4	GFF MDI 36/7.2	GP MDI 36
5	GFF MDI 36/7.2	FF MDI 9.6
6	GFF MDI 36/9.6	GFF MDI 18/9.6
7	GFF MDI 36/9.6	GFF MDI 9/9.6
8	GFF MDI 36/9.6	GP MDI 36
9	GFF MDI 36/9.6	FF MDI 9.6
10	GFF MDI 18/9.6	GFF MDI 9/9.6
11	GFF MDI 18/9.6	GP MDI 36
12	GFF MDI 18/9.6	FF MDI 9.6
13	GFF MDI 9/9.6	GP MDI 36
14	GFF MDI 9/9.6	FF MDI 9.6
15	GP MDI 36	FF MDI 9.6

GP MDI=Glycopyrrolate MDI; FF MDI = Formoterol Fumarate MDI; GFF MDI = Glycopyrolate and Formoterol Fumarate MDI.

9.2 Protocol Variables

9.2.1 Efficacy Endpoints

All efficacy assessments are relative to baseline, and will be compared with the individual components as active controls. Since pre-dose values are known to be variable, and an isolated time-point may not accurately reflect the true baseline, the following baseline will be used for statistical analyses unless otherwise specified for exploratory endpoints: the mean of available pre-dose values on the first day of each treatment cycle, i.e., the mean of pre-dose values at Visits 2 and 4, where the mean of the -60 and -30 minute value for each visit day is averaged and then both visit means are averaged. Previous studies showed that this average

baseline was a more effective covariate than with the mean of pre-dose values on the current day, or the mean of pre-dose values during Visit 2 alone.

9.2.1.1 Primary Efficacy Endpoint

Primary Efficacy Endpoint Evaluated on Treatment Day 7 (Visits 3 and 5, following chronic dosing)

- Forced expiratory volume in 1 second area under the curve (FEV_1 AUC_{0-12}) relative to baseline following chronic dosing (1 week). 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.

9.2.1.2 Secondary Efficacy Endpoints

Secondary Endpoints Evaluated on Treatment Day 1 (Visits 2 and 4) Relative to Baseline Defined as Average of Pre-Dose Values Across Visits 2 and 4:

- Peak change from baseline in FEV_1 (defined as change at highest value of FEV_1 post-dose)
- Time to onset of action (≥10% improvement in FEV_1 at baseline)
- Proportion of patients achieving ≥ 12% improvement in FEV_1 at baseline
- Peak change in Inspiratory Capacity (IC) (mean of 1 and 2 hour post-dose)

Secondary Endpoints Evaluated on Treatment Day 7 (Visits 3 and 5, following chronic dosing):

- Change from baseline in morning pre-dose FEV_1, defined as the average of the 60 and 30 minute pre-dose values on Treatment Day 7 – Baseline, defined as the average across Visits 2 and 4.
- Peak change from baseline in FEV_1 (defined as highest value of FEV_1 post-dose) where baseline is defined as the average of pre-dose values across Visits 2 and 4.
- Peak change from baseline in IC (mean of 1 and 2 hours post-dose assessments), where baseline is defined as the average IC pre-dose values across Visits 2 and 4.
- 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), where baseline is defined as the average of FEV_1 pre-dose values across Visits 2 and 4.
- Change from baseline morning (A.M.) pre-dose daily peak flow readings taken by subjects, during each treatment period (excluding reading taken pre-dose on Visit 2 (Treatment 1 Day 1), where baseline is defined as the pre-dose measurement on Treatment Day 1, taken with the home instrument.

- Change from baseline morning (A.M.) post-dose daily peak flow readings taken by subjects, during each treatment period (excluding reading taken pre-dose on Visit 2 (Treatment 1 Day 1), where baseline is defined as the pre-dose measurement on Treatment Day 1, taken with the home instrument.
- Change from baseline evening (P.M.) pre-dose daily peak flow readings taken by subjects, during each treatment period, where baseline is defined as the pre-dose measurement on Treatment Day 1, taken with the home instrument.
- Change from baseline evening (P.M.) post-dose daily peak flow readings taken by subjects, during each treatment period, where baseline is defined as the pre-dose measurement on Treatment Day 1, taken with the home instrument.

