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]
- Protocol Amendment 2 – [redacted]

Clinical Trial Protocol: PT003003-00

Study Title:	A Randomized, Double-blind, Parallel Group, 14-day, Multi-Center Study to Evaluate the Safety of PT003, PT005, PT001 and Foradil® Aerolizer® (12 µg, Open-Label) as Evaluated by Holter Monitoring, in Patients with Moderate to Severe Chronic Obstructive Pulmonary Disease (COPD)
Study Number:	PT003003-00
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; PT003
Formoterol Fumarate Inhalation Aerosol; PT005
Glycopyrrolate Inhalation Aerosol; PT001
Foradil® Aerolizer® (Formoterol Fumarate Dry Powder for Inhalation)

Name of Active Ingredients:
Glycopyrrolate (GP)
Formoterol Fumarate (FF)

Study Title:
A Randomized, Double-blind, Parallel Group, 14-day, Multi-Center Study to Evaluate the Safety of PT003, PT005, PT001 and Foradil® Aerolizer® (12 µg, Open-Label) as Evaluated by Holter Monitoring, in Patients with Moderate to Severe Chronic Obstructive Pulmonary Disease (COPD)

Study Number: PT003003-00

Study Phase: IIb

Study Objective(s):

This study is primarily a safety study. The primary and secondary endpoints are based on 24-hour Holter monitor assessments obtained on Day 14 relative to baseline (Visit 2).

Primary Safety Objective:
The primary safety objective of this study is to compare the change in mean heart rate averaged over 24 hours post-dose, following twice daily dosing over 14 days with Glycopyrrolate and Formoterol Fumarate Metered Dose Inhaler (GFF MDI), Formoterol Fumarate MDI (FF MDI), Glycopyrrolate MDI (GP MDI) or Foradil Aerolizer compared to heart rate averaged over 24 hours at baseline in patients with moderate to severe chronic obstructive pulmonary disease (COPD).

Secondary Safety Objective:
The secondary objective of the study is to further characterize additional cardiovascular safety parameters of all treatment groups including the maximum 24-hour heart rate, mean night-time [22:00 to 06:00) and day-time [06:00 to 22:00)[1] heart rate, ventricular ectopic events (including a single premature ventricular contraction [PVC]), ventricular couplets (defined as two PVCs preceded or followed by regular beats), ventricular runs (defined as

[1] Note the use of open and closed interval notation to specify endpoint relationships. $[a,b) = \{x \in \mathbb{R} | a \leq x < b\}$.

three or more PVCs preceded or followed by regular beats), the number of supraventricular runs, and sustained ventricular tachycardia (VT) [defined as PVCs lasting > 30 s at a rate > 120 beats/min], supraventricular ectopic events, and other clinically relevant arrhythmias (such as atrial fibrillation).

Additional Safety Assessments:
The additional safety objectives are to evaluate the safety of GFF MDI, FF MDI, and GP MDI in patients with moderate to severe COPD compared with Foradil® Aerolizer® (12 µg). Safety will be assessed by adverse events (AEs), vital signs, electrocardiograms (ECGs), and laboratory assessments.

Key Efficacy Objective:
The key efficacy objective of this study is to compare the change in pre-dose morning trough FEV_1 averaged for Day 7 and Day 14 relative to the mean of pre-dose values at baseline (Day 1).

Study Design:

This is a randomized, double-blind, parallel-group, repeated dose (14 days), multi-center study to assess the safety of twice-daily (BID) dosing of GFF MDI (36/9.6 µg, ex-actuator), GP MDI (36 µg, ex-actuator), FF MDI (9.6 µg, ex-actuator) and Foradil Aerolizer (12 µg) as monitored by 24-hour continuous Holter monitoring at the end of treatment.

This multi-center study will be conducted at approximately 20 sites, contributing approximately 10 to 15 patients per site, in Australia, New Zealand, and the United States. Across these sites, it is planned that approximately 220 patients with moderate to severe COPD will be randomized into the study to provide approximately 200 patients to complete the study.

The entire study period is scheduled to take approximately 5-7 weeks for each individual patient. The study is anticipated to run for approximately 9 months and should not exceed 18 months.

Study Design

← **Screening Period** →		← **Treatment Period** →			**Follow-up**
Screening Visits		Randomization		End of Treatment Final Visit	Follow-up Telephone Call
Days -28 to - 1		Day 1	Day 7 (±2)	Day 14 (-3)	Day 21 (+7)
Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	

Study Population:
Approximately 220 patients with moderate to severe COPD will be enrolled to provide approximately 200 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 Descriptions

Product Name & Potency	Dosage Form	Comments
Formoterol Fumarate 9.6 µg ex-actuator (FF MDI)	MDI	Taken as 2 inhalations of the 4.8 µg per actuation strength MDI
Glycopyrrolate 36 µg ex-actuator (GP MDI)	MDI	Taken as 2 inhalations of the 18 µg per actuation strength MDI
Glycopyrrolate 36 µg /Formoterol 9.6 µg ex-actuator combination (GFF MDI)	MDI	Taken as 2 inhalations of the Glycopyrrolate 18 µg / Formoterol 4.8 µg per actuation strength MDI
Formoterol Fumarate Inhalation Powder 12 µg†	DPI	US source: (Foradil® Aerolizer®) Taken as 1 capsule. Each capsule contains 12 µg corresponding to 10 µg formoterol fumarate dihydrate delivered from the mouthpiece *Supplies are open-label.*
Ipratropium Bromide inhalation aerosol 17 µg ex-actuator	MDI	US source: (Atrovent® HFA) Each inhalation contains 21 µg corresponding to 17 µg ipratropium bromide per actuation *Supplies are open-label.*
Albuterol Sulfate inhalation aerosol§ 90 µg ex-actuator	MDI	US source: (Ventolin® HFA) Each inhalation contains 108 µg corresponding to 90 µg albuterol base per actuation *Supplies are open-label.*
† Active control § Rescue medication **Note: All study drugs will be administered by oral inhalation.**		

The 18 µg ex-actuator delivery of glycopyrrolate is equivalent to 22 µg ex-valve of glycopyrrolate.

The 4.8 µg ex-actuator dose of formoterol fumarate is equivalent to 5 µg of formoterol fumarate *dihydrate*. The corresponding ex-valve dose for formoterol fumarate is 6 µg.

Duration of Treatment:
Each patient will receive a maximum of 14 days of study treatment with their assigned treatments. The entire study period is scheduled to take approximately 5-7 weeks for each individual patient from the time of screening (see Figure 1).

Safety Assessments:

The safety assessments include AE and serious adverse event (SAE) assessments, Holter monitoring, ECGs, vital signs, and clinical laboratory tests.

Efficacy Assessments:
Forced expiratory spirometry for derivation of FEV_1, FVC and PEFR will be assessed.

Statistical Methods:
Sample Size Determination: Sample size was based on the properties of the primary safety endpoint: mean heart rate over a 24 hour period. Assuming a standard deviation of 10 bpm, a sample size of 50 patients per treatment yields a 90% power for a true change of 6.5 bpm. 220 patients will be randomized in order to yield 50 completing patients per treatment group.

Efficacy Analyses: Efficacy analysis will be based on a linear model in which Treatment will be a fixed effect, using baseline as a covariate.

The primary efficacy analysis will involve *a priori* comparisons between the combination treatment and Formoterol 9.6 µg MDI and Glycopyrrolate 36 µg MDI for the primary endpoint: change from baseline in mean trough FEV_1 on Days 7 and 14 relative to the mean of pre-dose values at Visit 3. The comparisons will comprise:

- Glycopyrrolate 36 µg /Formoterol 9.6 µg ex-actuator combination vs Formoterol 9.6 µg ex-actuator
- Glycopyrrolate 36 µg /Formoterol 9.6 µg ex-actuator combination vs Glycopyrrolate 36 µg ex-actuator

Other efficacy parameters will include change from baseline FVC and PEFR.

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 with adverse events. Holter data will be analysed using a generalised linear model with quasi-binomial link (for percentage of ventricular ectopics, supraventricular ectopics) or quasi-Poisson link (number of ventricular couplets, supraventricular couplets, ventricular runs, supraventricular runs, tachycardia episodes, bradycardia episodes, and pauses (>= 2 seconds)), or using a linear model (mean heart rate). In all cases the value of the relevant variable during the baseline period will be transformed using the inverse canonical link (logit for quasi-binomial, log for quasi-poisson and identity for the linear model) and used as a covariate

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
BMI	Body mass index
BMP	Basic Metabolic Panel
BTPS	Body Temperature and Pressure Saturated
BUN	Blood urea nitrogen
$CaCl_2$	Calcium chloride
CFR	Code of Federal Regulations
COPD	Chronic Obstructive Pulmonary Disease
CRT	Cardiac resynchronization therapy
CRT_D	Cardiac resynchronization therapy defibrillator
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
FVC	Forced Vital Capacity
GCP	Good clinical practice
GFF MDI	Glycopyrrolate and Formoterol Fumarate MDI
GP MDI	Glycopyrrolate MDI
GGT	Gamma-glutamyl transferase
HCG	Human chorionic gonadotropin
HR	Heart Rate
HFA	Hydrofluroalkane
i.e.	*Id est*, that is
ICD	Implantable cardioverter defibrillator
ICF	Informed consent form
ICH	International Conference on Harmonization
ICMJE	International Committee of Medical Journal Editors
ICS	Inhaled Corticosteroid
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITT	Intention-to-treat
IUD	Intrauterine device
IV	Intravenous
IWRS	Interactive Web Response System
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
PEF	Peak expiratory flow
PEFR	Peak expiratory flow rate
PFT	Pulmonary function test
PK	Pharmacokinetics
PP	Per Protocol
PRN	pro re nata
PVC	premature ventricular contraction
Rx	Treatment
QID	quater in die; four times a day
QTcF	QT corrected using Fridericia's formula ($QT/(RR^{1/3})$)
SAE	Serious Adverse Event
SBP	Systolic blood pressure
SOP	Standard operating procedure
TLC	Total Lung Capacity
TNFα	Tumor necrosis factor α
US	United States
VPB	ventricular premature beats
VT	ventricular tachycardia

TRADEMARK INFORMATION

Trademarks Not Owned By Pearl Therapeutics

Aerolizer

Atrovent

Dulera

Foradil

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 monotherapy 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

was 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 death, 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 (36/9.6 and 72/9.6 µg); all references to doses of FF MDI will be to the ex-actuator or "delivered" doses (2.4, 4.8, 7.2 and 9.6 µg); all references to doses of GP MDI will be to the ex-actuator or "delivered" doses (18, 36, 72, and 144 µg); all references to the Foradil Aerolizer dose will be to the capsule content of 12 µg (corresponds to approximately 10 µg delivered dose); and all references to Spiriva (tiotropium bromide, 18 µg) will be to the capsule content of 18 µg (delivered via the Handihaler); all references to doses of Ventolin HFA (albuterol sulfate inhalation aerosol) will be to the ex-actuator or "delivered" doses (90 µg); all references to doses of Atrovent HFA (ipratropium bromide) will be to the ex-actuator or "delivered" doses (17 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 monotherapy 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.

A cardiovascular safety study provides additional safety assurance prior to proceeding into a longer-term chronic Phase III program. The doses selected for evaluation in this study are based on the prior clinical studies and represent the highest doses likely to be used in the Phase III program.

The duration of exposure to GFF MDI 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 the porous particles 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

This study is primarily a safety study. The primary and secondary endpoints are based on 24-hour Holter monitor assessments obtained on Day 14 relative to baseline (Visit 2).

2.1 Primary Objective

The primary safety objective of this study is to compare the change in mean heart rate averaged over 24 hours post-dose, following twice daily dosing over 14 days with GFF MDI, FF MDI, GP MDI or Foradil Aerolizer compared to heart rate averaged over 24 hours at baseline in patients with moderate to severe COPD.

2.2 Secondary Objectives

The secondary objective of the study is to further characterize additional cardiovascular safety parameters of all treatment groups including the maximum 24-hour heart rate, mean night-time [22:00 to 06:00) and day-time [06:00 to 22:00)[2] heart rate, ventricular ectopic events (including a single premature ventricular contraction [PVC]), ventricular couplets (defined as two PVCs preceded or followed by regular beats), ventricular runs (defined as three or more PVCs preceded or followed by regular beats), the number of supraventricular runs, and sustained ventricular tachycardia (VT) [defined as PVCs lasting > 30 s at a rate > 120 beats/min], supraventricular ectopic events, and other clinically relevant arrhythmias (such as atrial fibrillation).

2.3 Additional Safety Assessments

The additional safety objectives are to evaluate the safety of GFF MDI, FF MDI, and GP MDI in patients with moderate to severe COPD compared with Foradil Aerolizer (12 µg). Safety will be assessed by adverse events (AEs), vital signs, electrocardiograms (ECGs), and laboratory assessments.

2.4 Efficacy Objective

The key efficacy objective of this study is to compare the change in pre-dose morning trough FEV_1 averaged over Day 7 and Day 14, relative to the mean of pre-dose values at baseline (Day 1).

[2] Note the use of open and closed interval notation to specify endpoint relationships. $[a,b) = \{x \in \mathbb{R} | a \leq x < b\}$.

3 STUDY ENDPOINTS

3.1 Safety Endpoints

The safety assessments include AE and SAE assessments, Holter monitoring, ECGs, physical examination findings, vital signs, and clinical laboratory tests.

Primary Safety Endpoint:
The primary safety objective of this study is to compare the change in mean heart rate averaged over 24 hours post-dose, following twice daily dosing over 14 days with Glycopyrrolate and Formoterol Fumarate Metered Dose Inhaler (GFF MDI), Formoterol Fumarate MDI (FF MDI), Glycopyrrolate MDI (GP MDI) or Foradil Aerolizer compared to heart rate averaged over 24 hours at baseline in patients with moderate to severe chronic obstructive pulmonary disease (COPD).

Secondary Safety Endpoints

Based on Holter assessment at baseline and on Day 14: the maximum 24-hour heart rate, mean night-time (22:00 to 06:00) and day-time (06:00 to 22:00)[3] heart rate, ventricular ectopic events (including a single premature ventricular contraction [PVC]), ventricular couplets (defined as two PVCs preceded or followed by regular beats), ventricular runs (defined as three or more PVCs preceded or followed by regular beats), the number of supraventricular runs and sustained ventricular tachycardia (VT) [defined as PVCs lasting > 30 s at a rate > 120 beats/min], supraventricular ectopic events, and other clinically relevant arrhythmias (such as atrial fibrillation).

3.2 Efficacy Endpoints

Forced expiratory spirometry for derivation of FEV_1, FVC and PEFR will be assessed. The key efficacy endpoint will be average change in pre-dose morning trough FEV_1 on Day 7 and Day 14 relative to the mean of pre-dose values at baseline (Day 1, Visit 3 randomization).

[3] Note the use of open and closed interval notation to specify endpoint relationships. $[a,b) = \{x \in \mathbb{R} | a \leq x < b\}$.

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

This is a randomized, multi-center, double-blind, chronic dosing (14 days), parallel group study to assess the safety of twice-daily (BID) dosing of GFF MDI (36/9.6 μg), GP MDI (36 μg), and FF MDI (9.6 μg) compared to Foradil Aerolizer (12 μg) in patients with moderate to severe COPD.

This multi-center study will be conducted at approximately 20 sites, contributing approximately 10 to 15 patients per site, in Australia, New Zealand, and the US. Across these sites, it is planned that approximately 220 patients with moderate to severe COPD will be randomized into the study to provide approximately 200 patients to complete the study.

The entire study period is scheduled to take approximately 5-7 weeks for each individual patient. The study is anticipated to run for approximately 9 months and should not exceed 18 months.

Study Design

← Screening Period →		←——— Treatment Period ———→			Follow-up
Screening Visits		Randomization		End of Treatment Final Visit	Follow-up Telephone Call
Days -28 to - 1		Day 1	Day 7 (±2)	Day 14 (-3)	Day 21 (+7)
Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	

All patients will sign an informed consent form prior to the conduct of any screening assessments (Visit 1). The Investigator will obtain a medical history, physical examination, and any required documentation in order to determine eligibility for participation (inclusion/exclusion criteria). Reversibility of FEV_1 30 minutes following 4 puffs of Ventolin® HFA will be assessed at Screening to characterize the patient population but will not be used to determine eligibility to participate in the study.

Patients who meet all entry criteria will have their inhaled bronchodilator medication switched to Atrovent q.i.d. and Ventolin p.r.n. as rescue medication (see Section 5.4).

All patients will undergo a washout period of at least 1 week (≥2 weeks if taking tiotropium or phosphodiesterase inhibitors), but not greater than 3 weeks prior to returning to the clinic for Visit 2.

Patients will receive a study medication diary in which they will be asked to maintain a daily record of their study medication dosing and rescue medication. The next visit will be scheduled and the patient will be discharged.

Patients will return to the clinic at least 1 week (≥2 weeks if taking tiotropium or phosphodiesterase inhibitors) after screening for Visit 2. At Visit 2, a Holter monitor will be applied and patients will undergo 24-hour Holter monitoring to provide a baseline. During Holter monitoring, patients will complete a specific Holter monitoring diary.

When the patient returns to the clinic for Holter monitor removal the following day, the quality of the recordings will be assessed at the site. If the Holter monitor recordings fail to meet adequate quality criteria (acceptable tracings for a minimum of 18 hours), the Holter Monitor will be reconnected for another 24 hours using a new Holter hook-up kit. The patient will be instructed to continue his/ her medications as per study protocol and complete all necessary assessments on the patient diaries. The patient will return the following day for removal of the Holter Monitor. If the Holter monitoring quality remains unacceptable on the second attempt, the patient will be considered a screen-failure.

Once an acceptable (i.e. acceptable tracings for a minimum of 18 hours) baseline Holter monitor test is obtained, patients can proceed with Visit 3 (Randomization) provided no clinically significant findings are reported following review of the Holter monitoring report by [redacted]. The screening period of 7 to 28 days will be followed by randomization to one of the four treatment groups, with patients being allocated in approximately equal numbers to each group. Eligibility will be determined on the basis of their medical history, physical examination, clinical tests, and adequacy of 24-hour Holter monitoring at Screening.

For all treatment visits (Visits 3, 4 and 5), patients should withhold all study medications on the morning of their visit and should not take Ventolin HFA within 6 hours prior to their visit.

At Visit 3 (Randomization Visit; Treatment Day 1), patients will return to the clinic before 10:00 a.m. Patients who continue to meet entry inclusion/exclusion criteria and remain eligible for participation in the study will be randomized to treatment.

Randomization will be performed centrally, using an interactive web response system (IWRS).

During the treatment phase, all treatments will be administered twice daily. Each of the 4 treatments will be administered for 14 (-3) days. In addition, patients will be supplied by the investigator with open-label Ventolin HFA (90 µg emitted dose per puff) to be used when required as rescue medication throughout the trial.

At Visit 3, a Holter monitor will be placed for continuous 24-hour Holter monitoring and patients will receive a Holter monitoring diary. Patients will be dispensed study medication and a study medication diary 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 to the 2-hour post-dose time point, and be discharged. Patients will return to the clinic after 24 hours (Treatment Day 2) for removal of the Holter monitor and to return the Holter monitoring diary. **Note: If the Holter monitoring assessment collected on Treatment Day 1 is unacceptable, a repeat assessment will not be performed.**

Upon return of the Holter monitor and Holter monitoring diary, patients will be discharged from the clinic and will continue to administer study medication twice daily for 7 (±2) days at home until they return for Visit 4.

Patients will return to the clinic for Visit 4 (Treatment Day 7) at approximately the same time as Visit 3 (± 2 hours). 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). Patients will undergo all protocol-defined pre-dose assessments. Patients will have their final visit (Visit 5) scheduled approximately 1 week later and then be discharged.

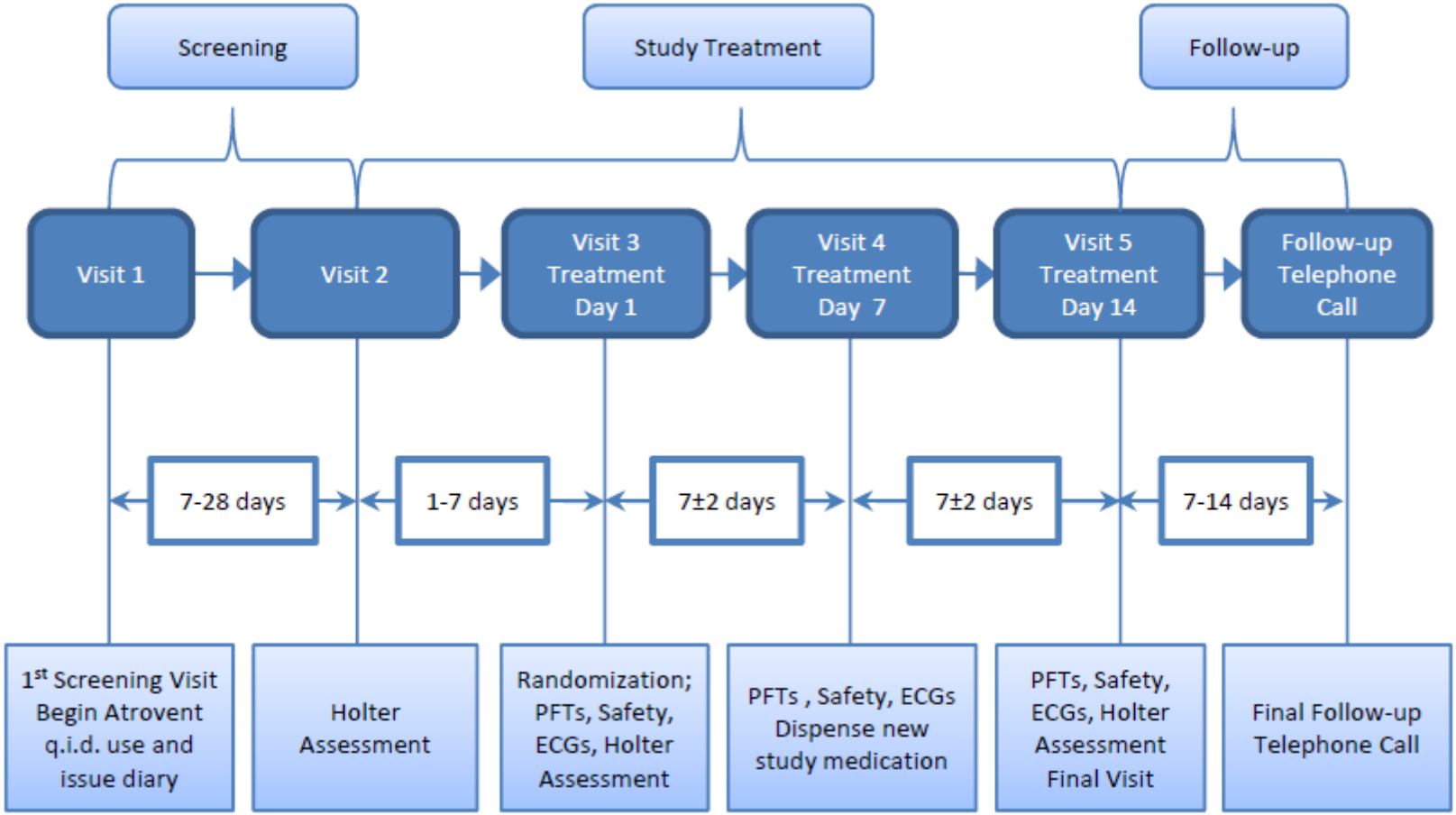
Patients will return to the clinic for Visit 5 (Treatment Day 14) at approximately the same time as Visit 3 (± 2 hours). To accommodate scheduling conflicts a window of 11-14 days is permitted (i.e., Treatment Day 14 procedures must be done within a minimum of 11 days and a maximum of 14 days). Patients will undergo all protocol defined pre-dose assessments. A Holter monitor will be placed and the Holter monitoring diary will be given to the patient. Patients will take their morning dose of study medication at the clinic. Patients will undergo all protocol-defined post-dose assessments. Patients will be discharged and instructed to return to the clinic the following day for removal of the Holter monitor and to return the Holter monitoring diary.