9.2.1.3 Exploratory Endpoints Evaluated on Treatment Day 7 (Visits 3 and 5, following chronic dosing)

- Peak expiratory flow rate (PEFR) AUC_{0-12} and change from baseline by post-dose time point. AUC will be normalized by dividing by time so that the units of AUC will be L. Baseline is average of PEFR pre-dose values across Visits 2 and 4.
- Forced vital capacity (FVC) AUC_{0-12} and change from baseline by post-dose time point. AUC will be normalized by dividing by 12 so that the units of AUC will be L. Baseline is average of pre-dose FVC values across Visits 2 and 4.
- Change from baseline for mean morning trough IC (mean of -60 and -30 min pre-dose), where baseline is the average of pre-dose IC values across Visits 2 and 4.
- Change from baseline for mean evening trough IC (mean of 11.5 and 12 hours post-dose), where baseline is the average of IC pre-dose values across Visits 2 and 4.
- Mean number of puffs of rescue medication recorded in patient diaries, during each treatment period and by treatment and number of days treated.

9.2.2 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, Dry Mouth, 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. QTcF prolongation increase of >30 msec from test day baseline (QTc interval obtained from Treatment Day 1 pre-dose) and QTcF >450 msec for males and >470 msec for females at any time after taking study drug (Days 1 to 7) will be recorded.

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 combination treatment compared to GP MDI 36 µg ex-actuator and FF MDI 9.6 µg ex-actuator. Baseline (as defined in 9.2.1.1 above) 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 model will include Period effects.

For the primary efficacy objective, the family-wise Type I error will be controlled by hierarchical testing. For the primary objective, family-wise Type I error will be controlled as follows:

1) No efficacy claims will be advanced unless the GFF MDI 36/9.6 µg ex-actuator treatment is statistically significantly superior to both the GP MDI 36 µg ex-actuator and the FF MDI 9.6 µg ex-actuator treatments. Both comparisons with the individual components must be statistically significant before an improvement over the individual components is claimed for this combination therapy.

2) If an improvement over the individual components is detected for the GFF MDI 36/9.6 µg ex-actuator treatment, then the GFF MDI 36/7.2 µg ex-actuator treatments will be compared with the individual components. Both comparisons with the individual components must be statistically significant before an improvement over the individual components is claimed for this combination therapy

3) If an improvement over the individual components is detected for the GFF MDI 36/9.6 µg ex-actuator treatment, then the GFF MDI 18/9.6 µg ex-actuator treatments will be compared with the individual components. Both comparisons with the individual components must be statistically significant before an improvement over the individual components is claimed for this combination therapy.

4) If an improvement over the individual components is detected for the GFF MDI 18/9.6 µg ex-actuator treatment, then the GFF MDI 9/9.6 µg ex-actuator treatments will be compared with the individual components. Both comparisons with the individual components must be statistically significant before an improvement over the individual components is claimed for this combination therapy.

The use of a hierarchical testing strategy obviates the need for any multiplicity adjustment (Bauer *et al*, 1998; page 2135).

9.3.2 Secondary Efficacy Analysis

Secondary and exploratory efficacy analysis will involve the same comparisons on secondary efficacy endpoints. For endpoints other than time to onset and puffs of rescue medication from diary entries, these comparisons will be performed using the same mixed model and the same algorithms as for the primary efficacy objective. Hierarchical testing will not be imposed for secondary endpoints.

Analysis of time to onset of action for FEV_1 effect evaluated on Day 1 will use baseline defined as the average of observed pre-dose values from Visits 2 and 4. The "event" is a greater than or equal to 10% improvement from baseline for FEV_1 post-dose, excluding subjects with a ≥10% improvement from baseline at the start of dosing (defined as pre-dose average of 30 minute and 60 minute pre-dose assessments of FEV_1 for a treatment period).

Time to onset 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).

The number of puffs of rescue mediation will be summarized using descriptive statistics only.

9.3.3 Safety Analysis

9.3.3.1 Adverse Events

Adverse events during each treatment regime 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 most recent version of MedDRA will be used throughout the study. If a new version of MedDRA is released during the study, any existing coded events will be updated to conform to the new version. 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.

9.3.3.2 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.

9.3.3.3 Dry Mouth

The incidence of dry mouth 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.

9.3.3.4 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.

9.3.3.5 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 (> 11.1 mmol/L) will also be listed and tabulated by treatment.

9.3.3.6 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.

9.3.3.7 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.

The percentage and number of patients with 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 will be tabulated. No hypothesis tests will be performed, but a Clopper person confidence interval may be provided for each group.

9.4 Randomization

Patients will be randomly assigned to a sequence number using an IWRS. The treatment allocation for each sequence is shown in Table 8. Each of the 30 possible sequences of two treatments chosen from six occurs 5 times.

Table 8 Treatment Sequences

Seq.	P1	P2	Seq.	P1	P2	Seq.	P1	P2
1	GFF36/9.6	GFF36/7.2	51	GFF36/9.6	GFF18/9.6	101	GP36	GFF18/9.6
2	GFF18/9.6	GFF36/7.2	52	GFF36/9.6	GFF9/9.6	102	FF9.6	GFF18/9.6
3	GFF9/9.6	GFF36/7.2	53	GFF36/9.6	GP36	103	GP36	GFF9/9.6
4	GP36	GFF36/7.2	54	GFF36/9.6	FF9.6	104	FF9.6	GFF9/9.6
5	FF9.6	GFF36/7.2	55	GFF18/9.6	GFF9/9.6	105	FF9.6	GP36
6	GFF18/9.6	GFF36/9.6	56	GFF18/9.6	GP36	106	GFF36/7.2	GFF36/9.6
7	GFF9/9.6	GFF36/9.6	57	GFF18/9.6	FF9.6	107	GFF36/7.2	GFF18/9.6
8	GP36	GFF36/9.6	58	GFF9/9.6	GP36	108	GFF36/7.2	GFF9/9.6
9	FF9.6	GFF36/9.6	59	GFF9/9.6	FF9.6	109	GFF36/7.2	GP36
10	GFF9/9.6	GFF18/9.6	60	GP36	FF9.6	110	GFF36/7.2	FF9.6
11	GP36	GFF18/9.6	61	GFF36/9.6	GFF36/7.2	111	GFF36/9.6	GFF18/9.6
12	FF9.6	GFF18/9.6	62	GFF18/9.6	GFF36/7.2	112	GFF36/9.6	GFF9/9.6
13	GP36	GFF9/9.6	63	GFF9/9.6	GFF36/7.2	113	GFF36/9.6	GP36
14	FF9.6	GFF9/9.6	64	GP36	GFF36/7.2	114	GFF36/9.6	FF9.6
15	FF9.6	GP36	65	FF9.6	GFF36/7.2	115	GFF18/9.6	GFF9/9.6
16	GFF36/7.2	GFF36/9.6	66	GFF18/9.6	GFF36/9.6	116	GFF18/9.6	GP36
17	GFF36/7.2	GFF18/9.6	67	GFF9/9.6	GFF36/9.6	117	GFF18/9.6	FF9.6
18	GFF36/7.2	GFF9/9.6	68	GP36	GFF36/9.6	118	GFF9/9.6	GP36
19	GFF36/7.2	GP36	69	FF9.6	GFF36/9.6	119	GFF9/9.6	FF9.6
20	GFF36/7.2	FF9.6	70	GFF9/9.6	GFF18/9.6	120	GP36	FF9.6
21	GFF36/9.6	GFF18/9.6	71	GP36	GFF18/9.6	121	GFF36/9.6	GFF36/7.2
22	GFF36/9.6	GFF9/9.6	72	FF9.6	GFF18/9.6	122	GFF18/9.6	GFF36/7.2
23	GFF36/9.6	GP36	73	GP36	GFF9/9.6	123	GFF9/9.6	GFF36/7.2
24	GFF36/9.6	FF9.6	74	FF9.6	GFF9/9.6	124	GP36	GFF36/7.2
25	GFF18/9.6	GFF9/9.6	75	FF9.6	GP36	125	FF9.6	GFF36/7.2