When the patient returns to the clinic the following day, i.e. Day 15 (-3), an ECG will be obtained prior to removal of the Holter monitoring equipment and the quality of the Holter monitor recordings will be assessed at the site. Provided the Holter monitor recording meets protocol defined criteria for acceptability, the patient will undergo a final physical examination, final laboratory assessments, and recording of any AEs. The patient will then be discharged from the study. Study staff will make a follow-up telephone call approximately 7 days later to ensure all post-study AEs (if any) have been captured.

If the Holter monitor recordings fail to meet adequate quality criteria (acceptable tracings for a minimum of 18 hours), the Holter Monitor will be reconnected for another 24 hours using a new Holter hook-up kit and no additional assessments (i.e. physical examination and laboratory assessments) will be perfomed. The patient will be instructed to continue his/ her medications as per study protocol and complete all necessary assessments on the patient diaries. The patient will return the following day for removal of the Holter Monitor and an ECG will be obtained prior to removal of the Holter monitoring equipment. Quality of the recordings will not be assessed at this repeat visit. Patients will undergo a final physical examination, final laboratory assessments, and recording of any AEs. The patient will then be discharged from the study. Study staff will make a follow-up telephone call approximately 7 days later to ensure all post-study AEs (if any) have been captured. **Note: It is advised that patients schedule their visit ahead of Day 14 because 14 days of dosing cannot be exceeded (i.e. if a subject returns for Holter placement on Day 14 and it is noted on Day 15 that the Holter assessment is inadequate, then a repeat Holter assessment will not be possible).**

A Study Flow Diagram is displayed in Figure 1.

Figure 1. Study Flow Diagram



PFT = pulmonary function test, Rx = treatment

Holter monitoring: 24-hour continuous monitoring during screening (Visit 2) and at Visit 3 and Visit 5. Patients are to return the morning following Visits 2, 3 and 5 to return the Holter monitor recorder and Holter monitoring diary.

5 STUDY POPULATION SELECTION AND WITHDRAWAL CRITERIA

5.1 Inclusion Criteria

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

1. Give their signed written informed consent to participate.
2. Are between 40-80 years of age at Visit 1.
3. A female is eligible to enter and participate in the study if she is of:
   - Non-child bearing potential (i.e., physiologically incapable of becoming pregnant, including any female who is 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 8):
     - Complete abstinence from intercourse from screening until 2 weeks after Visit 8 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 3), 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 Atrovent HFA q.i.d. with or without inhaled corticosteroid (ICS) as maintenance treatment for their COPD and Ventolin HFA p.r.n. for relief of COPD symptoms for at least 1 week prior to randomization.
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.
10. Acceptable baseline (Visit 2) Holter monitor recording (see Section 7.2.4).

5.2 Exclusion Criteria

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

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

7. Hospitalization: Patients who have been hospitalized due to poorly controlled COPD within 3 months of Screening (Visit 1).
8. Poorly Controlled COPD: Patients who have poorly controlled COPD, defined as acute worsening of COPD that requires treatment with corticosteroids or antibiotics in the 6-week interval prior to Screening (Visit 1), or between Screening and Randomization (Visit 3).
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 3acceptable 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), 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)].
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 (Type 2) or third degree atrioventricular (AV) block).
      Note: Isolated right bundle branch block does not constitute an exclusion criteria.
    - Clinically significant arrhythmias (e.g., sick sinus syndrome, current or prior history of atrial fibrillation, atrial flutter, 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).
    - Bradycardia with rate <45 bpm.
    - Pathological Q wave indicating prior myocardial infarction
    - Significant ST-T wave abnormalities (excluding non-specific ST-T wave abnormalities)
13. Clinically significant abnormal findings during the baseline Holter recording defined as (but not limited to) any of the following:
    - Average heart rate ≤ 40 beats per minute for any one hour
    - Second-degree Atrioventricular (AV) block (Type 2) or third-degree AV block. Transient type 1 second degree AV block lasting for more than 60 minutes.
    - Ventricular asystole of 2.5 seconds duration

- Any run of ventricular ectopic beats associated with symptoms (hypotension or syncope), regardless of the rate.
- Any episode of ventricular flutter and/or ventricular fibrillation.
- Any episode of sustained ventricular tachycardia (VT)
  - VT is defined as a run of 3 or more ventricular premature beats (VPB's) with a rate >120 beats per minute. Sustained VT is defined as VT lasting > 30 seconds or > 60 beats. Nonsustained VT is a run of 3 or more VPB's with a rate > 120 beats per minute which does not fulfill the criteria for sustained VT.
- Five or more events of non-sustained VT / 24 hours or any episode of non-sustained VT with > 15 VPB's in a row.
- > 200 VPB/HR
- Paroxysmal supraventricular tachycardia

14. Patients with a pacemaker or ICD/CRT/CRT_D devices
15. Uncontrolled Hypertension: Patients who have clinically significant uncontrolled hypertension.
16. 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.
17. 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.
18. 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 and/or constituents of the dry powder product (lactose).
19. Substance Abuse: Patients with a known or suspected history of alcohol or drug abuse within the last 2-year period prior to Screening.
20. 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.
21. 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.

22. 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.
23. 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.
24. 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.
25. 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.
26. 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.
27. 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.
28. 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.
29. A patient who requires the use of a spacer device to compensate for poor hand-to-breath coordination with a MDI.
30. Patients who were previously enrolled in a Pearl Therapeutics PT001 (GP MDI), PT005 (FF MDI) or PT003 (GFF MDI) studies.

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 3 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 Atrovent HFA qid as maintenance therapy of their COPD and Ventolin HFA prn as

rescue medication. During the treatment period (Visit 3 – Visit 5), patients will discontinue use of Atrovent HFA qid and continue use of Ventolin HFA prn as rescue medication. All short acting bronchodilators should be withheld for at least 6 hours before Visits 3, 4 and 5.

- 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 (Atrovent HFA q.i.d. for maintenance of COPD and Ventolin HFA p.r.n. as rescue medication during the screening period) per the protocol provided they have been maintained on a stable dose for at least 4 weeks.
- Patients receiving a maintenance dose of an ICS that is not administered as a fixed dose combination together with a LABA will be permitted to continue the ICS provided they have been maintained on a stable dose for at least 4 weeks.
- All patients treated with either a LABA (salmeterol, formoterol) or long-acting anti-muscarinic agent (LAMA) (tiotropium) administered alone or as a loose combination will have these medications discontinued and replaced with short-acting bronchodilators (Atrovent HFA q.i.d. for maintenance of COPD and Ventolin HFA p.r.n. as rescue medication during the screening period) per the protocol.

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) until the patient completes or discontinues from 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 Pearl Therapeutics. Each person accessing the IWRS system must be assigned an individual unique PIN. They must use only their assigned PIN to access the system and they must not share their assigned PIN with anyone.

6.2 Product Descriptions

Investigational materials will be provided by the Sponsor as summarized in Table 1.

Table 1. Product Descriptions

Product Name & Potency	Dosage Form	Comments
Formoterol 9.6 µg ex-actuator (FF MDI)	MDI	Taken as 2 inhalations of the 4.8 µg per actuation strength MDI
Glycopyrrolate 36 µg ex-actuator (GP MDI)	MDI	Taken as 2 inhalations of the 18 µg per actuation strength MDI
Glycopyrrolate 36 µg /Formoterol 9.6 µg ex-actuator combination (GFF MDI)	MDI	Taken as 2 inhalations of the Glycopyrrolate 18 µg / Formoerol 4.8 µg per actuation strength MDI
Formoterol Fumarate Inhalation Powder 12 µg[†]	DPI	US source: (Foradil Aerolizer) Taken as 1 capsule. Each capsule contains 12 µg corresponding to 10 µg formoterol fumarate dehydrate delivered from the mouthpiece *Supplies are open-label.*
Ipratropium Bromide inhalation aerosol 17 µg ex-actuator	MDI	US source: (Atrovent HFA) Each inhalation contains 21 µg corresponding to 17 µg ipratropium bromide per actuation *Supplies are open-label.*
Albuterol Sulfate inhalation aerosol[§] 90 µg ex-actuator	MDI	US source: (Ventolin HFA) Each inhalation contains 108 µg corresponding to 90 µg albuterol base per actuation *Supplies are open-label.*
[†] Active control [§] Rescue medication **Note: All study drugs will be administered by oral inhalation.**		

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

For open-label Atrovent HFA (ipratropium bromide, 17 µg), bulk commercial metered dose inhalers with dose counters will be provided. Manufacturer's instructions for study drug administration will be provided.

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

6.3 Primary Packaging and Labeling Information

Investigational materials will be packaged by the Sponsor as summarized in Table 2 below. Atrovent HFA and Ventolin HFA supplies will be supplied as open-label MDIs.

Table 2. Packaging of Clinical Supplies

Product Name and Potency	Fill Count	Dosing Instructions
Formoterol Fumarate 9.6 µg ex-actuator (FF MDI)	1 MDI 120 actuations	Take two inhalations as directed in the morning and evening.
Glycopyrrolate 36 µg ex-actuator (GP MDI)	1 MDI 120 actuations	Take two inhalations as directed in the morning and evening.
Glycopyrrolate 36 µg /Formoterol 9.6 µg ex-actuator combination (GFF MDI)	1 MDI 120 actuations	Take two inhalations as directed in the morning and evening.
Formoterol Fumarate Inhalation Powder 12 µg[†]	N/A	Take one capsule as directed in the morning and evening.
Ipratropium Bromide inhalation aerosol 17 µg ex-actuator[†]	1 MDI 200 actuations	Take two inhalations as directed four times a day.
Albuterol Sulfate inhalation aerosol[§] 90 µg ex-actuator	1 MDI 60 or 200 actuations	Use only as directed.
[†] Active control [§] Rescue medication		

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

Open-label Supplies: Open-label Foradil Aerolizer supplies will be provided as individually labeled DPIs and bulk labeled commercial blister packs packaged in sets of 4 blister pack per patient within a foil overwrap labeled with a two-part label. Each Foradil Aerolizer will have a single label.

Open-label Atrovent HFA and 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 the study will be packaged in boxes as outlined in Table 3. Open-label Atrovent HFA and 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
Foradil Aerolizer Device	1 DPI
Bulk Foradil Aerolizer Capsule	1 Foil Pouch Containing 4 Blister Packs Each
Ventolin HFA	1 MDI
Atrovent HFA	1 MDI

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

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

6.5 Unblinding Procedures

The IWRS should be used in order to unblind patients and to unmask drug identity. Pearl Therapeutics will not provide a disclosure envelope with the clinical supplies. The investigator or treating physician may unblind a subject's treatment assignment **only in the case of an emergency**, when knowledge of the study treatment is essential for the

appropriate clinical management or welfare of the subject. Whenever possible, the investigator must first discuss options with the Medical Monitor or appropriate study personnel **before** unblinding the subject's treatment assignment. If this is impractical, the investigator must notify Pearl Therapeutics as soon as possible, but without revealing the treatment assignment of the unblinded subject, unless that information is important for the safety of subjects currently in the study. The date and reason for the unblinding must be recorded in the appropriate data collection tool.

6.6 Storage Requirements

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

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

Atrovent HFA supplies: Store at 25°C (77°F). Brief storage between between 59 and 86°F (15 and 30°C) is permitted. Do not puncture. Do not use or store near heat or open flame. Exposure to temperatures above 120°F may cause bursting. Never throw the inhaler into a fire or incinerator. Avoid spraying in eyes.

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

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

6.7 Instructions for Preparation of Treatments for Administration and Dispensing

GFF MDI, GP MDI, and FF MDI

Individual 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 (puff).

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

Each dose will consist of 2 puffs from the MDI. 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, , until patient returns to the clinic. The MDI should be stored at room temperature by the patient, avoiding temperature extremes and storage in direct sunlight. See Appendix 4 for instructions on the administration of GFF MDI, GP MDI, and FF MDI.

Foradil Aerolizer

Individual Foradil Aerolizer devices will be packaged in a foil overwrap contained in an individual visit treatment carton. Both the visit treatment carton and the foil overwrap will have a label with a component ID number. Confirm that the identifier given by IWRS and the component ID number written on the label are the same. The foil overwrap is labeled with a two-part label. Write the patient number and treatment visit number on each of the two-part labels. The 'tear-off' part of the label is to be placed onto the IWRS confirmation report.

For open-label Foradil Aerolizer drug supplies, the bulk commercial blister packs will be stored refrigerated in a secured location within the clinic or pharmacy facilities. To ensure adequate time for equilibration (minimum 2 hours) to room temperature prior to administration, one foil pouch (containing 4 blister packs) should be kept in a secure location at room temperature. If a patient is randomized to Foradil Aerolizer, the equilibrated supplies will be dispensed and at an appropriate time following study drug administration, study staff will obtain new foil pouch (containing 4 blister packs) from the refrigerated bulk supplies. Retain new foil pouch at the site, stored at room temperature in a secured location for use with a subsequent patient.

The contents of 1 capsule each will be inhaled in the morning and in the evening approximately 12 hours apart, until patient returns to the clinic. See Appendix 5 for the manufacturer's instructions on the administration of Foradil Aerolizer.

Atrovent HFA (ipratropium bromide)

Individual Atrovent HFA MDIs will be contained in an individual visit treatment box. Both the visit treatment box and the foil overwrap will have a label with a component ID number. Confirm that the identifier given by IWRS and the component ID number written on the label are the same. The 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.

Atrovent HFA is a solution aerosol that does not require shaking. However, as with any other MDI, some coordination is required between actuating the canister and inhaling the medication. Atrovent HFA should be primed per manufacturer's instructions prior to dispensing to patient (i.e. "prime" or actuate Atrovent HFA before using for the first time by releasing 2 test sprays into the air away from the face). In cases where the inhaler has not been used for more than 3 days, prime the inhaler again by releasing 2 test sprays into the air away from the face. Patients should avoid spraying Atrovent HFA into their eyes.

Patients will be dispensed the MDI at Visit 1 to continue taking study medication four times a day (approximately 6 hours apart) during the run in period between Visits 1 to 3, 2 puffs with each administration. The MDI should be stored at room temperature by the patient, avoiding temperature extremes and storage in direct sunlight. See Appendix 6 for the manufacturer's instructions on the administration of Atrovent HFA.

Ventolin HFA (albuterol sulfate inhalation aerosol)

Bulk supplies of open-label Ventolin HFA will be provided by Pearl Therapeutics and stored in a secured location within the clinic or pharmacy facilities. 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 7 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 or destroyed as directed by Pearl Therapeutics.

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

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

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

7 STUDY PROCEDURES

A time and events schedule is provided in Table 4.

All assessments during Visits 2 through 5 will be conducted in the following order: ECGs, vital signs, clinical laboratory assessments, and spirometry.

7.1 Efficacy Assessments

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

The volume accuracy of the spirometer is to be checked daily using a 3 L syringe across 3 flow ranges e.g., 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).

At each visit during the treatment period (Visits 3, 4 and 5), spirometry will be conducted 60 minutes and 30 minutes prior to study drug administration. The average of the two pre-dose assessments will be used to establish a baseline FEV_1 at Visit 3 and a corresponding pre-dose trough value at Visits 4 and 5.

7.1.1 Pulmonary Function Tests

All pulmonary function tests including FEV_1, FVC and PEFR as defined in ATS/ERS guidelines (Miller, 2005) and will be performed in accordance with ATS criteria (Miller, 2005).

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

Refer to Section 7.3 for specific FEV_1 criteria that prompt patients to be discontinued from the study.

7.1.2 Patient Diaries

7.1.2.1 Study Medication 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 and rescue Ventolin HFA use. Two types of diaries will be provided – one for use during the screening period (between Visits 1 and 3) when patients are taking Atrovent HFA (17 μg) q.i.d. and Ventolin HFA p.r.n. as rescue medication and the other for use during the treatment period (between Visits 3 and 5) when patients are taking study medication b.i.d. and Ventolin HFA p.r.n. as rescue medication.

Beginning with the Screening Visit (Visit 1), the patient will be given a diary to be completed daily and returned at the next visit. Before giving the diary to the patient, the study coordinator will be responsible for entering the patient's identification (screening number for Visits 1 and 2, and randomization number for all other Study Visits), 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 a study visit, patients will return the diary provided at the previous visit.

At Visit 3, patients should demonstrate acceptable use of the diary. Patients who fail to demonstrate proper diary use should be retrained prior to randomization.

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.

7.1.2.2 Holter Monitoring Diary

Patients will complete a Holter Monitor Diary during the 24-hour collection period for holter monitoring. The diary will be in the form of a checklist and will ask patients to confirm whether certain predetermined events occurred during the 24-hour monitoring period.

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 Medication Compliance

Time of dosing with study medication will be recorded in the patient study medication 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 AE and SAE assessments, Holter monitoring, ECGs, physical examination findings, vital signs, and clinical laboratory tests.

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 3). A complete physical examination will be performed at Screening and the Final Visit (Visit 5). A complete physical examination will include the following: general appearance, skin, head, eyes, ears, nose, throat, neck (including thyroid), lymph nodes, chest, heart, abdomen, extremities, and nervous system. Weight, assessed in ordinary indoor clothing with shoes off, and height (Screening) will be recorded at the specified visits.

7.2.2 Vital Sign Measurements

Heart rate, systolic and diastolic blood pressure ('vital signs') will be assessed at each visit; assessments will be obtained after being supine for 10 minutes. 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, systolic and diastolic blood pressure readings that prompt patients to be discontinued from the study. When vital signs assessment are scheduled at the same time point as ECGs, blood draws and/or spirometry, the sequence of events should be: ECG, vital signs, laboratory assessments and spirometry.

Systolic and diastolic blood pressures, heart rate will be obtained 60 and 30 minutes prior to study drug administration on Days 1, 7 and 14 as well as 30 minutes and 2 hours after study drug on Days 1 and 14. On Days 2 and 15 systolic and diastolic blood pressures, heart rate will be obtained immediately after ECG assessment. Temperature will be obtained at Screening and once at each visit as part of the initial vital sign assessment (i.e. Once on Day 1, 2, 7, 14 and 15), and will not be repeated at subsequent time points unless clinically indicated.

7.2.3 12-Lead Electrocardiogram (ECG)

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.

ECGs will be obtained at:

- Screening (Visit 1)
- Treatment Day 1 (Visit 3): between 1 to 2 hours and 30 minutes to 1 hour prior to study drug and at 30 minutes and 2 hours after study drug.
- Treatment Day 2 prior to removal of the Holter monitor
- Treatment Day 7 (Visit 4): within 60 minutes prior to study drug administration.
- Treatment Day 14 (Visit 5): between 1 to 2 hours and 30 minutes to 1 hour prior to study drug and at 30 minutes and 2 hours after study drug.
- Day 15 prior to removal of the Holter monitor (Study drug not to be administered beyond Day 14)

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 manually calculated QTcF 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, a repeat ECG is to be recorded. If the prolonged QTc intervals are confirmed on review by the investigator (or designated ECG reviewer), the Investigator will make a

determination on the suitability of continuing the patient in the study. If QTcF interval prolongation exceeding these limits is verified during treatment, the patient's medical background should be examined closely for risk factors that may have contributed to the event, including genotyping for hereditary long QT syndromes, if appropriate. Refer to Section 7.3 for specific criteria for QTcF (Fridericia's Formula) that prompt patients to be discontinued from the study.

Additional ECGs will be obtained if the patient's resting 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 at Visit 3). Refer to Section 7.3 for specific criteria for heart rate that prompt patients to be discontinued from the study.

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 24-hour continuous electrocardiography (Holter monitoring)

The designated CRO for Holter monitoring will be [redacted]. All Holter monitor recordings will be assessed for cardiac arrhythmias by an independent cardiologist appointed by [redacted].

Continuous 12-lead ECGs (Holter assessment) will be obtained at Visit 2 (screening), Visit 3 (baseline) and Visit 5 [Day 14(-3); end of treatment]. The Visit 2, Visit 3 and Visit 5 Holter monitor recordings are to be initiated in the morning at approximately the same time (+/- 2 hours). The Visit 3 and Visit 5 Holter monitoring will be initiated 15-30 minutes prior to the administration of the morning dose of trial medication.

Continuous Holter monitor recording will be collected for a minimum of 24 hours. Holter monitor recordings should contain a minimum of 18 hours of acceptable quality recording in a 24-hour period to be deemed an acceptable Holter assessment.

The Holter recording obtained at Visit 2 will be used to determine the patient's eligibility for the study and will serve as the baseline for all comparisons. If the initial Holter monitor assessment at Visit 2 is unacceptable, the Holter Monitor will be reconnected for another 24 hours using a new Holter hook-up kit. The patient will be instructed to continue his/her

medications as per study protocol and complete all necessary assessments on the patient diaries. The patient will return the following day for removal of the Holter Monitor. If the second attempt is unacceptable, the patient will not be allowed to continue in the study and considered a screen-failure.

The Holter monitor assessment at Visits 3 will not be repeated even if it is unacceptable.

At Visit 5, the Holter monitor can be placed on Day 11, 12, 13 or 14. If the initial Holter monitor assessment at Visit 5 is unacceptable, the Holter monitor will be reconnected for another 24 hours using a new Holter hook-up kit provided that the initial Holter was placed on Day 11, 12 or 13. The patient will be instructed to continue his/her medications as per study protocol and complete all necessary assessments on the patient diaries. The patient will return the following day for removal of the second Holter Monitor. No further attempts are allowed if the second attempt is unacceptable. **If the initial Holter monitor is placed on Day 14 a repeat assessment is not allowed regardless of acceptability.**

Each patient will receive a Holter monitoring diary. Patients will record cardiovascular-related symptoms which occurred during the Holter monitor recording (e.g., chest pain, shortness of breath). Every effort must be made to instruct the patient to consistently record entries in the Holter monitoring diary. The information in the Holter monitoring diary may be used by [redacted] in the interpretation of the Holter monitor recordings. The patient's Holter monitoring diary will also be reviewed by the investigator to identify symptoms which the investigator considers to be appropriate for recording in the eCRFs as adverse events.

Data for analysis will include:

- General trends including heart rate
- Hourly rhythm comments
- Ventricular ectopy summary
- Ventricular run summary
- Supraventricular ectopy summary
- Supraventricular run summary
- Any other clinically relevant arrhythmias, including atrial fibrillation and pronounced bradycardia.

Manual summary interpretation of the data is sent as a report to the site and to Pearl Therapeutics.

7.2.5 Clinical Laboratory Tests

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

Hematology (Complete Blood Count) and chemistry (Comprehensive Metabolic Panel) will be obtained at Screening, within 60 minutes prior to dosing on Treatment Day 1, Treatment Day 2, and on Day 15 when patients return to have their Holter monitor removed.

Serum pregnancy testing will be performed at Screening and at the Final Visit (Visit 5) 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)
Alkaline phosphatase	Calcium
Bilirubin, total	Chloride
Gamma-glutamyl transferase	Cholesterol
	Bicarbonate
	Creatinine
	Glucose
	Magnesium
	Potassium
	Phosphate
	Protein, total
	Sodium
	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.

7.2.6 Adverse Events

7.2.6.1 Performing Adverse Events Assessments

The investigator is responsible for promptly documenting and reporting all AEs observed during the study in the subject's case report form and on the AE Reporting Form. If the AE is "alarming", the investigator must report the AE immediately to Pearl Therapeutics. In addition, certain AEs (as described in Section 7.2.6.7) are classified as "serious" and must be reported no later than 24 hours after the investigator recognizes/classifies the event as a serious adverse event to Pearl Therapeutics or its designee (Sponsor).

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

7.2.6.2 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).

7.2.6.3 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.

7.2.6.4 Severity

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

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

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

Severe: Associated with inability of 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.

7.2.6.5 Relationship

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

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

Probably: A reaction that follows a reasonable temporal sequence from administration of study drug; that follows a known or expected response pattern to the study drug; and/or that

could not be reasonably explained by other factors such as underlying disease, complications, concomitant drugs, or concurrent treatments.

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

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

7.2.6.6 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.

7.2.6.7 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 the 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 may include copies of hospital records, case reports, and autopsy reports, and other pertinent documents.

Post-study SAEs following the last dose of study drug must be reported to Pearl Therapeutics as described in Section 7.2.6.10.

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

7.2.6.8 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.

7.2.6.9 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.

7.2.6.10 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.

7.2.6.11 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.

7.2.6.12 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.

7.2.7 AEs of Interest

Syncope and atrial fibrillation are considered to be AEs of interest, and will be tabulated separately.

7.2.8 Overdose

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

7.2.9 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 Therpeutics 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.

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 rest as recorded on ECG 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 2-hour interval after taking study drug.
- Symptoms of dyspnea at any time within the 2-hour interval after taking study drug, that in the opinion of the investigator or designee requires additional spirometry assessments, which demonstrates a decrease in FEV_1 of more than 20% from test day baseline (before taking study drug) on two consecutive assessments obtained at least 15 minutes apart.

Holter monitoring criteria for discontinuation:

- Average heart rate ≤ 40 beats per minute for any one hour
- Development of transient or fixed complete heart block
- Development of type 2 second degree AV block
- Development of type 1 second degree AV block lasting more than 60 minutes
- Ventricular asystole of ≥ 2.5 seconds duration
- Development of Holter monitoring criteria for proarrhythmia (see Appendix 3)
  Other clinically relevant findings that the Investigator deems should lead to the subject being discontinued.

Other valid reasons for removing a patient from the study include:

- The patient does not adhere to study rules and procedures;
- The patient wishes to withdraw from the study;
- Continuation of the patient is in violation of the inclusion and exclusion criteria;
- The investigator feels it is in the patient's best interest to terminate participation;
- The study is terminated by Pearl Therapeutics.

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.

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. 7 or more deaths from any cause at any time during the course of the study.

Stopping criteria for 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 an approximately 99% chance of each patient surviving 50 days on study. Assuming that 220 patients are randomized, the probability of placing the study on hold if mortality is no greater than background is 0.3%. Should the criterion for study hold be reduced to 6 or more deaths, the probability of inappropriate hold increases to 1.25%.

8 STUDY ACTIVITIES

A time and events schedule is provided in Table 4.

Table 4. Schedule of Events

	Screening[a]		Treatment Period[a]					Follow-Up
	Visit 1	Visit 2	Visit 3 Randomization		Visit 4	Visit 5		Telephone Contact
Procedures	Day -7 to -28	Day -1 to -7	Day 1	Day 2	Day 7 (±2)	Day14 (-3)	Day15 (-3)	Day 21(+7)
Informed Consent	X							
Eligibility Criteria	X	X	X					
Verify Continued Eligibility		X	X	X	X	X	X	
Reversibility to Ventolin HFA[b]	X							
Demographics & Medical/Surgical History	X							
Concomitant Medications[c]	X		X		X	X		
Spirometry[d]	X		X	X	X	X		
Physical Examination[e]	X						X	
Vital Signs[f]	X	X	X	X	X	X	X	
12-Lead ECG[g]	X		X	X	X	X	X	
24-Hour Holter Monitoring[h]		X	X			X		
Pregnancy Test[i]	X		X		X		X	
Clinical laboratory testing[i]	X		X	X			X	
Adjust COPD Medications Per Protocol[j]	X							
Resume pre-study COPD medications as appropriate[k]							X	
Adverse Events	X	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			X		
Collect/Review Patient Diary		X	X		X	X		
Follow-up Telephone Call to assess Adverse Events and Safety								X

Table 4. Schedule of Events (continued)

[a] Screening period of at least 7 days and up to 28 days. Patients are required to take Atrovent HFA q.i.d. and Ventolin HFA p r n. and complete the patient study medication diary during the screening period. An acceptable baseline Holter monitoring assessment is required before patients can proceed to Visit 3.

[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, patients should withold short-acting bronchodilator and other COPD medications at least 6 hours prior to the start of visit procedures.

[d] Spirometry (FEV_1, FVC, and PEFR) will be assessed at Screening and Visits 3, 4, and 5. During the treatment period (Visits 3, 4 and 5), spirometry will be conducted 60 minutes and 30 minutes prior to study drug administration.

[e] Includes evaluation of height and weight at Screening.

[f] Vital signs will be obtained at each visit. Assessments will be obtained after being supine for 10 minutes. SBP, DBP and HR will be obtained in the supine position. On Days 2 and 15 systolic and diastolic blood pressures, heart rate will be obtained immediately after ECG assessment. Temperature will be obtained at Screening and once at each visit as part of the initial vital sign assessment (i.e. Once on Day 1, 2, 7, 14 and 15), and will not be repeated at subsequent time points unless clinically indicated.

[g] ECGs will be collected at Screening (Visit 1) and Treatment Days 1, 2, 7 and 14. A final ECG will be collected on Day 15 prior to removal of the Holter monitoring equipment. On Days 1 and 14 ECGs will be collected at 60 minutes (between 60 to 120 minutes) and 30 minutes (between 30 to 60 minutes) prior to dosing and 30 minutes and 2 hours post dosing. On Day 7 an ECG will only be conducted at 60 minutes (between 30 to 60 minutes) prior to dosing. An ECG should be collected prior to removal of the Holter monitoring equipment on Days 2 and 15.

[h] Holter monitoring: 24-hour continuous monitoring during screening (Visit 2) and at Visit 3 and Visit 5. Patients are to return the morning following Visits 2, 3 and 5 to return the Holter monitor recorder and Holter monitoring diary.

[i] All clinical laboratory tests will be obtained at Screening, Visit 3 (Treatment Day 1 and 2) and Visit 5 (Day 15). Pregnancy test (women of child-bearing potential only): serum [human chorionic gonadotropin (HCG)] at Screening and Visit 5 only and Urine HCG at all other visits.

[j] 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).

[k] At the end of the Visit 5, return patient to pre-study or other appropriate inhaled maintenance COPD medications.

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

8.1 Screening Visit (Visit 1)

- Obtain informed consent.
- Check inclusion/exclusion criteria.
- Obtain demographic data, including age, race, smoking history, and medical/surgical history including glaucoma and age of onset of COPD.
- Obtain medication history, including COPD medications.
- 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 a 12-lead ECG after being supine for 10 minutes.
- Obtain vital signs (heart rate and blood pressure in a supine position and oral or tympanic temperature), height and weight.
- Obtain laboratory samples (hematology and chemistry).
    - Perform 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 baseline spirometry assessments.
- Dispense Ventolin HFA and instruct patient on its use (See package insert for Ventolin HFA for proper inhaler use)
- 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).
- Complete an eye examination for glaucoma if not performed within the last 2 years (New Zealand Sites Only)
- 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). Dispense Atrovent HFA to be used as maintenance medication for COPD during the screening period. Instruct patients

on the proper use of Atrovent HFA and Ventolin HFA during the screening period (see Section 5.4).

- Complete Screening Log (basic demographics, spirometry, medications and reasons for screen failure) for patients who do not meet eligibility criteria.

- Record 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 as medical history and not as a study adverse event unless the event meets the definition of an SAE

- Dispense patient study medication diary and provide instructions on diary completion.

- Arrange date of Visit 2 as appropriate.

8.2 Screening Visit for Baseline Holter Assessment (Visit 2)

- Collect and review patient diary (if diary is not completed correctly, re-train patient).

- Review inclusion/exclusion criteria to confirm protocol eligibility.

- Review of clinical laboratory results from Visit 1. Please note whether the results are clinically significant and include comments where applicable.

- Obtain vital signs (heart rate and blood pressure in a supine position and oral or tympanic temperature)

- Record 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 as medical history and not as a study adverse event unless the event meets the definition of an SAE.

- Review concomitant medications to ensure adherence to COPD regimen.

- Note time of last dose of short-acting bronchodilator and other COPD medications in the source documents.

- Perform Holter Monitoring for 24 hours – see Section 7.2.4. Record the start time of Holter monitor recording in the eCRF. Dispense Holter monitoring diary and instruct patient regarding its use. The patient must return the next morning with the device, study medication and diaries.

24-hours post dose assessments

- After completion of the 24-hour Holter monitor recording determine acceptability of Holter monitor recording (see Section 7.2.4). If 24-hour Holter monitor

recording is unacceptable, see Section 7.2.4 for instructions. **Note: Patients should not be randomized unless an acceptable Holter monitor recording has been obtained.**

- Obtain vital signs (heart rate and blood pressure in a supine position and oral or tympanic temperature)
- Record adverse events, if any
- Instruct patient to continue Atrovent qid and Ventolin HFA prn as rescue medication until Visit 3
- Instruct patient to continue completion of the study medication diary until Visit 3 (re-train patient on diary completion if necessary)
- Schedule Visit 3, if appropriate, or record patient status as screen failure.
- Remind patients scheduled for Visit 3 to withhold all study medications on the morning of Visit 3 and instruct them to not take Atrovent HFA or Ventolin HFA within 6 hours prior to their visit.

8.3 Randomization Visit (Visit 3; Day 1)

- Check to see if the patient has received rescue medication within 6 hours prior to the start of the visit. Note time of last dose of short-acting bronchodilator and other COPD medications on the source documents.
- Collect and review patient study medication diary (if diary is not completed correctly, re-train patient).
- Review inclusion/exclusion criteria to confirm protocol eligibility.
- Record 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 as medical history and not as a study adverse event unless the event meets the definition of an SAE.
- Review concomitant medications to ensure adherence to COPD regimen.
- Perform urine pregnancy test (women of child-bearing potential only).
- Perform all pre-dose assessments.
- Attach and initiate 24-hour Holter Monitor 15-30 minutes prior to dosing (see Section 7.2.4). Dispense Holter monitoring diary and instruct patient regarding its use. This test to be performed for approximately 24 hours. Obtain patient treatment assignment information from IWRS. At this point the patient is randomized.

- At 15-30 minutes prior to dosing, the seal around the study day treatment box is to be opened and the instructions for administration of study drug on the inner flap of the study day treatment box are to be followed.
    - Refer to Section 6.7 for detailed instructions for preparation of treatments for administration. These instructions are to be adhered to and are relevant to all study treatment visits.
- Patient will administer first dose of study drug at the clinic.
- Record adverse events (if any).
- Enter Time of first dose of study medication into study medication diary
- Perform all post-dosing assessments.
- The patient should be instructed to take the evening dose of study medication while wearing the Holter. The patient must return the next morning with the device, which is to be removed prior to taking the next morning's dose of study medication. The Holter monitoring diary is to be collected at that time. The time of dosing with study medication and Ventolin HFA rescue medication during the Holter monitor recording will be recorded by the patient in the study medication diary and by the site personnel in the eCRF.

24-hours post dose assessments

- Collect ECG prior to removal of Holter monitor
- Remove Holter monitor. **Note: At this visit, the 24-hour Holter monitor recording will not be repeated regardless of whether or not it meets acceptability criteria**
- Obtain vital signs (heart rate and blood pressure in a supine position and oral or tympanic temperature)
- Obtain laboratory samples (hematology and chemistry)
- Record adverse events, if any
- Instruct patient to continue taking study medication twice daily and Ventolin HFA prn as rescue medication until Visit 4
- Instruct patient to continue completion of the study medication diary until Visit 4 (re-train patient on diary completion if necessary)
- Schedule Visit 4.
- Remind patients to withhold all study medications on the morning of Visit 4 and instruct them to not take Ventolin HFA within 6 hours prior to their visit.

8.4 Visit 4 (Day 7)

- Collect and review patient study medication diary.
- Note time of last dose of short-acting bronchodilator and other COPD medications on source documents.
- Review concomitant medications and ensure adherence to COPD regimen.
- Confirm eligibility to continue.
- Record adverse events (if any).
- Perform all pre-dose assessments.
- Patient will administer dose of study drug at the clinic under supervision.
- **For patients taking double-blind study medication**: Previously dispensed study medication will be collected and a new supply of study medication will be dispensed.
- **For patients taking open-label Foradil**: Previously dispensed study medication will be collected and a new supply of blister packs will be dispensed. Patients will continue to use their existing Aerolizer device for the remainder of the trial.
- Schedule Visit 5 and ensure patient has adequate supply of study drug and rescue Ventolin HFA.

8.5 Visit 5 (Day 14)

- Collect and review patient study medication diary.
- Confirm eligibility to continue.
- 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 source documents.
- Perform all pre-dose assessments.
- Attach and initiate 24-hour Holter Monitor 15-30 minutes prior to dosing (see Section 7.2.4).

- Dispense Holter monitoring diary and instruct patient regarding its use. This test to be performed for 24 hours.
- Patient will administer dose of study drug at the clinic under supervision.
- Perform all post-dosing assessments.
- Redispense study medication and instruct patient to take the evening dose of study medication, **but not to take a dose the following morning.**
- Redispense patient study medication diary and provide instructions on diary completion if appropriate.
- The patient must return the next morning with the Holter device, study medication and diaries.

24-hours post dose assessments

- Collect ECG prior to removing Holter
- After completion of the 24-hour Holter monitor recording determine acceptability of Holter monitor recording (see Section 7.2.4). If 24-hour Holter monitor recording is unacceptable, see Section 7.2.4 for instructions.
- Collect previously dispensed study medications
- Obtain vital signs (heart rate and blood pressure in a supine position and oral or tympanic temperature)
- 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 laboratory samples (hematology and chemistry).
    - Perform serum pregnancy test (women of child-bearing potential only).
- Record adverse events
- Record usage of COPD and other concomitant medications
- At completion of all Visit 5 assessments, return patient to pre-study or appropriate inhaled COPD medication(s).

8.6 Follow-Up Telephone Call (7-14 days post Visit 5)

- Study site staff will contact the patient via telephone and record adverse events (if any).
- 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 CRF. The following categories should be used to describe these events in the CRF:

- Patient discretion (document reason)
- Investigator considers it to be in the best interest of the patient
- Adverse events(s)
- Administrative reasons (e.g., early termination of the study)
- Patient lost-to-follow-up
- Major protocol violation (with approval by Pearl Therapeutics)
- 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 parallel group 4-treatment, randomized design evaluating the following 4 treatments in approximately 50 completing patients for each treatment:

- Formoterol Fumarate MDI 9.6 µg ex-actuator
- Glycopyrrolate MDI 36 µg ex-actuator
- Glycopyrrolate MDI 36 µg /Formoterol 9.6 µg ex-actuator combination
- Formoterol Fumarate Inhalation Powder 12 µg

The primary objective of this study is to assess the safety of the Glycopyrrolate 36 µg /Formoterol 9.6 µg ex-actuator combination relative to the component treatments (Formoterol Fumarate 9.6 µg ex-actuator and Glycopyrrolate 36 µg ex-actuator) and the active comparator (Formoterol Fumarate Inhalation Powder 12 µg) in patients with moderate to severe COPD.

9.2 Protocol Variables

9.2.1 Efficacy Endpoints

All efficacy assessments will be expressed as change from baseline, where baseline is defined as mean of the pre-dose assessments on Day 3.

9.2.1.1 Key Efficacy Endpoint

The key efficacy endpoint is mean change from baseline FEV_1 trough over Day 7 and Day 14 relative to the mean of pre-dose values at Visit 3.

9.2.1.2 Secondary Efficacy Endpoints

There are no secondary endpoints for which hypothesis testing will be performed. Change from baseline in FEV_1, FVC and PEFR on Days 2, 7, and 14 will be captured and characterized using descriptive statistics only.

9.2.2 Safety Endpoints

The safety endpoints for this study include:

9.2.2.1 Holter monitor summary data:

- 24 hour mean heart rate (primary safety endpoint)
- 24 hour maximum heart rate
- 24 hour minimum heart rate
- The total number of beats
- The proportion of ventricular ectopics

- The proportion of supraventricular ectopics
- The proportion of paced beats
- The number of ventricular couplets
- The number of ventricular runs
- The number of isolated ventricular events
- The number of supraventricular couplets
- The number of supraventricular runs
- The number of isolated supraventricular events
- The number of bradycardia episodes
- The number of tachycardia episodes

9.2.2.2 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.

9.2.2.3 Paradoxical Bronchospasm and Tremor

Will be regarded as adverse events of special significance, and tabulated separately.

9.2.2.4 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 on Day 1 (Visit 3).

9.2.2.5 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.

9.2.2.6 Clinical Laboratory Testing:

Full clinical laboratory testing at every sample time including hematology and clinical chemistry, characterized by change from baseline, where the baseline is defined as the value prior to dosing on Day 1 (Visit 3).

9.2.2.7 Vital Sign Measurements:

Change from baseline values where baseline is defined as the average of the values prior to dosing on Day 1 (Visit 3).

9.3 Analysis

9.3.1 Key Efficacy Analysis

Efficacy analysis will be based on a linear model in which Treatment will be a fixed effect using baseline as a covariate.

The key efficacy analysis will involve *a priori* comparisons between the combination treatment and Formoterol Fumarate MDI 9.6 µg and Glycopyrrolate MDI 36 µg for the primary endpoint: mean pre-dose FEV_1 on Visit 5 compared to pre-dose values at Visit 3. The comparisons will comprise:

- Glycopyrrolate 36 µg /Formoterol Fumarate 9.6 µg ex-actuator combination vs Formoterol Fumarate 9.6 µg ex-actuator. This is a superiority comparison.
- Glycopyrrolate 36 µg /Formoterol Fumarate 9.6 µg ex-actuator combination vs Glycopyrrolate 36 µg ex-actuator. This is a superiority comparison.

9.3.2 Other Efficacy Analysis

No other efficacy comparisons will be performed. Descriptive statistics (mean, median, range and standard deviation) will be presented for mean pre-dose FEV_1 n Day 1 and on Day 7, and for FVC and PFER on Days 1, 7 and 14.

9.3.3 Safety Analysis

9.3.3.1 Holter Monitor Results

The change from baseline (Visit 2) mean heart rate will be analysed using a linear model. The mean heart rate during the baseline period (Visit 2) will be used as a covariate.

The proportions of the following beats will be analysed using a generalized linear model with a quasi-binomial family (Wedderburn 1974):

- Ventricular ectopics
- Supraventricular ectopics
- Paced beats.

Extra-binomial variation will be accommodated by inflating the variance covariance matrix by the sum of squared Pearson residuals divided by the residual degrees of freedom (Venables and Ripley, 2002 page 208). For each proportion, the logit-transformed equivalent proportion during the baseline period (Visit 2) will be used as a covariate. Where the observed proportion is zero, the logit will be calculated assuming 1 event out of twice the total number of QRS complexes.

The numbers of the following events will be analysed using a generalized linear model with a quasi-Poisson family:

- Ventricular couplets
- Total ventricular runs
- Isolated ventricular events
- Supraventricular couplets
- Total supraventricular runs
- Isolated supraventricular events
- Bradycardia episodes
- Tachycardia episodes.

Extra-Poisson variation will be accommodated by inflating the variance covariance matrix by the sum of squared Pearson residuals divided by the residual degrees of freedom. The log-transformed number of the relevant event during the baseline period will be used as a covariate. A constant of 1 will be added to the number of each baseline event before log-transformation.

For each endpoint, the location parameter for the combination treatment will be compared with the location parameter for the other three treatments. No multiplicity adjustment will be imposed.

9.3.3.2 Adverse Events

Adverse events will be summarized by the number of patients experiencing an event for each treatment. They will be tabulated at the level of the MedDRA preferred term, and the MedDRA System Organ Class. The version of MedDRA current at the time the first subject is randomized will be used throughout the study. Tabulations will be broken down by severity and by relationship to study drug. No hypothesis tests will be performed.

9.3.3.3 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 for each treatment. No hypothesis tests will be performed, but a Clopper-Pearson confidence interval may be provided.

9.3.3.4 Clinical Laboratory Measurements

Summary statistics (mean, median, standard deviation and range) of change from baseline values will be tabulated for each treatment and each assessment time. For clinical laboratory measurements, baseline values will be defined by the value prior to dosing on Day 1 (Visit 3). Male and female patients will be tabulated separately.

9.3.3.5 Vital Signs

Summary statistics (mean, median, standard deviation and range) of change from baseline values will be tabulated for each treatment and each assessment time. For vital signs, baseline values will be defined by the value prior to dosing on Day 1 (Visit 3).

9.3.3.6 ECGs

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 on Day 1 (Visit 3).