26 GFF18/9.6	GP36	76 GFF36/7.2	GFF36/9.6	126 GFF18/9.6	GFF36/9.6
27 GFF18/9.6	FF9.6	77 GFF36/7.2	GFF18/9.6	127 GFF9/9.6	GFF36/9.6
28 GFF9/9.6	GP36	78 GFF36/7.2	GFF9/9.6	128 GP36	GFF36/9.6
29 GFF9/9.6	FF9.6	79 GFF36/7.2	GP36	129 FF9.6	GFF36/9.6
30 GP36	FF9.6	80 GFF36/7.2	FF9.6	130 GFF9/9.6	GFF18/9.6
31 GFF36/9.6	GFF36/7.2	81 GFF36/9.6	GFF18/9.6	131 GP36	GFF18/9.6
32 GFF18/9.6	GFF36/7.2	82 GFF36/9.6	GFF9/9.6	132 FF9.6	GFF18/9.6
33 GFF9/9.6	GFF36/7.2	83 GFF36/9.6	GP36	133 GP36	GFF9/9.6
34 GP36	GFF36/7.2	84 GFF36/9.6	FF9.6	134 FF9.6	GFF9/9.6
35 FF9.6	GFF36/7.2	85 GFF18/9.6	GFF9/9.6	135 FF9.6	GP36
36 GFF18/9.6	GFF36/9.6	86 GFF18/9.6	GP36	136 GFF36/7.2	GFF36/9.6
37 GFF9/9.6	GFF36/9.6	87 GFF18/9.6	FF9.6	137 GFF36/7.2	GFF18/9.6
38 GP36	GFF36/9.6	88 GFF9/9.6	GP36	138 GFF36/7.2	GFF9/9.6
39 FF9.6	GFF36/9.6	89 GFF9/9.6	FF9.6	139 GFF36/7.2	GP36
40 GFF9/9.6	GFF18/9.6	90 GP36	FF9.6	140 GFF36/7.2	FF9.6
41 GP36	GFF18/9.6	91 GFF36/9.6	GFF36/7.2	141 GFF36/9.6	GFF18/9.6
42 FF9.6	GFF18/9.6	92 GFF18/9.6	GFF36/7.2	142 GFF36/9.6	GFF9/9.6
43 GP36	GFF9/9.6	93 GFF9/9.6	GFF36/7.2	143 GFF36/9.6	GP36
44 FF9.6	GFF9/9.6	94 GP36	GFF36/7.2	144 GFF36/9.6	FF9.6
45 FF9.6	GP36	95 FF9.6	GFF36/7.2	145 GFF18/9.6	GFF9/9.6
46 GFF36/7.2	GFF36/9.6	96 GFF18/9.6	GFF36/9.6	146 GFF18/9.6	GP36
47 GFF36/7.2	GFF18/9.6	97 GFF9/9.6	GFF36/9.6	147 GFF18/9.6	FF9.6
48 GFF36/7.2	GFF9/9.6	98 GP36	GFF36/9.6	148 GFF9/9.6	GP36
49 GFF36/7.2	GP36	99 FF9.6	GFF36/9.6	149 GFF9/9.6	FF9.6
50 GFF36/7.2	FF9.6	100 GFF9/9.6	GFF18/9.6	150 GP36	FF9.6

The design is balanced for first order carry over effects and for period.

9.5 Sample Size Consideration

Power calculations were based on the primary endpoint, FEV_1 AUC_{0-12} on the last day of each dosing period following administration of the study drug.

Estimates of within subject standard deviation of FEV_1 AUC_{0-12} were obtained from published studies (D'Urzo et al, 2001; van Noord et al, 2005; Maesen et al 1995). A composite within-subjects variance component of 0.13 L was adopted. A between-subjects variance component of FEV_1 AUC_{0-12} was obtained from Dahl et al, 2001 and from Calverley et al, 2003. A composite value of 0.13 L was adopted. This represents a total standard deviation of 0.18 L. Note that variance components here are expressed as the standard deviation of the relevant random effect (not the variance).

For the efficacy comparisons, power was calculated as follows:

1. Between and within patients variance components were assumed to have standard deviations of 0.13 L.

2. The standard error of each contrast was calculated, assuming a generalized least squares analysis in which the ratio of between and within patient variance components was known. The generalized least squares estimates also assumed spherical errors. This is an approximation to the standard error of the REML estimates. It was assumed that there are no carryover effects.

3. The non-centrality parameter of the t-test was calculated, assuming the standard error from the generalized least squares analysis, and a difference of 0.1 L (the minimally clinically significant difference).

Power was calculated as the sample size was varied in sets of 15 patients (to ensure a completely balanced incomplete block design). The sample size required to achieve 91% power (assuming a significance test at the 5% level, with no multiplicity adjustment) is then 150 patients. Approximately 175 patients will be recruited in order to achieve approximately 150 completed patients at study termination.

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 signed before database lock.

9.7 Study Populations

The following analysis populations are defined in this study:

- The **Intent-To-Treat (ITT) Population** is defined as all subjects who are 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).

- A **Modified ITT (MITT) Population** will be used for analysis of efficacy variables, where subjects must have completed at least 1 treatment period, with minimally 2 hours post-dosing on Day 7 for that treatment period (i.e., no greater than one missing data-point from 15 minutes to 2 hours inclusive). Any evaluability criteria with a potential impact on efficacy results will be identified 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 time point within a treatment period. Protocol deviations for exclusion of data from the MITT Population will be agreed between the investigator, Pearl Therapeutics, and the biostatistician prior to data base lock and will be pre-specified in the Statistical Analysis Plan written prior to database lock.

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

Safety 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 ITT, MITT, PP, and Screen Failure 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 Populations, with the MITT Population being considered the primary population for these analyses. The ITT analyses on the primary parameter 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

Change from baseline in pre-dose FEV_1 on Day 7 is defined as the average of the 60 and 30 minute pre-dose values on Treatment Day 7 – baseline. In subjects missing either of these

pre-dose assessments, the value will be calculated from the single measurement. In subjects missing both pre-dose values, pre-dose FEV_1 on Day 7 will not be calculated, but other FEV_1 parameters will be calculated provided they meet the requirements below.

Peak change from baseline in FEV_1 will be included in analyses as long as there is complete FEV_1 data up to and including 2 hours (i.e., no greater than one missing data-point from 15 minutes to 2 hours, inclusive).

Missing data will not be imputed other than specified for the last-one-carried forward (last observation carried forward) as specified below for calculation of FEV_1 AUC_{0-12} as follows:

1. FEV_1 AUC_{0-12} will be calculated if the requirements for Peak FEV_1 are met and there are no 2 adjacent data-points missing at any time-point up to and including hour 12 post-dose and no more than 4 data points missing in the 0 - 12 hours post-dose time interval.

2. If the data obtained for a subject are deemed to be invalid by the study investigator, AUC will not be calculated for the visit;

3. If the final spirometry measurement (12 hours post-dose) is missing, (i.e., the values obtained at the 11.5-hour measurement will be carried forward. If the 11.5-hour measurement is also missing, AUC will not be calculated);

4. AUC will be calculated using last-one-carried forward;

5. Given the missing value rules specified above, AUC will be calculated using trapezoidal integration on the available time points.

AUC will be calculated similary for FVC AUC and PEFR AUC.

If either the 11.5 or 12-hour spirometry measurements is missing, but not both, trough values will be calculated using the other non-missing measurement (11.5 or 12 hour).

If both the 11.5 and 12-hour measurements are missing, trough values will be considered missing.

9.9 Statistical Software

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

10 ADMINISTRATIVE CONSIDERATIONS

10.1 Regulatory Authority Approval

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

10.2 Ethical Conduct of the Study and Institutional Review Board (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).
- United States (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 Laboratory Accreditation

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

10.5 Confidentiality

10.5.1 Confidentiality of Data

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

10.5.2 Confidentiality of Subject/Patient Records

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

10.6 Quality Control and Assurance

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

10.7 Data Management

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

10.8 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 10.9. The investigator will also permit inspection of the study files by Pearl Therapeutics's Quality Assurance auditors, and authorized representatives of the FDA or other applicable regulatory agencies.

10.9 Retention of Data

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

10.10 Financial Disclosure

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

10.11 Investigator's Final Report

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

10.12 Publication Policy

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

authorship will reflect the contribution made by Pearl Therapeutics personnel, the investigators and others involved, such as statisticians.