Summary statistics (mean, median, standard deviation and range) of change from baseline values will be tabulated for each treatment period and each assessment time. For ECG parameters, baseline values will be defined by the value prior to dosing on Day 1 (Visit 3).

The number of subjects with more than a 30 msec change from the pre-dose record on the test day or greater than a 50 msec change from the baseline will be tabulated. These stubjects will be listed, and a detailed narrative provided.

9.4 Randomization

Patients will be randomly assigned to treatment using an IWRS.

9.5 Sample Size Consideration

Stein et al (1998) reported a standard deviation of 10 beats per minute for 24 hour average heart rate in patients with COPD. Takabatake et al (2001) reported a standard deviation of 10.2 bpm, for patients with COPD. Power was calculated assuming that these standard deviations are relevant for this study, and based on a standard deviation opf 10.1 bpm. A sample size of 50 patients per treatment group gives a minimum detectable difference (with approximately 90% power) of 6.5 bpm. Power was calculated assuming a two sided t test at the 5% level. The power to detect a 5 bpm change is approximately 70%.

The ability of the design to detect low frequency cardiac anomalies was also considered. A sample size of 50 patients per group implies that, if no anomalies are detected, the maximum credible value for the true proportion of patients developing the anomaly is approximately 7% (based on the binomial distribution).

Sample size has been determined with respect to the safety objectives, since these form the primary objectives of the study. Nevertheless, power for the key efficacy objective may be evaluated. Previous studies have suggested that the between subject standard deviation of trough FEV_1 is 0.1L. If half of this variability represents variation between long-term averages of subjects, and half represents variation between repeated measurements on the same subject, then the estimated standard deviation of the average of two days' trough FEV_1 is 0.13L. For an effect size of 0.1L, the power is 97%; for an effect size of 0.07L the power is 76%. These power calculations assumed a two sided t test at the 5% level.

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 study unblinding.

9.7 Study Populations

The following analysis populations are defined in this study:

- The Intent-To-Treat (ITT) Population is defined as all subjects who are randomized to treatment, received at least one dose of the study treatment, and had both baseline and post-baseline data for efficacy analysis.
- A Modified ITT (MITT) Population used for analysis of efficacy variables; where subjects must have remained in the study for minimally 2 hours post-dosing on 1 or more test days (Visit 3, 4 or 5). A more detailed description of the MITT Population will be provided in the Statistical Analysis Plan.
- The Per-Protocol (PP) Population is defined as all subjects from the ITT group who completed Visits 3, 4, and 5 of the study with evaluable efficacy data for Visits 3, 4, and 5 as specified in the protocol. The PP Population will be used for sensitivity analyses. The PP Population will exclude any measurements excluded from the MITT Population.
- The Safety Population is defined as all subjects who are randomized to treatment, received at least one dose of the study treatment, and had safety data after starting study treatment.

Analyses will be performed as follows:

- Demographics analyses will be performed for the Safety, ITT, MITT, and PP patient populations, with the Safety Population being considered the primary population for these analyses.
- Efficacy Analyses will be performed for both the MITT and PP patient populations, with the MITT Population being considered the primary population for these analyses.
- Safety Analyses will be performed using the Safety Population.

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 and safety analyses will be based on the dose actually received, rather than the dose scheduled.

9.8 Handling of Missing Data

Missing data will not be imputed. If the spirometry data quality obtained for a patient at any time-point does not meet minimal acceptability requirements per ATS/ERS criteria, as determined during the blinded spirometry over read process, data for that time-point will be considered missing.

9.9 Statistical Software

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

10 ADMINISTRATIVE INFORMATION

10.1 Regulatory Authority Approval

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

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

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

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

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

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

10.3 Patient Information and Consent

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

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

10.4 Confidentiality

10.4.1 Confidentiality of Data

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

10.4.2 Confidentiality of Subject/Patient Records

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

10.5 Quality Control and Assurance

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

10.6 Data Management

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

10.7 Study Monitoring

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

During these contacts, the monitor will:

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

This will be done in order to verify that the:

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

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

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

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

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

10.8 Retention of Data

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

10.9 Financial Disclosure

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

10.10 Investigator's Final Report

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

10.11 Publication Policy

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

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

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Appendix 1 Spirometry Performance Recommendations

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

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

FEV_1 AND FVC MANEUVERS

Equipment Requirements

The spirometer must be capable of accumulating volume for $\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

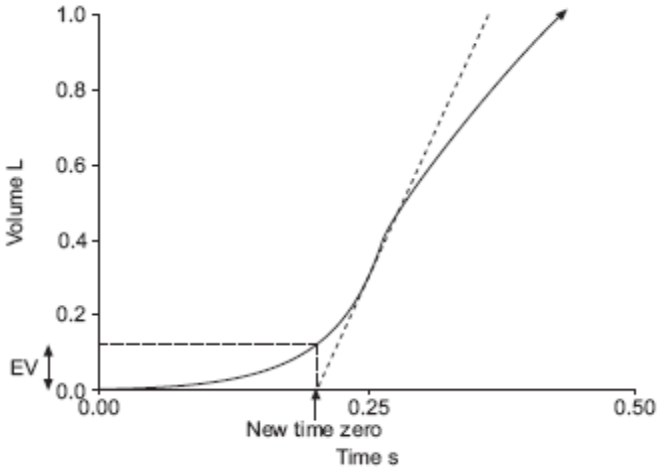
***Acceptable* Tests must meet the following 7 criteria:**

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 Holter Monitoring Criteria for Proarrhythmia

1. The 24-hour Holter monitor recordings obtained after the start of double-blind treatment will be reviewed for the development of or any increase in the incidence of cardiac dysrhythmic events, which could be considered indicative of proarrhythmic drug effects. The definition of proarrhythmia is based on the Morganroth criteria (Morganroth, et al, 1984, 1987). These criteria define proarrhythmia based on the change from the baseline visit in number of ventricular premature beats per hour (VPB/hr) and/or the frequency of ventricular tachycardia (VT) events (nonsustained or sustained) as follows:

BASELINE MEAN VPB/HR	REQUIREMENT FOR DEFINITION OF PROARRHYTHMIA (POSTBASELINE)
0 - 1	$\geq$ 10 Mean VPB/hour
1 - 100	increase of $\geq$ 10 times baseline
Over 100	increase of $\geq$ 3 times baseline

or

BASELINE NONSUSTAINED VT EVENTS*	REQUIREMENT FOR DEFINITION OF PROARRHYTHMIA (POSTBASELINE)
0	$\geq$ 5 events or > 15 beats in events/24 hrs
$\geq$ 1	increase of $\geq$ 10 times baseline events or beats

or

BASELINE SUSTAINED VT EVENTS*	POSTBASELINE SUSTAINED VT EVENTS FOR DEFINITION OF PROARRHYTHMIA*
0	$\geq$ 1

2. Any run of ventricular ectopic beats associated with symptoms (hypotension or syncope), regardless of the rate.

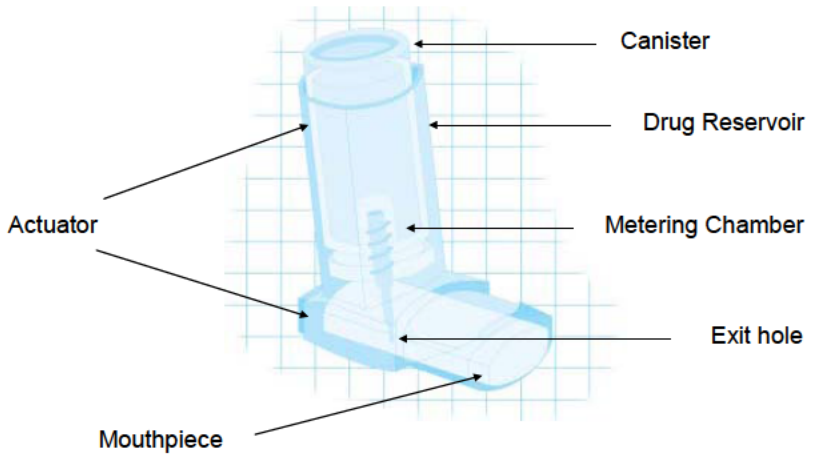
3. Any episode of ventricular flutter and/or ventricular fibrillation.

***** Ventricular tachycardia (VT) is defined as a run of 3 or more ventricular premature beats (VPB's) with a rate $\geq$100 beats per minute. Sustained VT is defined as VT lasting $\geq$ 30 seconds or $\geq$ 60 beats. Nonsustained VT is a run of 3 or more VPB's with a rate $\geq$ 100 beats per minute which does not fulfill the criteria for sustained VT.

Appendix 4 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



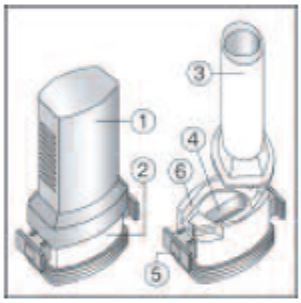
Appendix 5 Instructions for Use of Foradil Aerolizer Device

FORADIL AEROLIZER

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

Aluminum pouch covering the foil blister cards

Foil blister card



The Aerolizer consists of the following parts:
1. A cap to protect the mouth-piece of the base
2. A base that allows the proper release of medicine from the capsule

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

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

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

Taking a dose of FORADIL AEROLIZER requires the following steps:

1. Open the foil pouch containing a blister card of FORADIL capsules. Do not remove a FORADIL capsule until you are ready for a dose.
2. Pull off the AEROLIZER Inhaler cover. (Figure 1)

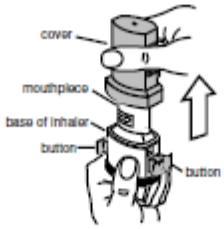


Figure 1

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

Figure 2

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

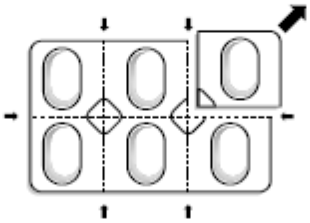


Figure 3

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

Figure 4

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

Figure 5

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

Figure 6

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

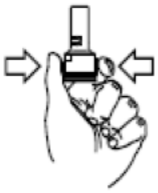


Figure 7

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

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

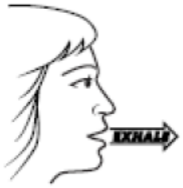


Figure 8

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

Figure 9 Figure 10

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

Figure 11

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

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

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

16. Close the mouthpiece and replace the cover.

Appendix 6 Instructions for Use of Atrovent HFA Inhalation Aerosol MDI Device

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

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

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

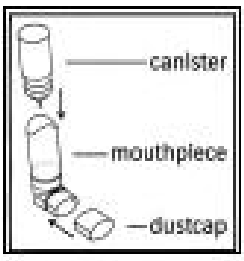


Figure 1

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

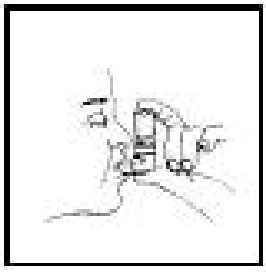


Figure 2

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

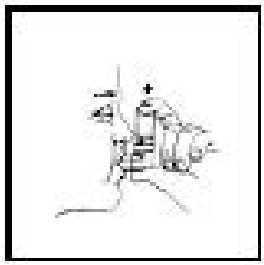


Figure 3

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

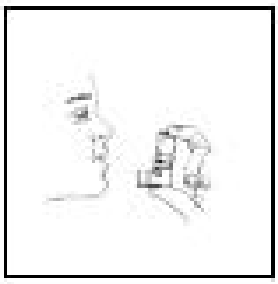


Figure 4

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

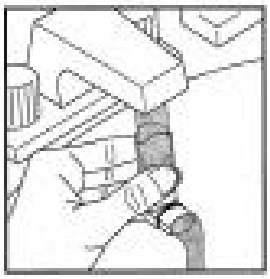


Figure 5

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

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

Appendix 7 Instructions for Use of Ventolin HFA Inhaler

The Parts of Your VENTOLIN HFA Inhaler

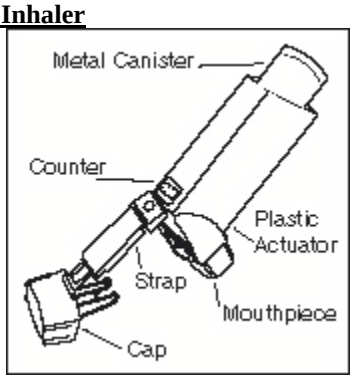


Figure 1

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.

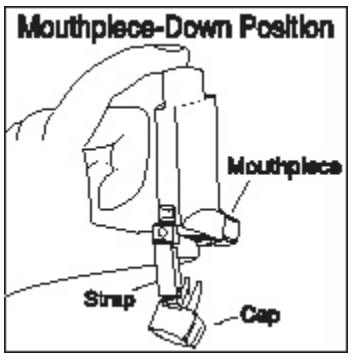


Figure 2

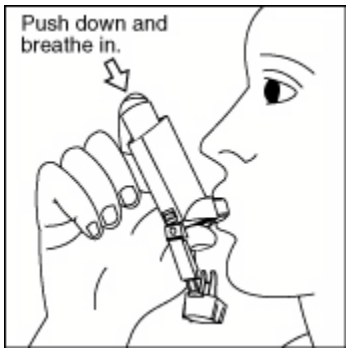


Figure 3

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).

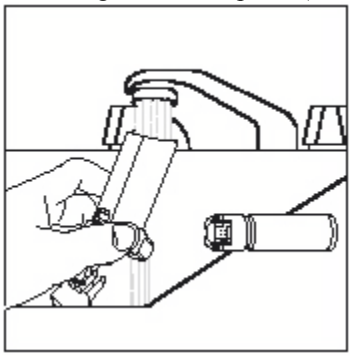


Figure 4

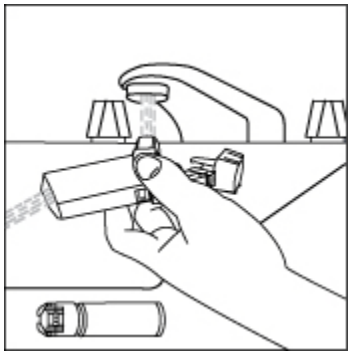


Figure 5

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).

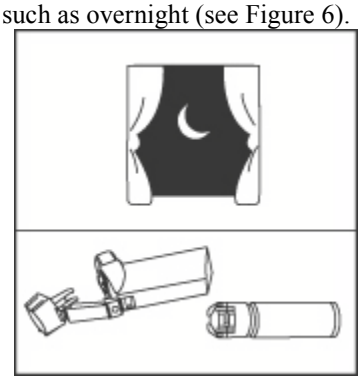


Figure 6

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.

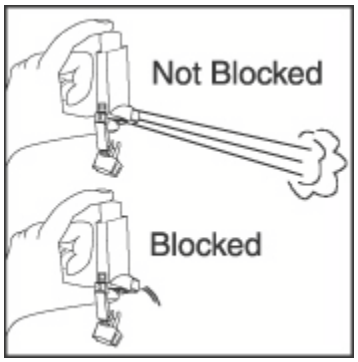


Figure 7

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 8 Sponsor Signatory

Study Title: A Randomized, Double-blind, Parallel Group, 14-day, Multi-Center Study to Evaluate the Safety of PT003, PT005, PT001 and Foradil® Aerolizer® (12 µg, Open-Label) as Evaluated by Holter Monitoring, in Patients with Moderate to Severe Chronic Obstructive Pulmonary Disease (COPD)

Study Number: PT003003-00

Final Date: [redacted]

Amendment 1 Date: N/A

Signature:_____ Date:_____

Name: [redacted]

Title: [redacted] Pearl Therapeutics, Inc

Appendix 9 Investigator's Agreement and Signature Page

Study Title: A Randomized, Double-blind, Parallel Group, 14-day, Multi-Center Study to Evaluate the Safety of PT003, PT005, PT001 and Foradil® Aerolizer® (12 µg, Open-Label) as Evaluated by Holter Monitoring, in Patients with Moderate to Severe Chronic Obstructive Pulmonary Disease (COPD)

Study Number: PT003003-00

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 Pearl Therapeutics and prior review and written approval from the IRB/IEC, except where necessary to eliminate an immediate hazard to the subjects, or for administrative aspects of the study (where permitted by all applicable regulatory requirements).
- That I am aware of, and will comply with good clinical practices (GCP) and all applicable regulatory requirements.
- That I am thoroughly familiar with the appropriate use of the investigational product(s), and other information provided by Pearl Therapeutics including, but not limited to, the following: the protocol and the current Investigators Brochure (IB).
- To ensure that all persons assisting me with the study are qualified, adequately informed about the investigational product(s) and of their study-related duties and functions.
- To supply Pearl Therapeutics with any necessary information regarding ownership interest and financial ties; to promptly update this information if any relevant changes occur during the course of the study and for 1 year following completion of the study; and agree that Pearl Therapeutics may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- I agree to report all information or data in accordance with the protocol and any other study conduct procedures provided by Pearl Therapeutics
- That since the information in this protocol and IB is confidential, I understand that its disclosure to any third parties, other than those involved in approval, supervision or conduct of the study is prohibited.
- To accurately transfer all required data from each patient's source document to the case report forms (CRFs). The CRFs will be provided to Pearl Therapeutics in a timely manner at the completion of the study, or as otherwise specified by Pearl Therapeutics.
- To allow authorized representatives of Pearl Therapeutics or regulatory authority representatives to conduct on-site visits to review, audit and copy study documents. I will personally meet with these representatives to answer any study-related questions.

Signature:_____ Date:_____

Name:_____

Affiliation: _____

_____

Clinical Trial Protocol: PT003003-01

Study Title:	A Randomized, Double-blind, Parallel Group, 14-day, Multi-Center Study to Evaluate the Safety of PT003, PT005, PT001 and Foradil® Aerolizer® (12 µg, Open-Label) as Evaluated by Holter Monitoring, in Patients with Moderate to Severe Chronic Obstructive Pulmonary Disease (COPD)
Study Number:	PT003003-01
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 exclusion criteria #11.

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

- In Section 8.3 Randomization Visit (Visit 3; Day 1), 24-hours post-dose assessments on Day 2, the procedure "Perform spirometry assessments (prior to AM dosing)" (bullet 4) was added to be consistent with the Schedule of Events (Table 4).

- In Section 5.2 Exclusion Criteria, the definition for Paroxysmal supraventricular tachycardia was added to exclusion criteria #13.

  "Paroxysmal supraventricular tachycardia (non-sinus rhythm inclusive of atrial fibrillation or atrial flutter) lasting continuously for over 1 minute."

SYNOPSIS

Sponsor:
Pearl Therapeutics

Names of Finished Products:
Glycopyrrolate and Formoterol Fumarate Inhalation Aerosol; PT003
Formoterol Fumarate Inhalation Aerosol; PT005
Glycopyrrolate Inhalation Aerosol; PT001
Foradil® Aerolizer® (Formoterol Fumarate Dry Powder for Inhalation)

Name of Active Ingredients:
Glycopyrrolate (GP)
Formoterol Fumarate (FF)

Study Title:
A Randomized, Double-blind, Parallel Group, 14-day, Multi-Center Study to Evaluate the Safety of PT003, PT005, PT001 and Foradil® Aerolizer® (12 µg, Open-Label) as Evaluated by Holter Monitoring, in Patients with Moderate to Severe Chronic Obstructive Pulmonary Disease (COPD)

Study Number: PT003003-01

Study Phase: IIb

Study Objective(s):

This study is primarily a safety study. The primary and secondary endpoints are based on 24-hour Holter monitor assessments obtained on Day 14 relative to baseline (Visit 2).

Primary Safety Objective:
The primary safety objective of this study is to compare the change in mean heart rate averaged over 24 hours post-dose, following twice daily dosing over 14 days with Glycopyrrolate and Formoterol Fumarate Metered Dose Inhaler (GFF MDI), Formoterol Fumarate MDI (FF MDI), Glycopyrrolate MDI (GP MDI) or Foradil Aerolizer compared to heart rate averaged over 24 hours at baseline in patients with moderate to severe chronic obstructive pulmonary disease (COPD).

Secondary Safety Objective:
The secondary objective of the study is to further characterize additional cardiovascular safety parameters of all treatment groups including the maximum 24-hour heart rate, mean night-time [22:00 to 06:00) and day-time [06:00 to 22:00)[1] heart rate, ventricular ectopic events (including a single premature ventricular contraction [PVC]), ventricular couplets (defined as two PVCs preceded or followed by regular beats), ventricular runs (defined as

[1] Note the use of open and closed interval notation to specify endpoint relationships. $[a,b) = \{x \in \mathbb{R} | a \leq x < b\}$.

three or more PVCs preceded or followed by regular beats), the number of supraventricular runs, and sustained ventricular tachycardia (VT) [defined as PVCs lasting > 30 s at a rate > 120 beats/min], supraventricular ectopic events, and other clinically relevant arrhythmias (such as atrial fibrillation).

Additional Safety Assessments:
The additional safety objectives are to evaluate the safety of GFF MDI, FF MDI, and GP MDI in patients with moderate to severe COPD compared with Foradil® Aerolizer® (12 µg). Safety will be assessed by adverse events (AEs), vital signs, electrocardiograms (ECGs), and laboratory assessments.

Key Efficacy Objective:
The key efficacy objective of this study is to compare the change in pre-dose morning trough FEV_1 averaged for Day 7 and Day 14 relative to the mean of pre-dose values at baseline (Day 1).

Study Design:

This is a randomized, double-blind, parallel-group, repeated dose (14 days), multi-center study to assess the safety of twice-daily (BID) dosing of GFF MDI (36/9.6 µg, ex-actuator), GP MDI (36 µg, ex-actuator), FF MDI (9.6 µg, ex-actuator) and Foradil Aerolizer (12 µg) as monitored by 24-hour continuous Holter monitoring at the end of treatment.

This multi-center study will be conducted at approximately 20 sites, contributing approximately 10 to 15 patients per site, in Australia, New Zealand, and the United States. Across these sites, it is planned that approximately 220 patients with moderate to severe COPD will be randomized into the study to provide approximately 200 patients to complete the study.

The entire study period is scheduled to take approximately 5-7 weeks for each individual patient. The study is anticipated to run for approximately 9 months and should not exceed 18 months.

Study Design

← **Screening Period** →		← **Treatment Period** →			**Follow-up**
Screening Visits		Randomization		End of Treatment Final Visit	Follow-up Telephone Call
Days -28 to - 1		Day 1	Day 7 (±2)	Day 14 (-3)	Day 21 (+7)
Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	

Study Population:
Approximately 220 patients with moderate to severe COPD will be enrolled to provide approximately 200 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 Descriptions

Product Name & Potency	Dosage Form	Comments
Formoterol Fumarate 9.6 µg ex-actuator (FF MDI)	MDI	Taken as 2 inhalations of the 4.8 µg per actuation strength MDI
Glycopyrrolate 36 µg ex-actuator (GP MDI)	MDI	Taken as 2 inhalations of the 18 µg per actuation strength MDI
Glycopyrrolate 36 µg /Formoterol 9.6 µg ex-actuator combination (GFF MDI)	MDI	Taken as 2 inhalations of the Glycopyrrolate 18 µg / Formoterol 4.8 µg per actuation strength MDI
Formoterol Fumarate Inhalation Powder 12 µg†	DPI	US source: (Foradil® Aerolizer®) Taken as 1 capsule. Each capsule contains 12 µg corresponding to 10 µg formoterol fumarate dihydrate delivered from the mouthpiece *Supplies are open-label.*
Ipratropium Bromide inhalation aerosol 17 µg ex-actuator	MDI	US source: (Atrovent® HFA) Each inhalation contains 21 µg corresponding to 17 µg ipratropium bromide per actuation *Supplies are open-label.*
Albuterol Sulfate inhalation aerosol§ 90 µg ex-actuator	MDI	US source: (Ventolin® HFA) Each inhalation contains 108 µg corresponding to 90 µg albuterol base per actuation *Supplies are open-label.*
† Active control § Rescue medication **Note: All study drugs will be administered by oral inhalation.**		

The 18 µg ex-actuator delivery of glycopyrrolate is equivalent to 22 µg ex-valve of glycopyrrolate.

The 4.8 µg ex-actuator dose of formoterol fumarate is equivalent to 5 µg of formoterol fumarate *dihydrate*. The corresponding ex-valve dose for formoterol fumarate is 6 µg.

Duration of Treatment:
Each patient will receive a maximum of 14 days of study treatment with their assigned treatments. The entire study period is scheduled to take approximately 5-7 weeks for each individual patient from the time of screening (see Figure 1).

Safety Assessments:

The safety assessments include AE and serious adverse event (SAE) assessments, Holter monitoring, ECGs, vital signs, and clinical laboratory tests.

Efficacy Assessments:
Forced expiratory spirometry for derivation of FEV_1, FVC and PEFR will be assessed.

Statistical Methods:
Sample Size Determination: Sample size was based on the properties of the primary safety endpoint: mean heart rate over a 24 hour period. Assuming a standard deviation of 10 bpm, a sample size of 50 patients per treatment yields a 90% power for a true change of 6.5 bpm. 220 patients will be randomized in order to yield 50 completing patients per treatment group.

Efficacy Analyses: Efficacy analysis will be based on a linear model in which Treatment will be a fixed effect, using baseline as a covariate.

The primary efficacy analysis will involve *a priori* comparisons between the combination treatment and Formoterol 9.6 µg MDI and Glycopyrrolate 36 µg MDI for the primary endpoint: change from baseline in mean trough FEV_1 on Days 7 and 14 relative to the mean of pre-dose values at Visit 3. The comparisons will comprise:

- Glycopyrrolate 36 µg /Formoterol 9.6 µg ex-actuator combination vs Formoterol 9.6 µg ex-actuator
- Glycopyrrolate 36 µg /Formoterol 9.6 µg ex-actuator combination vs Glycopyrrolate 36 µg ex-actuator

Other efficacy parameters will include change from baseline FVC and PEFR.

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 with adverse events. Holter data will be analysed using a generalised linear model with quasi-binomial link (for percentage of ventricular ectopics, supraventricular ectopics) or quasi-Poisson link (number of ventricular couplets, supraventricular couplets, ventricular runs, supraventricular runs, tachycardia episodes, bradycardia episodes, and pauses (>= 2 seconds)), or using a linear model (mean heart rate). In all cases the value of the relevant variable during the baseline period will be transformed using the inverse canonical link (logit for quasi-binomial, log for quasi-poisson and identity for the linear model) and used as a covariate

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
BMI	Body mass index
BMP	Basic Metabolic Panel
BTPS	Body Temperature and Pressure Saturated
BUN	Blood urea nitrogen
$CaCl_2$	Calcium chloride
CFR	Code of Federal Regulations
COPD	Chronic Obstructive Pulmonary Disease
CRT	Cardiac resynchronization therapy
CRT_D	Cardiac resynchronization therapy defibrillator
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
FVC	Forced Vital Capacity
GCP	Good clinical practice
GFF MDI	Glycopyrrolate and Formoterol Fumarate MDI
GP MDI	Glycopyrrolate MDI
GGT	Gamma-glutamyl transferase
HCG	Human chorionic gonadotropin
HR	Heart Rate
HFA	Hydrofluroalkane
i.e.	*Id est*, that is
ICD	Implantable cardioverter defibrillator
ICF	Informed consent form
ICH	International Conference on Harmonization
ICMJE	International Committee of Medical Journal Editors
ICS	Inhaled Corticosteroid
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITT	Intention-to-treat
IUD	Intrauterine device
IV	Intravenous
IWRS	Interactive Web Response System
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
PEF	Peak expiratory flow
PEFR	Peak expiratory flow rate
PFT	Pulmonary function test
PK	Pharmacokinetics
PP	Per Protocol
PRN	pro re nata
PVC	premature ventricular contraction
Rx	Treatment
QID	quater in die; four times a day
QTcF	QT corrected using Fridericia's formula ($QT/(RR^{1/3})$)
SAE	Serious Adverse Event
SBP	Systolic blood pressure
SOP	Standard operating procedure
TLC	Total Lung Capacity
TNFα	Tumor necrosis factor α
US	United States
VPB	ventricular premature beats
VT	ventricular tachycardia

TRADEMARK INFORMATION

Trademarks Not Owned By Pearl Therapeutics

Aerolizer

Atrovent

Dulera

Foradil

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 monotherapy 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

was 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 death, 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 (36/9.6 and 72/9.6 µg); all references to doses of FF MDI will be to the ex-actuator or "delivered" doses (2.4, 4.8, 7.2 and 9.6 µg); all references to doses of GP MDI will be to the ex-actuator or "delivered" doses (18, 36, 72, and 144 µg); all references to the Foradil Aerolizer dose will be to the capsule content of 12 µg (corresponds to approximately 10 µg delivered dose); and all references to Spiriva (tiotropium bromide, 18 µg) will be to the capsule content of 18 µg (delivered via the Handihaler); all references to doses of Ventolin HFA (albuterol sulfate inhalation aerosol) will be to the ex-actuator or "delivered" doses (90 µg); all references to doses of Atrovent HFA (ipratropium bromide) will be to the ex-actuator or "delivered" doses (17 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 monotherapy 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.

A cardiovascular safety study provides additional safety assurance prior to proceeding into a longer-term chronic Phase III program. The doses selected for evaluation in this study are based on the prior clinical studies and represent the highest doses likely to be used in the Phase III program.

The duration of exposure to GFF MDI 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 the porous particles 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

This study is primarily a safety study. The primary and secondary endpoints are based on 24-hour Holter monitor assessments obtained on Day 14 relative to baseline (Visit 2).

2.1 Primary Objective

The primary safety objective of this study is to compare the change in mean heart rate averaged over 24 hours post-dose, following twice daily dosing over 14 days with GFF MDI, FF MDI, GP MDI or Foradil Aerolizer compared to heart rate averaged over 24 hours at baseline in patients with moderate to severe COPD.

2.2 Secondary Objectives

The secondary objective of the study is to further characterize additional cardiovascular safety parameters of all treatment groups including the maximum 24-hour heart rate, mean night-time [22:00 to 06:00) and day-time [06:00 to 22:00)[2] heart rate, ventricular ectopic events (including a single premature ventricular contraction [PVC]), ventricular couplets (defined as two PVCs preceded or followed by regular beats), ventricular runs (defined as three or more PVCs preceded or followed by regular beats), the number of supraventricular runs, and sustained ventricular tachycardia (VT) [defined as PVCs lasting > 30 s at a rate > 120 beats/min], supraventricular ectopic events, and other clinically relevant arrhythmias (such as atrial fibrillation).

2.3 Additional Safety Assessments

The additional safety objectives are to evaluate the safety of GFF MDI, FF MDI, and GP MDI in patients with moderate to severe COPD compared with Foradil Aerolizer (12 µg). Safety will be assessed by adverse events (AEs), vital signs, electrocardiograms (ECGs), and laboratory assessments.

2.4 Efficacy Objective

The key efficacy objective of this study is to compare the change in pre-dose morning trough FEV_1 averaged over Day 7 and Day 14, relative to the mean of pre-dose values at baseline (Day 1).

[2] Note the use of open and closed interval notation to specify endpoint relationships. $[a,b) = \{x \in \mathbb{R} | a \leq x < b\}$.

3 STUDY ENDPOINTS

3.1 Safety Endpoints

The safety assessments include AE and SAE assessments, Holter monitoring, ECGs, physical examination findings, vital signs, and clinical laboratory tests.

Primary Safety Endpoint:
The primary safety objective of this study is to compare the change in mean heart rate averaged over 24 hours post-dose, following twice daily dosing over 14 days with Glycopyrrolate and Formoterol Fumarate Metered Dose Inhaler (GFF MDI), Formoterol Fumarate MDI (FF MDI), Glycopyrrolate MDI (GP MDI) or Foradil Aerolizer compared to heart rate averaged over 24 hours at baseline in patients with moderate to severe chronic obstructive pulmonary disease (COPD).

Secondary Safety Endpoints

Based on Holter assessment at baseline and on Day 14: the maximum 24-hour heart rate, mean night-time (22:00 to 06:00) and day-time (06:00 to 22:00)[3] heart rate, ventricular ectopic events (including a single premature ventricular contraction [PVC]), ventricular couplets (defined as two PVCs preceded or followed by regular beats), ventricular runs (defined as three or more PVCs preceded or followed by regular beats), the number of supraventricular runs and sustained ventricular tachycardia (VT) [defined as PVCs lasting > 30 s at a rate > 120 beats/min], supraventricular ectopic events, and other clinically relevant arrhythmias (such as atrial fibrillation).

3.2 Efficacy Endpoints

Forced expiratory spirometry for derivation of FEV_1, FVC and PEFR will be assessed. The key efficacy endpoint will be average change in pre-dose morning trough FEV_1 on Day 7 and Day 14 relative to the mean of pre-dose values at baseline (Day 1, Visit 3 randomization).

[3] Note the use of open and closed interval notation to specify endpoint relationships. $[a,b) = \{x \in \mathbb{R} | a \leq x < b\}$.

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

This is a randomized, multi-center, double-blind, chronic dosing (14 days), parallel group study to assess the safety of twice-daily (BID) dosing of GFF MDI (36/9.6 μg), GP MDI (36 μg), and FF MDI (9.6 μg) compared to Foradil Aerolizer (12 μg) in patients with moderate to severe COPD.

This multi-center study will be conducted at approximately 20 sites, contributing approximately 10 to 15 patients per site, in Australia, New Zealand, and the US. Across these sites, it is planned that approximately 220 patients with moderate to severe COPD will be randomized into the study to provide approximately 200 patients to complete the study.

The entire study period is scheduled to take approximately 5-7 weeks for each individual patient. The study is anticipated to run for approximately 9 months and should not exceed 18 months.

Study Design

← Screening Period →		←——— Treatment Period ———→			Follow-up
Screening Visits		Randomization		End of Treatment Final Visit	Follow-up Telephone Call
Days -28 to - 1		Day 1	Day 7 (±2)	Day 14 (-3)	Day 21 (+7)
Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	

All patients will sign an informed consent form prior to the conduct of any screening assessments (Visit 1). The Investigator will obtain a medical history, physical examination, and any required documentation in order to determine eligibility for participation (inclusion/exclusion criteria). Reversibility of FEV_1 30 minutes following 4 puffs of Ventolin® HFA will be assessed at Screening to characterize the patient population but will not be used to determine eligibility to participate in the study.

Patients who meet all entry criteria will have their inhaled bronchodilator medication switched to Atrovent q.i.d. and Ventolin p.r.n. as rescue medication (see Section 5.4).

All patients will undergo a washout period of at least 1 week (≥2 weeks if taking tiotropium or phosphodiesterase inhibitors), but not greater than 3 weeks prior to returning to the clinic for Visit 2.

Patients will receive a study medication diary in which they will be asked to maintain a daily record of their study medication dosing and rescue medication. The next visit will be scheduled and the patient will be discharged.

Patients will return to the clinic at least 1 week (≥2 weeks if taking tiotropium or phosphodiesterase inhibitors) after screening for Visit 2. At Visit 2, a Holter monitor will be applied and patients will undergo 24-hour Holter monitoring to provide a baseline. During Holter monitoring, patients will complete a specific Holter monitoring diary.

When the patient returns to the clinic for Holter monitor removal the following day, the quality of the recordings will be assessed at the site. If the Holter monitor recordings fail to meet adequate quality criteria (acceptable tracings for a minimum of 18 hours), the Holter Monitor will be reconnected for another 24 hours using a new Holter hook-up kit. The patient will be instructed to continue his/ her medications as per study protocol and complete all necessary assessments on the patient diaries. The patient will return the following day for removal of the Holter Monitor. If the Holter monitoring quality remains unacceptable on the second attempt, the patient will be considered a screen-failure.

Once an acceptable (i.e. acceptable tracings for a minimum of 18 hours) baseline Holter monitor test is obtained, patients can proceed with Visit 3 (Randomization) provided no clinically significant findings are reported following review of the Holter monitoring report by [redacted]. The screening period of 7 to 28 days will be followed by randomization to one of the four treatment groups, with patients being allocated in approximately equal numbers to each group. Eligibility will be determined on the basis of their medical history, physical examination, clinical tests, and adequacy of 24-hour Holter monitoring at Screening.

For all treatment visits (Visits 3, 4 and 5), patients should withhold all study medications on the morning of their visit and should not take Ventolin HFA within 6 hours prior to their visit.

At Visit 3 (Randomization Visit; Treatment Day 1), patients will return to the clinic before 10:00 a.m. Patients who continue to meet entry inclusion/exclusion criteria and remain eligible for participation in the study will be randomized to treatment.

Randomization will be performed centrally, using an interactive web response system (IWRS).

During the treatment phase, all treatments will be administered twice daily. Each of the 4 treatments will be administered for 14 (-3) days. In addition, patients will be supplied by the investigator with open-label Ventolin HFA (90 µg emitted dose per puff) to be used when required as rescue medication throughout the trial.

At Visit 3, a Holter monitor will be placed for continuous 24-hour Holter monitoring and patients will receive a Holter monitoring diary. Patients will be dispensed study medication and a study medication diary 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 to the 2-hour post-dose time point, and be discharged. Patients will return to the clinic after 24 hours (Treatment Day 2) for removal of the Holter monitor and to return the Holter monitoring diary. **Note: If the Holter monitoring assessment collected on Treatment Day 1 is unacceptable, a repeat assessment will not be performed.**

Upon return of the Holter monitor and Holter monitoring diary, patients will be discharged from the clinic and will continue to administer study medication twice daily for 7 (±2) days at home until they return for Visit 4.

Patients will return to the clinic for Visit 4 (Treatment Day 7) at approximately the same time as Visit 3 (± 2 hours). 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). Patients will undergo all protocol-defined pre-dose assessments. Patients will have their final visit (Visit 5) scheduled approximately 1 week later and then be discharged.

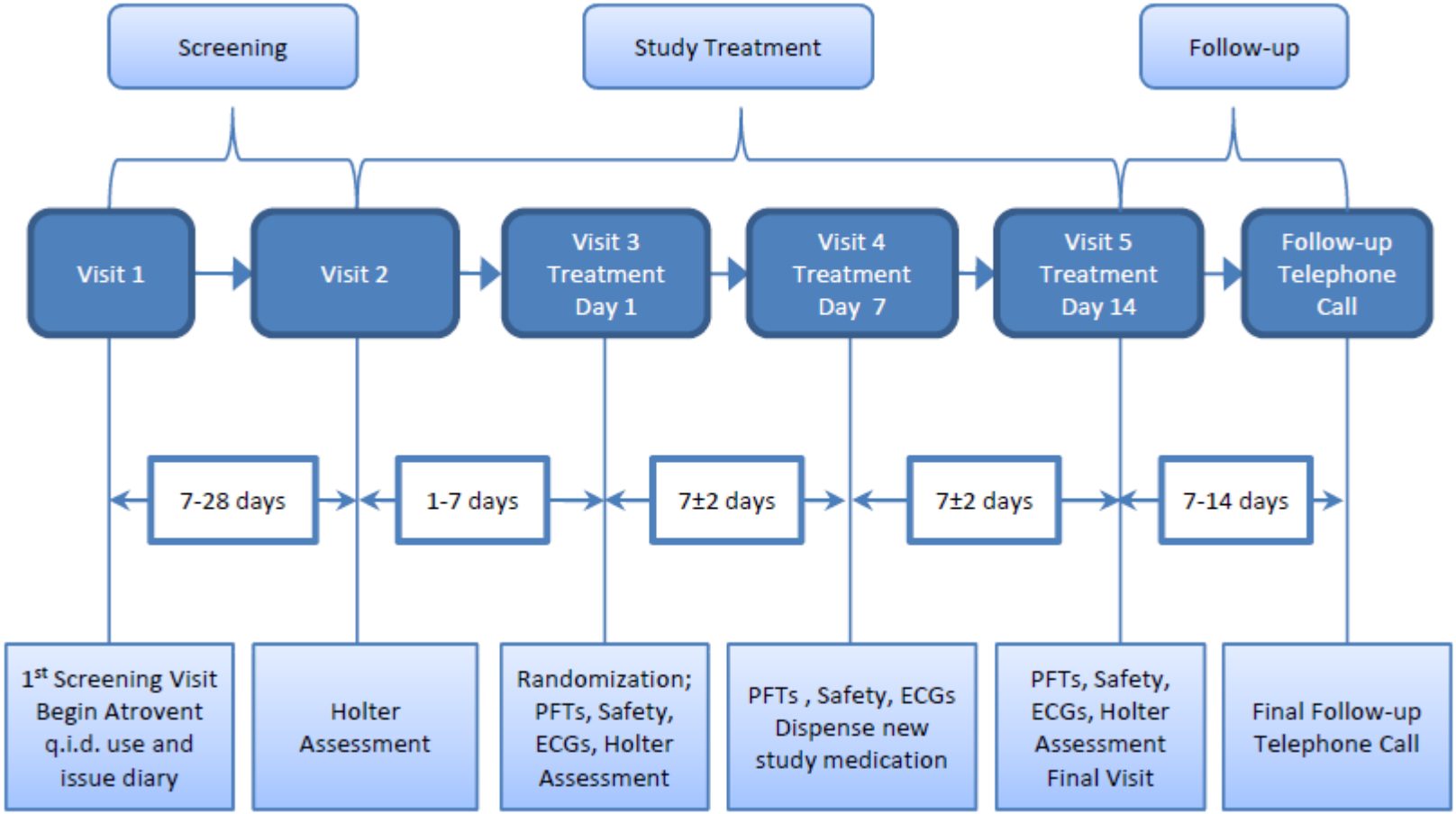
Patients will return to the clinic for Visit 5 (Treatment Day 14) at approximately the same time as Visit 3 (± 2 hours). To accommodate scheduling conflicts a window of 11-14 days is permitted (i.e., Treatment Day 14 procedures must be done within a minimum of 11 days and a maximum of 14 days). Patients will undergo all protocol defined pre-dose assessments. A Holter monitor will be placed and the Holter monitoring diary will be given to the patient. Patients will take their morning dose of study medication at the clinic. Patients will undergo all protocol-defined post-dose assessments. Patients will be discharged and instructed to return to the clinic the following day for removal of the Holter monitor and to return the Holter monitoring diary.

When the patient returns to the clinic the following day, i.e. Day 15 (-3), an ECG will be obtained prior to removal of the Holter monitoring equipment and the quality of the Holter monitor recordings will be assessed at the site. Provided the Holter monitor recording meets protocol defined criteria for acceptability, the patient will undergo a final physical examination, final laboratory assessments, and recording of any AEs. The patient will then be discharged from the study. Study staff will make a follow-up telephone call approximately 7 days later to ensure all post-study AEs (if any) have been captured.

If the Holter monitor recordings fail to meet adequate quality criteria (acceptable tracings for a minimum of 18 hours), the Holter Monitor will be reconnected for another 24 hours using a new Holter hook-up kit and no additional assessments (i.e. physical examination and laboratory assessments) will be perfomed. The patient will be instructed to continue his/ her medications as per study protocol and complete all necessary assessments on the patient diaries. The patient will return the following day for removal of the Holter Monitor and an ECG will be obtained prior to removal of the Holter monitoring equipment. Quality of the recordings will not be assessed at this repeat visit. Patients will undergo a final physical examination, final laboratory assessments, and recording of any AEs. The patient will then be discharged from the study. Study staff will make a follow-up telephone call approximately 7 days later to ensure all post-study AEs (if any) have been captured. **Note: It is advised that patients schedule their visit ahead of Day 14 because 14 days of dosing cannot be exceeded (i.e. if a subject returns for Holter placement on Day 14 and it is noted on Day 15 that the Holter assessment is inadequate, then a repeat Holter assessment will not be possible).**

A Study Flow Diagram is displayed in Figure 1.

Figure 1. Study Flow Diagram



PFT = pulmonary function test, Rx = treatment

Holter monitoring: 24-hour continuous monitoring during screening (Visit 2) and at Visit 3 and Visit 5. Patients are to return the morning following Visits 2, 3 and 5 to return the Holter monitor recorder and Holter monitoring diary.

5 STUDY POPULATION SELECTION AND WITHDRAWAL CRITERIA

5.1 Inclusion Criteria

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

1. Give their signed written informed consent to participate.
2. Are between 40-80 years of age at Visit 1.
3. A female is eligible to enter and participate in the study if she is of:
   - Non-child bearing potential (i.e., physiologically incapable of becoming pregnant, including any female who is 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 8):
     - Complete abstinence from intercourse from screening until 2 weeks after Visit 8 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 3), 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 Atrovent HFA q.i.d. with or without inhaled corticosteroid (ICS) as maintenance treatment for their COPD and Ventolin HFA p.r.n. for relief of COPD symptoms for at least 1 week prior to randomization.
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.
10. Acceptable baseline (Visit 2) Holter monitor recording (see Section 7.2.4).