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

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

11 REFERENCE LIST

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

Akaike H. A new look at the statistical model identification. IEEE Transactions on Automatic Control. 1974;19(6):716–723.

Bauer, P., Röhmel, J., Maurer, W., and Hothorn, L. (1998). Testing strategies in multi- dose experiments including active control. Statistics in Medicine, 17(18):2133–2146.

Calverley P, Lee A, Towse L, et al. Effect of tiotropium bromide on circadian variation in airflow limitation in chronic obstructive pulmonary disease. Br Medical J. 2003;58(10):855–860.

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

Campbell SC, Criner GJ, Levine BE, et al. Cardiac safety of formoterol 12 µg twice daily in patients with chronic obstructive pulmonary disease. Pulm Pharmacol Ther 2007;20:571-579.

Casaburi R, Kukafka D, Cooper CB, Witek TJ Jr, Kesten S. Improvement in exercise tolerance with the combination of tiotropium and pulmonary rehabilitation in patients with COPD. Chest 2005;127:809–817.

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

Dahl R, Greefhorst LA, Nowak D, et al. Inhaled formoterol dry powder versus ipratropium bromide in chronic obstructive pulmonary disease. American Journal of Respiratory and Critical Care Medicine 2001; 164:778–84.

D'Urzo A, Salvo M D, Ramirez-Rivera A, et al. In patients with copd, treatment with a combination of formoterol and ipratropium is more effective than a combination of salbutamol and ipratropium a 3-week, randomized, double-blind, within-patient, multicenter study. Chest. 2001;119(5):1347–1356.

GOLD (Global Initiative for Chronic Obstructive Lung Disease). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. National Institutes of Health, updated 2008 (www.goldcopd.com). Accessed February 16, 2009.

Hansel TT, Barnes PJ. Tiotropium bromide: a novel once daily anticholinergic bronchodilator for the treatment of COPD. Drugs Today 2002; 38: 585–600.

Kuna P, Vinkler I, Overend T, Snape S, Tansley R. Efficacy and tolerability of NVA237 a once daily long acting muscarinic antagonist in COPD patients [abstract]. European Respiratory Journal 2007; P213.

MIMS Online Australia, 2008. CMPMedica Australia Pty Ltd.

Murray, S. (2001). Using Weighted Kaplan–Meier Statistics in Nonparametric Comparisons of Paired Censored Survival Outcomes. Biometrics, 57(2):361–368.

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

Noord JAV. Comparison of tiotropium once daily, formoterol twice daily and both combined once daily in patients with COPD. European Respiratory Journal. 2005;26(2):214–222.

Patterson H and Thompson R. Recovery of inter-block information when block sizes are unequal. Biometrika, 1971; 58:545–554.

Rossi A, Kristufek P, Levine BE, et al. Comparison of the efficacy, tolerability, and safety of formoterol dry powder and oral, slowrelease theophylline in the treatment of COPD. Chest 2002;121:1058-1069.

Sears MR. Adverse effects of beta-agonists. Journal of Allergy and Clinical Immunology 2002;110:S322–8.

Vogelmeier, C. Verkindre, C, Cheung D, Galdiz J. B., Guclu S. Z., Spangenthal S, Overend T, Henley M, Mizutani G, Zeldin R, Geba G. Safety and tolerability of NVA237, a once daily long-acting muscarinic antagonist, in patients with COPD[abstract]. European Respiratory Journal 2008; CP629S.

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 $\geq$15 s (longer times are recommended) and measuring volumes of $\geq$8 L (body temperature (i.e., 37°C), ambient pressure, saturated with water vapor, BTPS) with an accuracy of at least $\pm$3% of reading or $\pm$0.050 L, whichever is greater, with flows between 0 and 14 L-s^{-1}. The total resistance to airflow at 14.0 L-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 $\geq$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%.

VC AND IC MANEUVERS

Equipment

For measurements of VC and IC, the spirometer or flow meter must comply with the requirements for FVC (as described previously) and be capable of accumulating volume for

≥30 s. Expiratory maneuvers or, ideally, both inspiratory and expiratory maneuvers should be included in the display of VC maneuver. Regardless of whether the inspiratory or expiratory maneuver is used for deriving measurements, a display of the entire recorded VC maneuver must be provided. The maximal expiratory volume must be assessed to determine whether the subject has obtained a plateau in the expiratory effort. For display of the slow VC, the time scale may be reduced to 5 mm-s^{-1}.