5.2 Exclusion Criteria

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

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

7. Hospitalization: Patients who have been hospitalized due to poorly controlled COPD within 3 months of Screening (Visit 1).
8. Poorly Controlled COPD: Patients who have poorly controlled COPD, defined as acute worsening of COPD that requires treatment with corticosteroids or antibiotics in the 6-week interval prior to Screening (Visit 1), or between Screening and Randomization (Visit 3).
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 3acceptable 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), 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)]. **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 (Type 2) or third degree atrioventricular (AV) block).
      Note: Isolated right bundle branch block does not constitute an exclusion criteria.
    - Clinically significant arrhythmias (e.g., sick sinus syndrome, current or prior history of atrial fibrillation, atrial flutter, 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).
    - Bradycardia with rate <45 bpm.
    - Pathological Q wave indicating prior myocardial infarction
    - Significant ST-T wave abnormalities (excluding non-specific ST-T wave abnormalities)
13. Clinically significant abnormal findings during the baseline Holter recording defined as (but not limited to) any of the following:
    - Average heart rate ≤ 40 beats per minute for any one hour

- Second-degree Atrioventricular (AV) block (Type 2) or third-degree AV block. Transient type 1 second degree AV block lasting for more than 60 minutes.
- Ventricular asystole of 2.5 seconds duration
- Any run of ventricular ectopic beats associated with symptoms (hypotension or syncope), regardless of the rate.
- Any episode of ventricular flutter and/or ventricular fibrillation.
- Any episode of sustained ventricular tachycardia (VT)
  - VT is defined as a run of 3 or more ventricular premature beats (VPB's) with a rate >120 beats per minute. Sustained VT is defined as VT lasting > 30 seconds or > 60 beats. Nonsustained VT is a run of 3 or more VPB's with a rate > 120 beats per minute which does not fulfill the criteria for sustained VT.
- Five or more events of non-sustained VT / 24 hours or any episode of non-sustained VT with > 15 VPB's in a row.
- > 200 VPB/HR
- Paroxysmal supraventricular tachycardia (non-sinus rhythm inclusive of atrial fibrillation or atrial flutter) lasting continuously for over 1 minute.

14. Patients with a pacemaker or ICD/CRT/CRT_D devices
15. Uncontrolled Hypertension: Patients who have clinically significant uncontrolled hypertension.
16. 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.
17. 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.
18. 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 and/or constituents of the dry powder product (lactose).
19. Substance Abuse: Patients with a known or suspected history of alcohol or drug abuse within the last 2-year period prior to Screening.
20. 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.
21. 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.

22. 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.
23. 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.
24. 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.
25. 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.
26. 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.
27. 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.
28. 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.
29. A patient who requires the use of a spacer device to compensate for poor hand-to-breath coordination with a MDI.
30. Patients who were previously enrolled in a Pearl Therapeutics PT001 (GP MDI), PT005 (FF MDI) or PT003 (GFF MDI) studies.

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 3 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 Atrovent HFA qid as maintenance therapy of their COPD and Ventolin HFA prn as rescue medication. During the treatment period (Visit 3 – Visit 5), patients will discontinue use of Atrovent HFA qid and continue use of Ventolin HFA prn as rescue medication. All short acting bronchodilators should be withheld for at least 6 hours before Visits 3, 4 and 5.
- 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 (Atrovent HFA q.i.d. for maintenance of COPD and Ventolin HFA p.r.n. as rescue medication during the screening period) per the protocol provided they have been maintained on a stable dose for at least 4 weeks.
- Patients receiving a maintenance dose of an ICS that is not administered as a fixed dose combination together with a LABA will be permitted to continue the ICS provided they have been maintained on a stable dose for at least 4 weeks.
- All patients treated with either a LABA (salmeterol, formoterol) or long-acting anti-muscarinic agent (LAMA) (tiotropium) administered alone or as a loose combination will have these medications discontinued and replaced with short-acting bronchodilators (Atrovent HFA q.i.d. for maintenance of COPD and Ventolin HFA p.r.n. as rescue medication during the screening period) per the protocol.

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) until the patient completes or discontinues from 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 Pearl Therapeutics. Each person accessing the IWRS system must be assigned an individual unique PIN. They must use only their assigned PIN to access the system and they must not share their assigned PIN with anyone.

6.2 Product Descriptions

Investigational materials will be provided by the Sponsor as summarized in Table 1.

Table 1. Product Descriptions

Product Name & Potency	Dosage Form	Comments
Formoterol 9.6 µg ex-actuator (FF MDI)	MDI	Taken as 2 inhalations of the 4.8 µg per actuation strength MDI
Glycopyrrolate 36 µg ex-actuator (GP MDI)	MDI	Taken as 2 inhalations of the 18 µg per actuation strength MDI
Glycopyrrolate 36 µg /Formoterol 9.6 µg ex-actuator combination (GFF MDI)	MDI	Taken as 2 inhalations of the Glycopyrrolate 18 µg / Formoerol 4.8 µg per actuation strength MDI
Formoterol Fumarate Inhalation Powder 12 µg[†]	DPI	US source: (Foradil Aerolizer) Taken as 1 capsule. Each capsule contains 12 µg corresponding to 10 µg formoterol fumarate dehydrate delivered from the mouthpiece *Supplies are open-label.*
Ipratropium Bromide inhalation aerosol 17 µg ex-actuator	MDI	US source: (Atrovent HFA) Each inhalation contains 21 µg corresponding to 17 µg ipratropium bromide per actuation *Supplies are open-label.*
Albuterol Sulfate inhalation aerosol[§] 90 µg ex-actuator	MDI	US source: (Ventolin HFA) Each inhalation contains 108 µg corresponding to 90 µg albuterol base per actuation *Supplies are open-label.*
[†] Active control [§] Rescue medication **Note: All study drugs will be administered by oral inhalation.**		

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

For open-label Atrovent HFA (ipratropium bromide, 17 µg), bulk commercial metered dose inhalers with dose counters will be provided. Manufacturer's instructions for study drug administration will be provided.

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

6.3 Primary Packaging and Labeling Information

Investigational materials will be packaged by the Sponsor as summarized in Table 2 below. Atrovent HFA and Ventolin HFA supplies will be supplied as open-label MDIs.

Table 2. Packaging of Clinical Supplies

Product Name and Potency	Fill Count	Dosing Instructions
Formoterol Fumarate 9.6 µg ex-actuator (FF MDI)	1 MDI 120 actuations	Take two inhalations as directed in the morning and evening.
Glycopyrrolate 36 µg ex-actuator (GP MDI)	1 MDI 120 actuations	Take two inhalations as directed in the morning and evening.
Glycopyrrolate 36 µg /Formoterol 9.6 µg ex-actuator combination (GFF MDI)	1 MDI 120 actuations	Take two inhalations as directed in the morning and evening.
Formoterol Fumarate Inhalation Powder 12 µg[†]	N/A	Take one capsule as directed in the morning and evening.
Ipratropium Bromide inhalation aerosol 17 µg ex-actuator[†]	1 MDI 200 actuations	Take two inhalations as directed four times a day.
Albuterol Sulfate inhalation aerosol[§] 90 µg ex-actuator	1 MDI 60 or 200 actuations	Use only as directed.

[†] Active control
[§] Rescue medication

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

Open-label Supplies: Open-label Foradil Aerolizer supplies will be provided as individually labeled DPIs and bulk labeled commercial blister packs packaged in sets of 4 blister pack per patient within a foil overwrap labeled with a two-part label. Each Foradil Aerolizer will have a single label.

Open-label Atrovent HFA and 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 the study will be packaged in boxes as outlined in Table 3. Open-label Atrovent HFA and 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
Foradil Aerolizer Device	1 DPI
Bulk Foradil Aerolizer Capsule	1 Foil Pouch Containing 4 Blister Packs Each
Ventolin HFA	1 MDI
Atrovent HFA	1 MDI

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

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

6.5 Unblinding Procedures

The IWRS should be used in order to unblind patients and to unmask drug identity. Pearl Therapeutics will not provide a disclosure envelope with the clinical supplies. The investigator or treating physician may unblind a subject's treatment assignment **only in the case of an emergency**, when knowledge of the study treatment is essential for the

appropriate clinical management or welfare of the subject. Whenever possible, the investigator must first discuss options with the Medical Monitor or appropriate study personnel **before** unblinding the subject's treatment assignment. If this is impractical, the investigator must notify Pearl Therapeutics as soon as possible, but without revealing the treatment assignment of the unblinded subject, unless that information is important for the safety of subjects currently in the study. The date and reason for the unblinding must be recorded in the appropriate data collection tool.

6.6 Storage Requirements

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

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

Atrovent HFA supplies: Store at 25°C (77°F). Brief storage between between 59 and 86°F (15 and 30°C) is permitted. Do not puncture. Do not use or store near heat or open flame. Exposure to temperatures above 120°F may cause bursting. Never throw the inhaler into a fire or incinerator. Avoid spraying in eyes.

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

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

6.7 Instructions for Preparation of Treatments for Administration and Dispensing

GFF MDI, GP MDI, and FF MDI

Individual 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 (puff).

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

Each dose will consist of 2 puffs from the MDI. 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, , until patient returns to the clinic. The MDI should be stored at room temperature by the patient, avoiding temperature extremes and storage in direct sunlight. See Appendix 4 for instructions on the administration of GFF MDI, GP MDI, and FF MDI.

Foradil Aerolizer

Individual Foradil Aerolizer devices will be packaged in a foil overwrap contained in an individual visit treatment carton. Both the visit treatment carton and the foil overwrap will have a label with a component ID number. Confirm that the identifier given by IWRS and the component ID number written on the label are the same. The foil overwrap is labeled with a two-part label. Write the patient number and treatment visit number on each of the two-part labels. The 'tear-off' part of the label is to be placed onto the IWRS confirmation report.

For open-label Foradil Aerolizer drug supplies, the bulk commercial blister packs will be stored refrigerated in a secured location within the clinic or pharmacy facilities. To ensure adequate time for equilibration (minimum 2 hours) to room temperature prior to administration, one foil pouch (containing 4 blister packs) should be kept in a secure location at room temperature. If a patient is randomized to Foradil Aerolizer, the equilibrated supplies will be dispensed and at an appropriate time following study drug administration, study staff will obtain new foil pouch (containing 4 blister packs) from the refrigerated bulk supplies. Retain new foil pouch at the site, stored at room temperature in a secured location for use with a subsequent patient.

The contents of 1 capsule each will be inhaled in the morning and in the evening approximately 12 hours apart, until patient returns to the clinic. See Appendix 5 for the manufacturer's instructions on the administration of Foradil Aerolizer.

Atrovent HFA (ipratropium bromide)

Individual Atrovent HFA MDIs will be contained in an individual visit treatment box. Both the visit treatment box and the foil overwrap will have a label with a component ID number. Confirm that the identifier given by IWRS and the component ID number written on the label are the same. The 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.

Atrovent HFA is a solution aerosol that does not require shaking. However, as with any other MDI, some coordination is required between actuating the canister and inhaling the medication. Atrovent HFA should be primed per manufacturer's instructions prior to dispensing to patient (i.e. "prime" or actuate Atrovent HFA before using for the first time by releasing 2 test sprays into the air away from the face). In cases where the inhaler has not been used for more than 3 days, prime the inhaler again by releasing 2 test sprays into the air away from the face. Patients should avoid spraying Atrovent HFA into their eyes.

Patients will be dispensed the MDI at Visit 1 to continue taking study medication four times a day (approximately 6 hours apart) during the run in period between Visits 1 to 3, 2 puffs with each administration. The MDI should be stored at room temperature by the patient, avoiding temperature extremes and storage in direct sunlight. See Appendix 6 for the manufacturer's instructions on the administration of Atrovent HFA.

Ventolin HFA (albuterol sulfate inhalation aerosol)

Bulk supplies of open-label Ventolin HFA will be provided by Pearl Therapeutics and stored in a secured location within the clinic or pharmacy facilities. 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 7 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 or destroyed as directed by Pearl Therapeutics.

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

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

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

7 STUDY PROCEDURES

A time and events schedule is provided in Table 4.

All assessments during Visits 2 through 5 will be conducted in the following order: ECGs, vital signs, clinical laboratory assessments, and spirometry.

7.1 Efficacy Assessments

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

The volume accuracy of the spirometer is to be checked daily using a 3 L syringe across 3 flow ranges e.g., 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).

At each visit during the treatment period (Visits 3, 4 and 5), spirometry will be conducted 60 minutes and 30 minutes prior to study drug administration. The average of the two pre-dose assessments will be used to establish a baseline FEV_1 at Visit 3 and a corresponding pre-dose trough value at Visits 4 and 5.

7.1.1 Pulmonary Function Tests

All pulmonary function tests including FEV_1, FVC and PEFR as defined in ATS/ERS guidelines (Miller, 2005) and will be performed in accordance with ATS criteria (Miller, 2005).

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

Refer to Section 7.3 for specific FEV_1 criteria that prompt patients to be discontinued from the study.

7.1.2 Patient Diaries

7.1.2.1 Study Medication 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 and rescue Ventolin HFA use. Two types of diaries will be provided – one for use during the screening period (between Visits 1 and 3) when patients are taking Atrovent HFA (17 μg) q.i.d. and Ventolin HFA p.r.n. as rescue medication and the other for use during the treatment period (between Visits 3 and 5) when patients are taking study medication b.i.d. and Ventolin HFA p.r.n. as rescue medication.

Beginning with the Screening Visit (Visit 1), the patient will be given a diary to be completed daily and returned at the next visit. Before giving the diary to the patient, the study coordinator will be responsible for entering the patient's identification (screening number for Visits 1 and 2, and randomization number for all other Study Visits), 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 a study visit, patients will return the diary provided at the previous visit.

At Visit 3, patients should demonstrate acceptable use of the diary. Patients who fail to demonstrate proper diary use should be retrained prior to randomization.

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.

7.1.2.2 Holter Monitoring Diary

Patients will complete a Holter Monitor Diary during the 24-hour collection period for holter monitoring. The diary will be in the form of a checklist and will ask patients to confirm whether certain predetermined events occurred during the 24-hour monitoring period.

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 Medication Compliance

Time of dosing with study medication will be recorded in the patient study medication 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 AE and SAE assessments, Holter monitoring, ECGs, physical examination findings, vital signs, and clinical laboratory tests.

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 3). A complete physical examination will be performed at Screening and the Final Visit (Visit 5). A complete physical examination will include the following: general appearance, skin, head, eyes, ears, nose, throat, neck (including thyroid), lymph nodes, chest, heart, abdomen, extremities, and nervous system. Weight, assessed in ordinary indoor clothing with shoes off, and height (Screening) will be recorded at the specified visits.

7.2.2 Vital Sign Measurements

Heart rate, systolic and diastolic blood pressure ('vital signs') will be assessed at each visit; assessments will be obtained after being supine for 10 minutes. 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, systolic and diastolic blood pressure readings that prompt patients to be discontinued from the study. When vital signs assessment are scheduled at the same time point as ECGs, blood draws and/or spirometry, the sequence of events should be: ECG, vital signs, laboratory assessments and spirometry.

Systolic and diastolic blood pressures, heart rate will be obtained 60 and 30 minutes prior to study drug administration on Days 1, 7 and 14 as well as 30 minutes and 2 hours after study drug on Days 1 and 14. On Days 2 and 15 systolic and diastolic blood pressures, heart rate will be obtained immediately after ECG assessment. Temperature will be obtained at Screening and once at each visit as part of the initial vital sign assessment (i.e. Once on Day 1, 2, 7, 14 and 15), and will not be repeated at subsequent time points unless clinically indicated.

7.2.3 12-Lead Electrocardiogram (ECG)

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.

ECGs will be obtained at:

- Screening (Visit 1)
- Treatment Day 1 (Visit 3): between 1 to 2 hours and 30 minutes to 1 hour prior to study drug and at 30 minutes and 2 hours after study drug.
- Treatment Day 2 prior to removal of the Holter monitor
- Treatment Day 7 (Visit 4): within 60 minutes prior to study drug administration.
- Treatment Day 14 (Visit 5): between 1 to 2 hours and 30 minutes to 1 hour prior to study drug and at 30 minutes and 2 hours after study drug.
- Day 15 prior to removal of the Holter monitor (Study drug not to be administered beyond Day 14)

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 manually calculated QTcF 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, a repeat ECG is to be recorded. If the prolonged QTc intervals are confirmed on review by the investigator (or designated ECG reviewer), the Investigator will make a

determination on the suitability of continuing the patient in the study. If QTcF interval prolongation exceeding these limits is verified during treatment, the patient's medical background should be examined closely for risk factors that may have contributed to the event, including genotyping for hereditary long QT syndromes, if appropriate. Refer to Section 7.3 for specific criteria for QTcF (Fridericia's Formula) that prompt patients to be discontinued from the study.

Additional ECGs will be obtained if the patient's resting 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 at Visit 3). Refer to Section 7.3 for specific criteria for heart rate that prompt patients to be discontinued from the study.

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 24-hour continuous electrocardiography (Holter monitoring)

The designated CRO for Holter monitoring will be [redacted]. All Holter monitor recordings will be [redacted]sessed for cardiac arrhythmias by an independent cardiologist appointed by [redacted].

Continuous 12-lead ECGs (Holter assessment) will be obtained at Visit 2 (screening), Visit 3 (baseline) and Visit 5 [Day 14(-3); end of treatment]. The Visit 2, Visit 3 and Visit 5 Holter monitor recordings are to be initiated in the morning at approximately the same time (+/- 2 hours). The Visit 3 and Visit 5 Holter monitoring will be initiated 15-30 minutes prior to the administration of the morning dose of trial medication.

Continuous Holter monitor recording will be collected for a minimum of 24 hours. Holter monitor recordings should contain a minimum of 18 hours of acceptable quality recording in a 24-hour period to be deemed an acceptable Holter assessment.

The Holter recording obtained at Visit 2 will be used to determine the patient's eligibility for the study and will serve as the baseline for all comparisons. If the initial Holter monitor assessment at Visit 2 is unacceptable, the Holter Monitor will be reconnected for another 24 hours using a new Holter hook-up kit. The patient will be instructed to continue his/her

medications as per study protocol and complete all necessary assessments on the patient diaries. The patient will return the following day for removal of the Holter Monitor. If the second attempt is unacceptable, the patient will not be allowed to continue in the study and considered a screen-failure.

The Holter monitor assessment at Visits 3 will not be repeated even if it is unacceptable.

At Visit 5, the Holter monitor can be placed on Day 11, 12, 13 or 14. If the initial Holter monitor assessment at Visit 5 is unacceptable, the Holter monitor will be reconnected for another 24 hours using a new Holter hook-up kit provided that the initial Holter was placed on Day 11, 12 or 13. The patient will be instructed to continue his/her medications as per study protocol and complete all necessary assessments on the patient diaries. The patient will return the following day for removal of the second Holter Monitor. No further attempts are allowed if the second attempt is unacceptable. **If the initial Holter monitor is placed on Day 14 a repeat assessment is not allowed regardless of acceptability.**

Each patient will receive a Holter monitoring diary. Patients will record cardiovascular-related symptoms which occurred during the Holter monitor recording (e.g., chest pain, shortness of breath). Every effort must be made to instruct the patient to consistently record entries in the Holter monitoring diary. The information in the Holter monitoring diary may be used by [redacted] in the interpretation of the Holter monitor recordings. The patient's Holter monitoring diary will also be reviewed by the investigator to identify symptoms which the investigator considers to be appropriate for recording in the eCRFs as adverse events.

Data for analysis will include:

- General trends including heart rate
- Hourly rhythm comments
- Ventricular ectopy summary
- Ventricular run summary
- Supraventricular ectopy summary
- Supraventricular run summary
- Any other clinically relevant arrhythmias, including atrial fibrillation and pronounced bradycardia.

Manual summary interpretation of the data is sent as a report to the site and to Pearl Therapeutics.

7.2.5 Clinical Laboratory Tests

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

Hematology (Complete Blood Count) and chemistry (Comprehensive Metabolic Panel) will be obtained at Screening, within 60 minutes prior to dosing on Treatment Day 1, Treatment Day 2, and on Day 15 when patients return to have their Holter monitor removed.

Serum pregnancy testing will be performed at Screening and at the Final Visit (Visit 5) 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)
Alkaline phosphatase	Calcium
Bilirubin, total	Chloride
Gamma-glutamyl transferase	Cholesterol
	Bicarbonate
	Creatinine
	Glucose
	Magnesium
	Potassium
	Phosphate
	Protein, total
	Sodium
	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.

7.2.6 Adverse Events

7.2.6.1 Performing Adverse Events Assessments

The investigator is responsible for promptly documenting and reporting all AEs observed during the study in the subject's case report form and on the AE Reporting Form. If the AE is "alarming", the investigator must report the AE immediately to Pearl Therapeutics. In addition, certain AEs (as described in Section 7.2.6.7) are classified as "serious" and must be reported no later than 24 hours after the investigator recognizes/classifies the event as a serious adverse event to Pearl Therapeutics or its designee (Sponsor).

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

7.2.6.2 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).

7.2.6.3 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.

7.2.6.4 Severity

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

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

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

Severe: Associated with inability of 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.

7.2.6.5 Relationship

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

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

Probably: A reaction that follows a reasonable temporal sequence from administration of study drug; that follows a known or expected response pattern to the study drug; and/or that

could not be reasonably explained by other factors such as underlying disease, complications, concomitant drugs, or concurrent treatments.

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

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

7.2.6.6 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.

7.2.6.7 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 the 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 may include copies of hospital records, case reports, and autopsy reports, and other pertinent documents.

Post-study SAEs following the last dose of study drug must be reported to Pearl Therapeutics as described in Section 7.2.6.10.

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

7.2.6.8 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.

7.2.6.9 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.

7.2.6.10 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.

7.2.6.11 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.

7.2.6.12 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.

7.2.7 AEs of Interest

Syncope and atrial fibrillation are considered to be AEs of interest, and will be tabulated separately.

7.2.8 Overdose

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

7.2.9 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 Therpeutics 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.

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 rest as recorded on ECG 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 2-hour interval after taking study drug.
- Symptoms of dyspnea at any time within the 2-hour interval after taking study drug, that in the opinion of the investigator or designee requires additional spirometry assessments, which demonstrates a decrease in FEV_1 of more than 20% from test day baseline (before taking study drug) on two consecutive assessments obtained at least 15 minutes apart.

Holter monitoring criteria for discontinuation:

- Average heart rate ≤ 40 beats per minute for any one hour
- Development of transient or fixed complete heart block
- Development of type 2 second degree AV block
- Development of type 1 second degree AV block lasting more than 60 minutes
- Ventricular asystole of ≥ 2.5 seconds duration
- Development of Holter monitoring criteria for proarrhythmia (see Appendix 3)
  Other clinically relevant findings that the Investigator deems should lead to the subject being discontinued.

Other valid reasons for removing a patient from the study include:

- The patient does not adhere to study rules and procedures;
- The patient wishes to withdraw from the study;
- Continuation of the patient is in violation of the inclusion and exclusion criteria;
- The investigator feels it is in the patient's best interest to terminate participation;
- The study is terminated by Pearl Therapeutics.

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.

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. 7 or more deaths from any cause at any time during the course of the study.

Stopping criteria for 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 an approximately 99% chance of each patient surviving 50 days on study. Assuming that 220 patients are randomized, the probability of placing the study on hold if mortality is no greater than background is 0.3%. Should the criterion for study hold be reduced to 6 or more deaths, the probability of inappropriate hold increases to 1.25%.

8 STUDY ACTIVITIES

A time and events schedule is provided in Table 4.

Table 4. Schedule of Events

	Screening[a]		Treatment Period[a]					Follow-Up
	Visit 1	Visit 2	Visit 3 Randomization		Visit 4	Visit 5		Telephone Contact
Procedures	Day -7 to -28	Day -1 to -7	Day 1	Day 2	Day 7 (±2)	Day14 (-3)	Day15 (-3)	Day 21(+7)
Informed Consent	X							
Eligibility Criteria	X	X	X					
Verify Continued Eligibility		X	X	X	X	X	X	
Reversibility to Ventolin HFA[b]	X							
Demographics & Medical/Surgical History	X							
Concomitant Medications[c]	X		X		X	X		
Spirometry[d]	X		X	X	X	X		
Physical Examination[e]	X						X	
Vital Signs[f]	X	X	X	X	X	X	X	
12-Lead ECG[g]	X		X	X	X	X	X	
24-Hour Holter Monitoring[h]		X	X			X		
Pregnancy Test[i]	X		X				X	
Clinical laboratory testing[i]	X		X	X			X	
Adjust COPD Medications Per Protocol[j]	X							
Resume pre-study COPD medications as appropriate[k]							X	
Adverse Events	X	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			X		
Collect/Review Patient Diary		X	X		X	X		
Follow-up Telephone Call to assess Adverse Events and Safety								X

Table 4. Schedule of Events (continued)

[a] Screening period of at least 7 days and up to 28 days. Patients are required to take Atrovent HFA q.i.d. and Ventolin HFA p r n. and complete the patient study medication diary during the screening period. An acceptable baseline Holter monitoring assessment is required before patients can proceed to Visit 3.

[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, patients should withold short-acting bronchodilator and other COPD medications at least 6 hours prior to the start of visit procedures.

[d] Spirometry (FEV_1, FVC, and PEFR) will be assessed at Screening and Visits 3, 4, and 5. During the treatment period (Visits 3, 4 and 5), spirometry will be conducted 60 minutes and 30 minutes prior to study drug administration.

[e] Includes evaluation of height and weight at Screening.

[f] Vital signs will be obtained at each visit. Assessments will be obtained after being supine for 10 minutes. SBP, DBP and HR will be obtained in the supine position. On Days 2 and 15 systolic and diastolic blood pressures, heart rate will be obtained immediately after ECG assessment. Temperature will be obtained at Screening and once at each visit as part of the initial vital sign assessment (i.e. Once on Day 1, 2, 7, 14 and 15), and will not be repeated at subsequent time points unless clinically indicated.

[g] ECGs will be collected at Screening (Visit 1) and Treatment Days 1, 2, 7 and 14. A final ECG will be collected on Day 15 prior to removal of the Holter monitoring equipment. On Days 1 and 14 ECGs will be collected at 60 minutes (between 60 to 120 minutes) and 30 minutes (between 30 to 60 minutes) prior to dosing and 30 minutes and 2 hours post dosing. On Day 7 an ECG will only be conducted at 60 minutes (between 30 to 60 minutes) prior to dosing. An ECG should be collected prior to removal of the Holter monitoring equipment on Days 2 and 15.

[h] Holter monitoring: 24-hour continuous monitoring during screening (Visit 2) and at Visit 3 and Visit 5. Patients are to return the morning following Visits 2, 3 and 5 to return the Holter monitor recorder and Holter monitoring diary.

[i] All clinical laboratory tests will be obtained at Screening, Visit 3 (Treatment Day 1 and 2) and Visit 5 (Day 15). Pregnancy test (women of child-bearing potential only): serum [human chorionic gonadotropin (HCG)] at Screening and Visit 5 only and Urine HCG at all other visits.

[j] 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).

[k] At the end of the Visit 5, return patient to pre-study or other appropriate inhaled maintenance COPD medications.

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

8.1 Screening Visit (Visit 1)

- Obtain informed consent.
- Check inclusion/exclusion criteria.
- Obtain demographic data, including age, race, smoking history, and medical/surgical history including glaucoma and age of onset of COPD.
- Obtain medication history, including COPD medications.
- 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 a 12-lead ECG after being supine for 10 minutes.
- Obtain vital signs (heart rate and blood pressure in a supine position and oral or tympanic temperature), height and weight.
- Obtain laboratory samples (hematology and chemistry).
    - Perform 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 baseline spirometry assessments.
- Dispense Ventolin HFA and instruct patient on its use (See package insert for Ventolin HFA for proper inhaler use)
- 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).
- Complete an eye examination for glaucoma if not performed within the last 2 years (New Zealand Sites Only)
- 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). Dispense Atrovent HFA to be used as maintenance medication for COPD during the screening period. Instruct patients

on the proper use of Atrovent HFA and Ventolin HFA during the screening period (see Section 5.4).

- Complete Screening Log (basic demographics, spirometry, medications and reasons for screen failure) for patients who do not meet eligibility criteria.

- Record 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 as medical history and not as a study adverse event unless the event meets the definition of an SAE

- Dispense patient study medication diary and provide instructions on diary completion.

- Arrange date of Visit 2 as appropriate.

8.2 Screening Visit for Baseline Holter Assessment (Visit 2)

- Collect and review patient diary (if diary is not completed correctly, re-train patient).

- Review inclusion/exclusion criteria to confirm protocol eligibility.

- Review of clinical laboratory results from Visit 1. Please note whether the results are clinically significant and include comments where applicable.

- Obtain vital signs (heart rate and blood pressure in a supine position and oral or tympanic temperature)

- Record 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 as medical history and not as a study adverse event unless the event meets the definition of an SAE.

- Review concomitant medications to ensure adherence to COPD regimen.

- Note time of last dose of short-acting bronchodilator and other COPD medications in the source documents.

- Perform Holter Monitoring for 24 hours – see Section 7.2.4. Record the start time of Holter monitor recording in the eCRF. Dispense Holter monitoring diary and instruct patient regarding its use. The patient must return the next morning with the device, study medication and diaries.

24-hours post dose assessments

- After completion of the 24-hour Holter monitor recording determine acceptability of Holter monitor recording (see Section 7.2.4). If 24-hour Holter monitor

recording is unacceptable, see Section 7.2.4 for instructions. **Note: Patients should not be randomized unless an acceptable Holter monitor recording has been obtained.**

- Obtain vital signs (heart rate and blood pressure in a supine position and oral or tympanic temperature)
- Record adverse events, if any
- Instruct patient to continue Atrovent qid and Ventolin HFA prn as rescue medication until Visit 3
- Instruct patient to continue completion of the study medication diary until Visit 3 (re-train patient on diary completion if necessary)
- Schedule Visit 3, if appropriate, or record patient status as screen failure.
- Remind patients scheduled for Visit 3 to withhold all study medications on the morning of Visit 3 and instruct them to not take Atrovent HFA or Ventolin HFA within 6 hours prior to their visit.

8.3 Randomization Visit (Visit 3; Day 1)

- Check to see if the patient has received rescue medication within 6 hours prior to the start of the visit. Note time of last dose of short-acting bronchodilator and other COPD medications on the source documents.
- Collect and review patient study medication diary (if diary is not completed correctly, re-train patient).
- Review inclusion/exclusion criteria to confirm protocol eligibility.
- Record 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 as medical history and not as a study adverse event unless the event meets the definition of an SAE.
- Review concomitant medications to ensure adherence to COPD regimen.
- Perform urine pregnancy test (women of child-bearing potential only).
- Perform all pre-dose assessments.
- Attach and initiate 24-hour Holter Monitor 15-30 minutes prior to dosing (see Section 7.2.4). Dispense Holter monitoring diary and instruct patient regarding its use. This test to be performed for approximately 24 hours. Obtain patient treatment assignment information from IWRS. At this point the patient is randomized.

- At 15-30 minutes prior to dosing, the seal around the study day treatment box is to be opened and the instructions for administration of study drug on the inner flap of the study day treatment box are to be followed.
    - Refer to Section 6.7 for detailed instructions for preparation of treatments for administration. These instructions are to be adhered to and are relevant to all study treatment visits.
- Patient will administer first dose of study drug at the clinic.
- Record adverse events (if any).
- Enter Time of first dose of study medication into study medication diary
- Perform all post-dosing assessments.
- The patient should be instructed to take the evening dose of study medication while wearing the Holter. The patient must return the next morning with the device, which is to be removed prior to taking the next morning's dose of study medication. The Holter monitoring diary is to be collected at that time. The time of dosing with study medication and Ventolin HFA rescue medication during the Holter monitor recording will be recorded by the patient in the study medication diary and by the site personnel in the eCRF.

24-hours post dose assessments

- Collect ECG prior to removal of Holter monitor
- Remove Holter monitor. **Note: At this visit, the 24-hour Holter monitor recording will not be repeated regardless of whether or not it meets acceptability criteria**
- Obtain vital signs (heart rate and blood pressure in a supine position and oral or tympanic temperature)
- Perform spirometry assessments (prior to AM dosing)
- Obtain laboratory samples (hematology and chemistry)
- Record adverse events, if any
- Instruct patient to continue taking study medication twice daily and Ventolin HFA prn as rescue medication until Visit 4
- Instruct patient to continue completion of the study medication diary until Visit 4 (re-train patient on diary completion if necessary)
- Schedule Visit 4.
- Remind patients to withhold all study medications on the morning of Visit 4 and instruct them to not take Ventolin HFA within 6 hours prior to their visit.

8.4 Visit 4 (Day 7)

- Collect and review patient study medication diary.
- Note time of last dose of short-acting bronchodilator and other COPD medications on source documents.
- Review concomitant medications and ensure adherence to COPD regimen.
- Confirm eligibility to continue.
- Record adverse events (if any).
- Perform all pre-dose assessments.
- Patient will administer dose of study drug at the clinic under supervision.
- **For patients taking double-blind study medication**: Previously dispensed study medication will be collected and a new supply of study medication will be dispensed.
- **For patients taking open-label Foradil**: Previously dispensed study medication will be collected and a new supply of blister packs will be dispensed. Patients will continue to use their existing Aerolizer device for the remainder of the trial.
- Schedule Visit 5 and ensure patient has adequate supply of study drug and rescue Ventolin HFA.

8.5 Visit 5 (Day 14)

- Collect and review patient study medication diary.
- Confirm eligibility to continue.
- 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 source documents.
- Perform all pre-dose assessments.
- Attach and initiate 24-hour Holter Monitor 15-30 minutes prior to dosing (see Section 7.2.4).

- Dispense Holter monitoring diary and instruct patient regarding its use. This test to be performed for 24 hours.
- Patient will administer dose of study drug at the clinic under supervision.
- Perform all post-dosing assessments.
- Redispense study medication and instruct patient to take the evening dose of study medication, **but not to take a dose the following morning.**
- Redispense patient study medication diary and provide instructions on diary completion if appropriate.
- The patient must return the next morning with the Holter device, study medication and diaries.

24-hours post dose assessments

- Collect ECG prior to removing Holter
- After completion of the 24-hour Holter monitor recording determine acceptability of Holter monitor recording (see Section 7.2.4). If 24-hour Holter monitor recording is unacceptable, see Section 7.2.4 for instructions.
- Collect previously dispensed study medications
- Obtain vital signs (heart rate and blood pressure in a supine position and oral or tympanic temperature)
- 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 laboratory samples (hematology and chemistry).
    - Perform serum pregnancy test (women of child-bearing potential only).
- Record adverse events
- Record usage of COPD and other concomitant medications
- At completion of all Visit 5 assessments, return patient to pre-study or appropriate inhaled COPD medication(s).

8.6 Follow-Up Telephone Call (7-14 days post Visit 5)

- Study site staff will contact the patient via telephone and record adverse events (if any).
- 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 CRF. The following categories should be used to describe these events in the CRF:

- Patient discretion (document reason)
- Investigator considers it to be in the best interest of the patient
- Adverse events(s)
- Administrative reasons (e.g., early termination of the study)
- Patient lost-to-follow-up
- Major protocol violation (with approval by Pearl Therapeutics)
- 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 parallel group 4-treatment, randomized design evaluating the following 4 treatments in approximately 50 completing patients for each treatment:

- Formoterol Fumarate MDI 9.6 µg ex-actuator
- Glycopyrrolate MDI 36 µg ex-actuator
- Glycopyrrolate MDI 36 µg /Formoterol 9.6 µg ex-actuator combination
- Formoterol Fumarate Inhalation Powder 12 µg

The primary objective of this study is to assess the safety of the Glycopyrrolate 36 µg /Formoterol 9.6 µg ex-actuator combination relative to the component treatments (Formoterol Fumarate 9.6 µg ex-actuator and Glycopyrrolate 36 µg ex-actuator) and the active comparator (Formoterol Fumarate Inhalation Powder 12 µg) in patients with moderate to severe COPD.

9.2 Protocol Variables

9.2.1 Efficacy Endpoints

All efficacy assessments will be expressed as change from baseline, where baseline is defined as mean of the pre-dose assessments on Day 3.

9.2.1.1 Key Efficacy Endpoint

The key efficacy endpoint is mean change from baseline FEV_1 trough over Day 7 and Day 14 relative to the mean of pre-dose values at Visit 3.

9.2.1.2 Secondary Efficacy Endpoints

There are no secondary endpoints for which hypothesis testing will be performed. Change from baseline in FEV_1, FVC and PEFR on Days 2, 7, and 14 will be captured and characterized using descriptive statistics only.

9.2.2 Safety Endpoints

The safety endpoints for this study include:

9.2.2.1 Holter monitor summary data:

- 24 hour mean heart rate (primary safety endpoint)
- 24 hour maximum heart rate
- 24 hour minimum heart rate
- The total number of beats
- The proportion of ventricular ectopics

- The proportion of supraventricular ectopics
- The proportion of paced beats
- The number of ventricular couplets
- The number of ventricular runs
- The number of isolated ventricular events
- The number of supraventricular couplets
- The number of supraventricular runs
- The number of isolated supraventricular events
- The number of bradycardia episodes
- The number of tachycardia episodes

9.2.2.2 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.

9.2.2.3 Paradoxical Bronchospasm and Tremor

Will be regarded as adverse events of special significance, and tabulated separately.

9.2.2.4 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 on Day 1 (Visit 3).

9.2.2.5 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.

9.2.2.6 Clinical Laboratory Testing:

Full clinical laboratory testing at every sample time including hematology and clinical chemistry, characterized by change from baseline, where the baseline is defined as the value prior to dosing on Day 1 (Visit 3).

9.2.2.7 Vital Sign Measurements:

Change from baseline values where baseline is defined as the average of the values prior to dosing on Day 1 (Visit 3).

9.3 Analysis

9.3.1 Key Efficacy Analysis

Efficacy analysis will be based on a linear model in which Treatment will be a fixed effect using baseline as a covariate.

The key efficacy analysis will involve *a priori* comparisons between the combination treatment and Formoterol Fumarate MDI 9.6 µg and Glycopyrrolate MDI 36 µg for the primary endpoint: mean pre-dose FEV_1 on Visit 5 compared to pre-dose values at Visit 3. The comparisons will comprise:

- Glycopyrrolate 36 µg /Formoterol Fumarate 9.6 µg ex-actuator combination vs Formoterol Fumarate 9.6 µg ex-actuator. This is a superiority comparison.
- Glycopyrrolate 36 µg /Formoterol Fumarate 9.6 µg ex-actuator combination vs Glycopyrrolate 36 µg ex-actuator. This is a superiority comparison.

9.3.2 Other Efficacy Analysis

No other efficacy comparisons will be performed. Descriptive statistics (mean, median, range and standard deviation) will be presented for mean pre-dose FEV_1 n Day 1 and on Day 7, and for FVC and PFER on Days 1, 7 and 14.

9.3.3 Safety Analysis

9.3.3.1 Holter Monitor Results

The change from baseline (Visit 2) mean heart rate will be analysed using a linear model. The mean heart rate during the baseline period (Visit 2) will be used as a covariate.

The proportions of the following beats will be analysed using a generalized linear model with a quasi-binomial family (Wedderburn 1974):

- Ventricular ectopics
- Supraventricular ectopics
- Paced beats.

Extra-binomial variation will be accommodated by inflating the variance covariance matrix by the sum of squared Pearson residuals divided by the residual degrees of freedom (Venables and Ripley, 2002 page 208). For each proportion, the logit-transformed equivalent proportion during the baseline period (Visit 2) will be used as a covariate. Where the observed proportion is zero, the logit will be calculated assuming 1 event out of twice the total number of QRS complexes.

The numbers of the following events will be analysed using a generalized linear model with a quasi-Poisson family:

- Ventricular couplets
- Total ventricular runs
- Isolated ventricular events
- Supraventricular couplets
- Total supraventricular runs
- Isolated supraventricular events
- Bradycardia episodes
- Tachycardia episodes.

Extra-Poisson variation will be accommodated by inflating the variance covariance matrix by the sum of squared Pearson residuals divided by the residual degrees of freedom. The log-transformed number of the relevant event during the baseline period will be used as a covariate. A constant of 1 will be added to the number of each baseline event before log-transformation.

For each endpoint, the location parameter for the combination treatment will be compared with the location parameter for the other three treatments. No multiplicity adjustment will be imposed.

9.3.3.2 Adverse Events

Adverse events will be summarized by the number of patients experiencing an event for each treatment. They will be tabulated at the level of the MedDRA preferred term, and the MedDRA System Organ Class. The version of MedDRA current at the time the first subject is randomized will be used throughout the study. Tabulations will be broken down by severity and by relationship to study drug. No hypothesis tests will be performed.

9.3.3.3 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 for each treatment. No hypothesis tests will be performed, but a Clopper-Pearson confidence interval may be provided.

9.3.3.4 Clinical Laboratory Measurements

Summary statistics (mean, median, standard deviation and range) of change from baseline values will be tabulated for each treatment and each assessment time. For clinical laboratory measurements, baseline values will be defined by the value prior to dosing on Day 1 (Visit 3). Male and female patients will be tabulated separately.

9.3.3.5 Vital Signs

Summary statistics (mean, median, standard deviation and range) of change from baseline values will be tabulated for each treatment and each assessment time. For vital signs, baseline values will be defined by the value prior to dosing on Day 1 (Visit 3).

9.3.3.6 ECGs

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 on Day 1 (Visit 3).

Summary statistics (mean, median, standard deviation and range) of change from baseline values will be tabulated for each treatment period and each assessment time. For ECG parameters, baseline values will be defined by the value prior to dosing on Day 1 (Visit 3).

The number of subjects with more than a 30 msec change from the pre-dose record on the test day or greater than a 50 msec change from the baseline will be tabulated. These stubjects will be listed, and a detailed narrative provided.

9.4 Randomization

Patients will be randomly assigned to treatment using an IWRS.

9.5 Sample Size Consideration

Stein et al (1998) reported a standard deviation of 10 beats per minute for 24 hour average heart rate in patients with COPD. Takabatake et al (2001) reported a standard deviation of 10.2 bpm, for patients with COPD. Power was calculated assuming that these standard deviations are relevant for this study, and based on a standard deviation opf 10.1 bpm. A sample size of 50 patients per treatment group gives a minimum detectable difference (with approximately 90% power) of 6.5 bpm. Power was calculated assuming a two sided t test at the 5% level. The power to detect a 5 bpm change is approximately 70%.

The ability of the design to detect low frequency cardiac anomalies was also considered. A sample size of 50 patients per group implies that, if no anomalies are detected, the maximum credible value for the true proportion of patients developing the anomaly is approximately 7% (based on the binomial distribution).

Sample size has been determined with respect to the safety objectives, since these form the primary objectives of the study. Nevertheless, power for the key efficacy objective may be evaluated. Previous studies have suggested that the between subject standard deviation of trough FEV_1 is 0.1L. If half of this variability represents variation between long-term averages of subjects, and half represents variation between repeated measurements on the same subject, then the estimated standard deviation of the average of two days' trough FEV_1 is 0.13L. For an effect size of 0.1L, the power is 97%; for an effect size of 0.07L the power is 76%. These power calculations assumed a two sided t test at the 5% level.

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 study unblinding.

9.7 Study Populations

The following analysis populations are defined in this study:

- The Intent-To-Treat (ITT) Population is defined as all subjects who are randomized to treatment, received at least one dose of the study treatment, and had both baseline and post-baseline data for efficacy analysis.
- A Modified ITT (MITT) Population used for analysis of efficacy variables; where subjects must have remained in the study for minimally 2 hours post-dosing on 1 or more test days (Visit 3, 4 or 5). A more detailed description of the MITT Population will be provided in the Statistical Analysis Plan.
- The Per-Protocol (PP) Population is defined as all subjects from the ITT group who completed Visits 3, 4, and 5 of the study with evaluable efficacy data for Visits 3, 4, and 5 as specified in the protocol. The PP Population will be used for sensitivity analyses. The PP Population will exclude any measurements excluded from the MITT Population.
- The Safety Population is defined as all subjects who are randomized to treatment, received at least one dose of the study treatment, and had safety data after starting study treatment.

Analyses will be performed as follows:

- Demographics analyses will be performed for the Safety, ITT, MITT, and PP patient populations, with the Safety Population being considered the primary population for these analyses.
- Efficacy Analyses will be performed for both the MITT and PP patient populations, with the MITT Population being considered the primary population for these analyses.
- Safety Analyses will be performed using the Safety Population.

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 and safety analyses will be based on the dose actually received, rather than the dose scheduled.

9.8 Handling of Missing Data

Missing data will not be imputed. If the spirometry data quality obtained for a patient at any time-point does not meet minimal acceptability requirements per ATS/ERS criteria, as determined during the blinded spirometry over read process, data for that time-point will be considered missing.