TECHNICAL CONSIDERATIONS

Minimal recommendations for spirometry systems

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

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

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

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

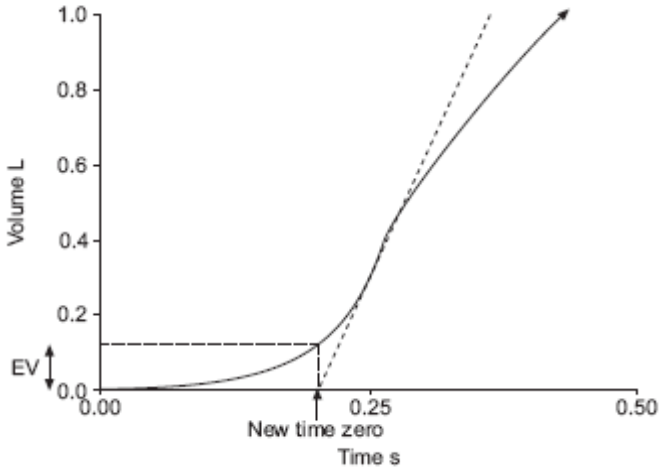
***Acceptable* Tests must meet the following 7 Criteria:**

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

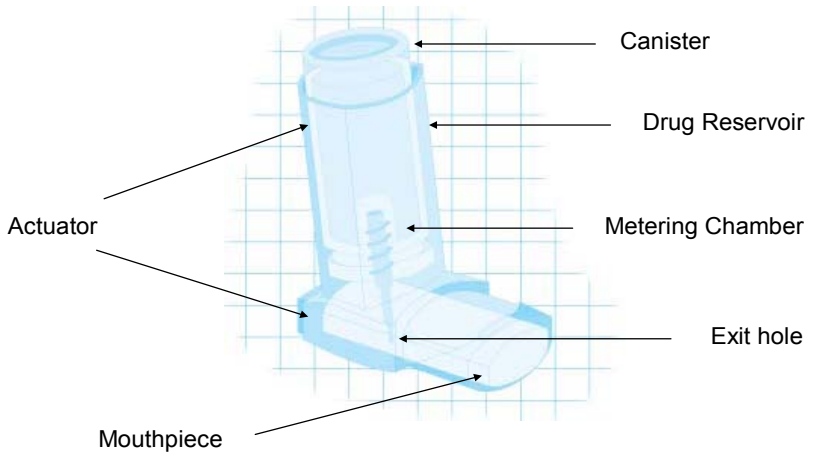
If these criteria are met, the spirometry testing for that time-point may conclude. The highest FEV_1 and the highest FVC obtained at each testing time-point (even if from different reproducible tracings), will be collected.

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 Patient Instructions for Use of GFF MDI, GP MDI, and FF MDI Devices

1. The inhaler should be stored at room temperature.
2. Take the cap off the mouthpiece of the actuator.
3. Inspect the front of the inhaler and make sure there is nothing inside the mouthpiece of the inhaler. Make sure the canister is fully and firmly inserted into the actuator.
4. All MDIs must be primed before the first use. Priming involves releasing a certain number of sprays (4) into the air before the first use of the inhaler. Shaking and priming the inhaler fills a chamber inside the canister with the correct dose and mix of medication so that it'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 7, 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 4 Instructions for Use of Ventolin HFA Inhaler

The Parts of Your VENTOLIN HFA Inhaler

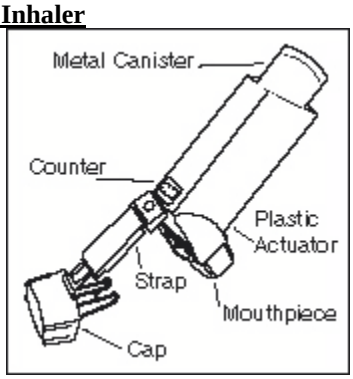


Figure 1

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:

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

Priming your VENTOLIN HFA:

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

Instructions for taking a dose from your VENTOLIN HFA:

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

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

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

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

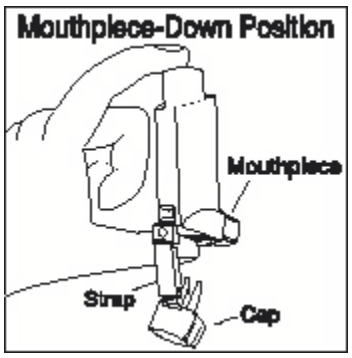


Figure 2

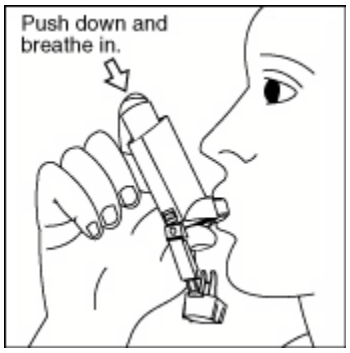


Figure 3

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

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

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

When to Replace Your VENTOLIN HFA

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

How to Clean Your VENTOLIN HFA

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

Wash the actuator at least once a week.

Cleaning instructions:

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

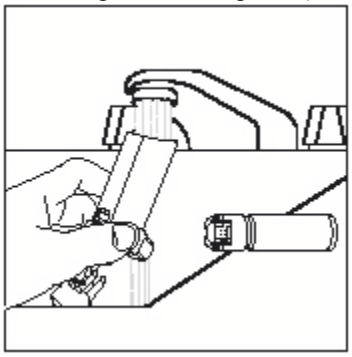


Figure 4

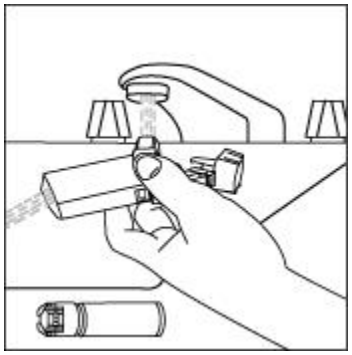


Figure 5

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

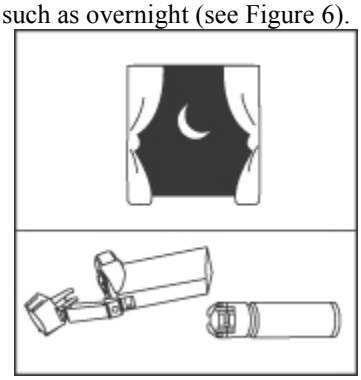


Figure 6

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

If your actuator becomes blocked:

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

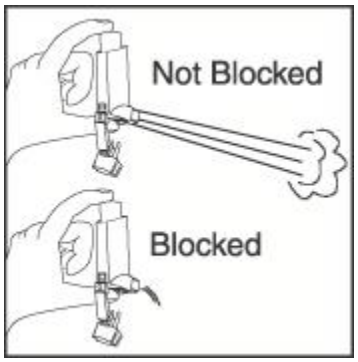


Figure 7

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 5 Sponsor Signatory

Study Title: A Randomized, Double-Blind, Chronic Dosing (7 Days), Two-Period, Six-Treatment, Incomplete Block, Cross-Over, Multi-Center Study to Assess Efficacy and Safety of Four Doses of GFF MDI in Patients With Moderate to Severe COPD, Compared With Its Individual Components (FF MDI and GP MDI) as Active Controls

Study Number: PT003004-01

Final Date: [redacted]

Amendment 1 Date: [redacted]

Signature: [redacted] Date: [redacted]

Name: [redacted]

Title: [redacted]
Pearl Therapeutics, Inc

Appendix 6 Investigator's Agreement and Signature Page

Study Title: A Randomized, Double-Blind, Chronic Dosing (7 Days), Two-Period, Six-Treatment, Incomplete Block, Cross-Over, Multi-Center Study to Assess Efficacy and Safety of Four Doses of GFF MDI in Patients With Moderate to Severe COPD, Compared With Its Individual Components (FF MDI and GP MDI) as Active Controls

Study Number: PT003004-00

Final Date [redacted]

Amendment 1: [redacted]

I agree:

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

Signature:_____ Date:_____

Name:_____

Affiliation: _____

_____