9.9 Statistical Software

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

10 ADMINISTRATIVE INFORMATION

10.1 Regulatory Authority Approval

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

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

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

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

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

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

10.3 Patient Information and Consent

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

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

10.4 Confidentiality

10.4.1 Confidentiality of Data

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

10.4.2 Confidentiality of Subject/Patient Records

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

10.5 Quality Control and Assurance

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

10.6 Data Management

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

10.7 Study Monitoring

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

During these contacts, the monitor will:

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

This will be done in order to verify that the:

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

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

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

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

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

10.8 Retention of Data

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

10.9 Financial Disclosure

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

10.10 Investigator's Final Report

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

10.11 Publication Policy

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

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

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Appendix 1 Spirometry Performance Recommendations

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

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

FEV_1 AND FVC MANEUVERS

Equipment Requirements

The spirometer must be capable of accumulating volume for $\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-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

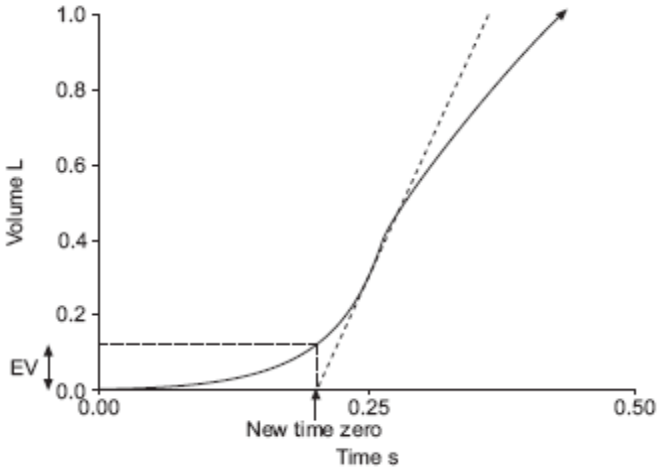
***Acceptable* Tests must meet the following 7 criteria:**

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 Holter Monitoring Criteria for Proarrhythmia

1. The 24-hour Holter monitor recordings obtained after the start of double-blind treatment will be reviewed for the development of or any increase in the incidence of cardiac dysrhythmic events, which could be considered indicative of proarrhythmic drug effects. The definition of proarrhythmia is based on the Morganroth criteria (Morganroth, et al, 1984, 1987). These criteria define proarrhythmia based on the change from the baseline visit in number of ventricular premature beats per hour (VPB/hr) and/or the frequency of ventricular tachycardia (VT) events (nonsustained or sustained) as follows:

BASELINE MEAN VPB/HR	REQUIREMENT FOR DEFINITION OF PROARRHYTHMIA (POSTBASELINE)
0 - 1	$\geq$ 10 Mean VPB/hour
1 - 100	increase of $\geq$ 10 times baseline
Over 100	increase of $\geq$ 3 times baseline

or

BASELINE NONSUSTAINED VT EVENTS*	REQUIREMENT FOR DEFINITION OF PROARRHYTHMIA (POSTBASELINE)
0	$\geq$ 5 events or > 15 beats in events/24 hrs
$\geq$ 1	increase of $\geq$ 10 times baseline events or beats

or

BASELINE SUSTAINED VT EVENTS*	POSTBASELINE SUSTAINED VT EVENTS FOR DEFINITION OF PROARRHYTHMIA*
0	$\geq$ 1

2. Any run of ventricular ectopic beats associated with symptoms (hypotension or syncope), regardless of the rate.

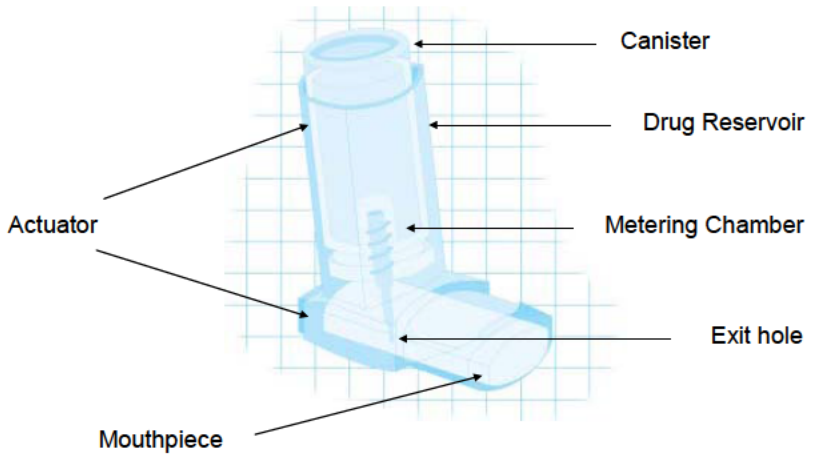
3. Any episode of ventricular flutter and/or ventricular fibrillation.

* Ventricular tachycardia (VT) is defined as a run of 3 or more ventricular premature beats (VPB's) with a rate $\geq$100 beats per minute. Sustained VT is defined as VT lasting $\geq$ 30 seconds or $\geq$ 60 beats. Nonsustained VT is a run of 3 or more VPB's with a rate $\geq$ 100 beats per minute which does not fulfill the criteria for sustained VT.

Appendix 4 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



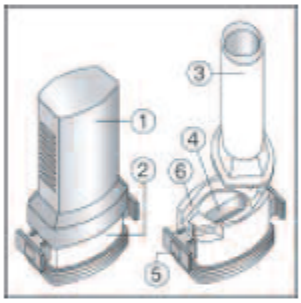
Appendix 5 Instructions for Use of Foradil Aerolizer Device

FORADIL AEROLIZER

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

Aluminum pouch covering the foil blister cards

Foil blister card



The Aerolizer consists of the following parts:
1. A cap to protect the mouth-piece of the base
2. A base that allows the proper release of medicine from the capsule

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

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

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

Taking a dose of FORADIL AEROLIZER requires the following steps:

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

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

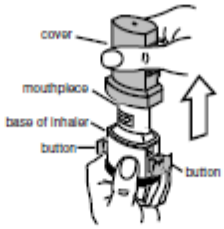


Figure 1

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

Figure 2

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

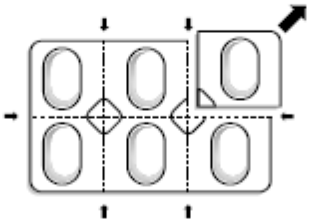


Figure 3

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

Figure 4

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

Figure 5

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

Figure 6

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

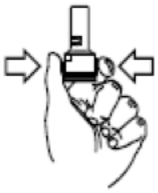


Figure 7

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

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

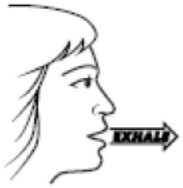


Figure 8

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

CORRECT

Figure 9

INCORRECT

Figure 10

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

Figure 11

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

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

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

16. Close the mouthpiece and replace the cover.

Appendix 6 Instructions for Use of Atrovent HFA Inhalation Aerosol MDI Device

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

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

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

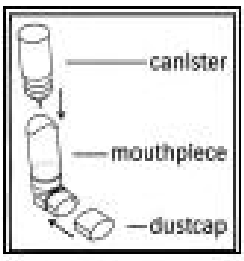


Figure 1

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

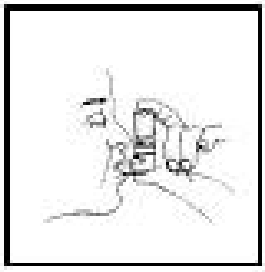


Figure 2

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

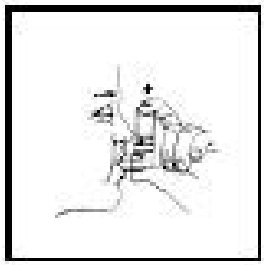


Figure 3

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

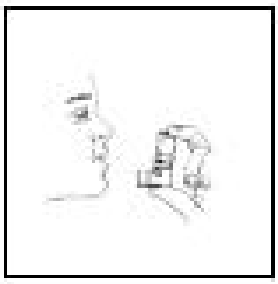


Figure 4

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

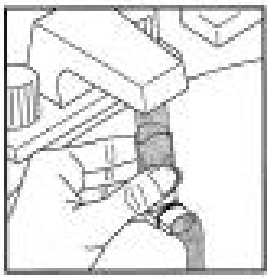


Figure 5

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

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

Appendix 7 Instructions for Use of Ventolin HFA Inhaler

The Parts of Your VENTOLIN HFA Inhaler

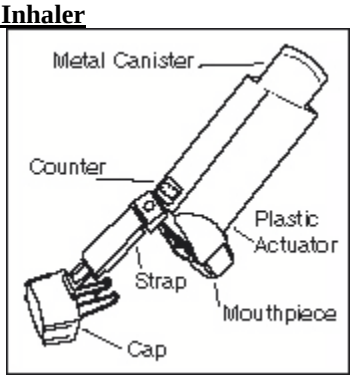


Figure 1

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.

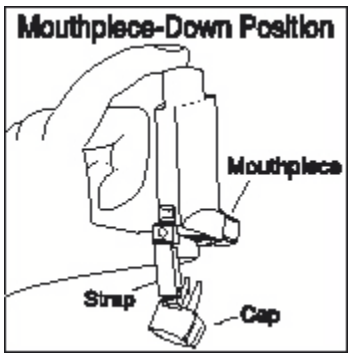


Figure 2

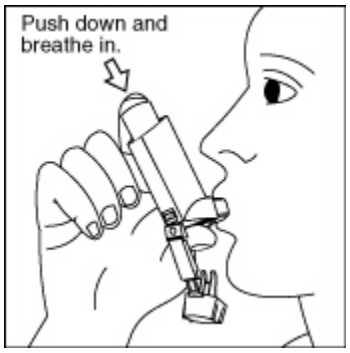


Figure 3

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).

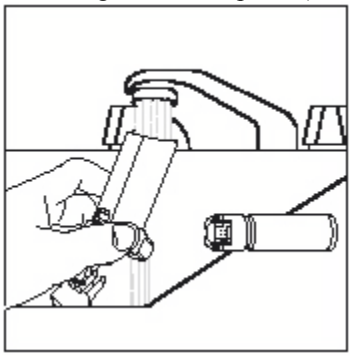


Figure 4

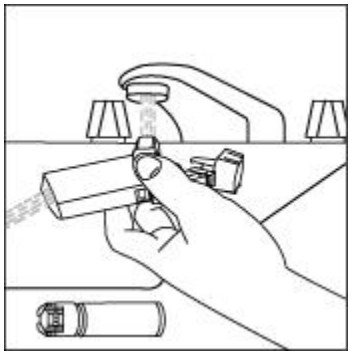


Figure 5

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).

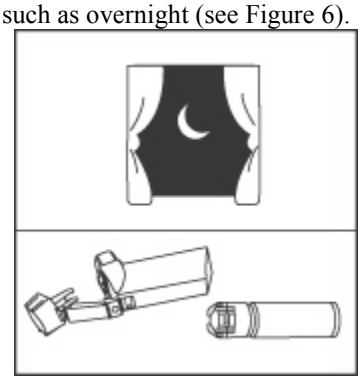


Figure 6

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.

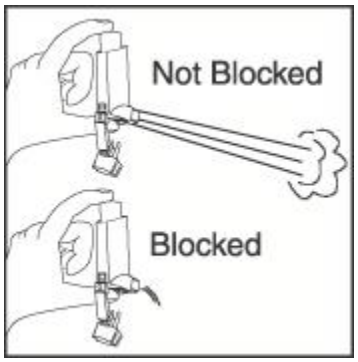


Figure 7

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 8 Sponsor Signatory

Study Title: A Randomized, Double-blind, Parallel Group, 14-day, Multi-Center Study to Evaluate the Safety of PT003, PT005, PT001 and Foradil® Aerolizer® (12 µg, Open-Label) as Evaluated by Holter Monitoring, in Patients with Moderate to Severe Chronic Obstructive Pulmonary Disease (COPD)

Study Number: PT003003-01

Original Protocol Date: [redacted]

Amendment 1 Date: [redacted]

Signature: [redacted] Date: [redacted]

Name: [redacted]

Title: [redacted] Pearl Therapeutics, Inc

Appendix 9 Investigator's Agreement and Signature Page

Study Title: A Randomized, Double-blind, Parallel Group, 14-day, Multi-Center Study to Evaluate the Safety of PT003, PT005, PT001 and Foradil® Aerolizer® (12 µg, Open-Label) as Evaluated by Holter Monitoring, in Patients with Moderate to Severe Chronic Obstructive Pulmonary Disease (COPD)

Study Number: PT003003-01

Original Protocol Date: [redacted]

Amendment 1 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 Pearl Therapeutics and prior review and written approval from the IRB/IEC, except where necessary to eliminate an immediate hazard to the subjects, or for administrative aspects of the study (where permitted by all applicable regulatory requirements).
- That I am aware of, and will comply with, good clinical practices (GCP) and all applicable regulatory requirements.
- That I am thoroughly familiar with the appropriate use of the investigational product(s), and other information provided by Pearl Therapeutics including, but not limited to, the following: the protocol and the current Investigators Brochure (IB).
- To ensure that all persons assisting me with the study are qualified, adequately informed about the investigational product(s) and of their study-related duties and functions.
- To supply Pearl Therapeutics with any necessary information regarding ownership interest and financial ties; to promptly update this information if any relevant changes occur during the course of the study and for 1 year following completion of the study; and agree that Pearl Therapeutics may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- I agree to report all information or data in accordance with the protocol and any other study conduct procedures provided by Pearl Therapeutics
- That since the information in this protocol and IB is confidential, I understand that its disclosure to any third parties, other than those involved in approval, supervision or conduct of the study is prohibited.
- To accurately transfer all required data from each patient's source document to the case report forms (CRFs). The CRFs will be provided to Pearl Therapeutics in a timely manner at the completion of the study, or as otherwise specified by Pearl Therapeutics.
- To allow authorized representatives of Pearl Therapeutics or regulatory authority representatives to conduct on-site visits to review, audit and copy study documents. I will personally meet with these representatives to answer any study-related questions.

Signature:_____ Date:_____

Name:_____

Affiliation: _____

_____

Clinical Trial Protocol: PT003003-02

Study Title:	A Randomized, Double-blind, Parallel Group, 14-day, Multi-Center Study to Evaluate the Safety of PT003, PT005, PT001 and Foradil® Aerolizer® (12 µg, Open-Label) as Evaluated by Holter Monitoring, in Patients with Moderate to Severe Chronic Obstructive Pulmonary Disease (COPD)
Study Number:	PT003003-02
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]
Amendment 2	Version 3.0	[redacted]

SUMMARY OF CHANGES TO PROTOCOL AMENDMENT 1 VERSION 2.0, 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~~.

Exclusion criteria #11:

- 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 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), endocrine (including uncontrolled diabetes or thyroid disease[redacted] 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.

Exclusion criteria #12:

- In Section 5.2 Exclusion Criteria, the following change to text for exclusion criteria #12 to clarify significant abnormal ECG findings.

  Pathological Q ~~wave indicating prior myocardial infarction~~ waves of 1 year or less

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

The protocol is amended to clarify exclusion criteria #11.

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

- In Section 8.3 Randomization Visit (Visit 3; Day 1), 24-hours post-dose assessments on Day 2, the procedure "Perform spirometry assessments (prior to AM dosing)" (bullet 4) was added to be consistent with the Schedule of Events (Table 4).

SYNOPSIS

Sponsor:
Pearl Therapeutics

Names of Finished Products:
Glycopyrrolate and Formoterol Fumarate Inhalation Aerosol; PT003
Formoterol Fumarate Inhalation Aerosol; PT005
Glycopyrrolate Inhalation Aerosol; PT001
Foradil® Aerolizer® (Formoterol Fumarate Dry Powder for Inhalation)

Name of Active Ingredients:
Glycopyrrolate (GP)
Formoterol Fumarate (FF)

Study Title:
A Randomized, Double-blind, Parallel Group, 14-day, Multi-Center Study to Evaluate the Safety of PT003, PT005, PT001 and Foradil® Aerolizer® (12 µg, Open-Label) as Evaluated by Holter Monitoring, in Patients with Moderate to Severe Chronic Obstructive Pulmonary Disease (COPD)

Study Number: PT003003-02

Study Phase: IIb

Study Objective(s):

This study is primarily a safety study. The primary and secondary endpoints are based on 24-hour Holter monitor assessments obtained on Day 14 relative to baseline (Visit 2).

Primary Safety Objective:
The primary safety objective of this study is to compare the change in mean heart rate averaged over 24 hours post-dose, following twice daily dosing over 14 days with Glycopyrrolate and Formoterol Fumarate Metered Dose Inhaler (GFF MDI), Formoterol Fumarate MDI (FF MDI), Glycopyrrolate MDI (GP MDI) or Foradil Aerolizer compared to heart rate averaged over 24 hours at baseline in patients with moderate to severe chronic obstructive pulmonary disease (COPD).

Secondary Safety Objective:
The secondary objective of the study is to further characterize additional cardiovascular safety parameters of all treatment groups including the maximum 24-hour heart rate, mean night-time [22:00 to 06:00) and day-time [06:00 to 22:00)[1] heart rate, ventricular ectopic events (including a single premature ventricular contraction [PVC]), ventricular couplets (defined as two PVCs preceded or followed by regular beats), ventricular runs (defined as

[1] Note the use of open and closed interval notation to specify endpoint relationships. $[a,b) = \{x \in \mathbb{R} | a \leq x < b\}$.

three or more PVCs preceded or followed by regular beats), the number of supraventricular runs, and sustained ventricular tachycardia (VT) [defined as PVCs lasting > 30 s at a rate > 120 beats/min], supraventricular ectopic events, and other clinically relevant arrhythmias (such as atrial fibrillation).

Additional Safety Assessments:
The additional safety objectives are to evaluate the safety of GFF MDI, FF MDI, and GP MDI in patients with moderate to severe COPD compared with Foradil® Aerolizer® (12 µg). Safety will be assessed by adverse events (AEs), vital signs, electrocardiograms (ECGs), and laboratory assessments.

Key Efficacy Objective:
The key efficacy objective of this study is to compare the change in pre-dose morning trough FEV_1 averaged for Day 7 and Day 14 relative to the mean of pre-dose values at baseline (Day 1).

Study Design:

This is a randomized, double-blind, parallel-group, repeated dose (14 days), multi-center study to assess the safety of twice-daily (BID) dosing of GFF MDI (36/9.6 µg, ex-actuator), GP MDI (36 µg, ex-actuator), FF MDI (9.6 µg, ex-actuator) and Foradil Aerolizer (12 µg) as monitored by 24-hour continuous Holter monitoring at the end of treatment.

This multi-center study will be conducted at approximately 20 sites, contributing approximately 10 to 15 patients per site, in Australia, New Zealand, and the United States. Across these sites, it is planned that approximately 220 patients with moderate to severe COPD will be randomized into the study to provide approximately 200 patients to complete the study.

The entire study period is scheduled to take approximately 5-7 weeks for each individual patient. The study is anticipated to run for approximately 9 months and should not exceed 18 months.

Study Design

← **Screening Period** →		← **Treatment Period** →			**Follow-up**
Screening Visits		Randomization		End of Treatment Final Visit	Follow-up Telephone Call
Days -28 to - 1		Day 1	Day 7 (±2)	Day 14 (-3)	Day 21 (+7)
Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	

Study Population:
Approximately 220 patients with moderate to severe COPD will be enrolled to provide approximately 200 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 Descriptions

Product Name & Potency	Dosage Form	Comments
Formoterol Fumarate 9.6 µg ex-actuator (FF MDI)	MDI	Taken as 2 inhalations of the 4.8 µg per actuation strength MDI
Glycopyrrolate 36 µg ex-actuator (GP MDI)	MDI	Taken as 2 inhalations of the 18 µg per actuation strength MDI
Glycopyrrolate 36 µg /Formoterol 9.6 µg ex-actuator combination (GFF MDI)	MDI	Taken as 2 inhalations of the Glycopyrrolate 18 µg / Formoterol 4.8 µg per actuation strength MDI
Formoterol Fumarate Inhalation Powder 12 µg†	DPI	US source: (Foradil® Aerolizer®) Taken as 1 capsule. Each capsule contains 12 µg corresponding to 10 µg formoterol fumarate dihydrate delivered from the mouthpiece *Supplies are open-label.*
Ipratropium Bromide inhalation aerosol 17 µg ex-actuator	MDI	US source: (Atrovent® HFA) Each inhalation contains 21 µg corresponding to 17 µg ipratropium bromide per actuation *Supplies are open-label.*
Albuterol Sulfate inhalation aerosol§ 90 µg ex-actuator	MDI	US source: (Ventolin® HFA) Each inhalation contains 108 µg corresponding to 90 µg albuterol base per actuation *Supplies are open-label.*
† Active control § Rescue medication **Note: All study drugs will be administered by oral inhalation.**		

The 18 µg ex-actuator delivery of glycopyrrolate is equivalent to 22 µg ex-valve of glycopyrrolate.

The 4.8 µg ex-actuator dose of formoterol fumarate is equivalent to 5 µg of formoterol fumarate *dihydrate*. The corresponding ex-valve dose for formoterol fumarate is 6 µg.

Duration of Treatment:
Each patient will receive a maximum of 14 days of study treatment with their assigned treatments. The entire study period is scheduled to take approximately 5-7 weeks for each individual patient from the time of screening (see Figure 1).

Safety Assessments:

The safety assessments include AE and serious adverse event (SAE) assessments, Holter monitoring, ECGs, vital signs, and clinical laboratory tests.

Efficacy Assessments:
Forced expiratory spirometry for derivation of FEV_1, FVC and PEFR will be assessed.

Statistical Methods:
Sample Size Determination: Sample size was based on the properties of the primary safety endpoint: mean heart rate over a 24 hour period. Assuming a standard deviation of 10 bpm, a sample size of 50 patients per treatment yields a 90% power for a true change of 6.5 bpm. 220 patients will be randomized in order to yield 50 completing patients per treatment group.

Efficacy Analyses: Efficacy analysis will be based on a linear model in which Treatment will be a fixed effect, using baseline as a covariate.

The primary efficacy analysis will involve *a priori* comparisons between the combination treatment and Formoterol 9.6 µg MDI and Glycopyrrolate 36 µg MDI for the primary endpoint: change from baseline in mean trough FEV_1 on Days 7 and 14 relative to the mean of pre-dose values at Visit 3. The comparisons will comprise:

- Glycopyrrolate 36 µg /Formoterol 9.6 µg ex-actuator combination vs Formoterol 9.6 µg ex-actuator
- Glycopyrrolate 36 µg /Formoterol 9.6 µg ex-actuator combination vs Glycopyrrolate 36 µg ex-actuator

Other efficacy parameters will include change from baseline FVC and PEFR.

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 with adverse events. Holter data will be analysed using a generalised linear model with quasi-binomial link (for percentage of ventricular ectopics, supraventricular ectopics) or quasi-Poisson link (number of ventricular couplets, supraventricular couplets, ventricular runs, supraventricular runs, tachycardia episodes, bradycardia episodes, and pauses (>= 2 seconds)), or using a linear model (mean heart rate). In all cases the value of the relevant variable during the baseline period will be transformed using the inverse canonical link (logit for quasi-binomial, log for quasi-poisson and identity for the linear model) and used as a covariate

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
BMI	Body mass index
BMP	Basic Metabolic Panel
BTPS	Body Temperature and Pressure Saturated
BUN	Blood urea nitrogen
$CaCl_2$	Calcium chloride
CFR	Code of Federal Regulations
COPD	Chronic Obstructive Pulmonary Disease
CRT	Cardiac resynchronization therapy
CRT_D	Cardiac resynchronization therapy defibrillator
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
FVC	Forced Vital Capacity
GCP	Good clinical practice
GFF MDI	Glycopyrrolate and Formoterol Fumarate MDI
GP MDI	Glycopyrrolate MDI
GGT	Gamma-glutamyl transferase
HCG	Human chorionic gonadotropin
HR	Heart Rate
HFA	Hydrofluroalkane
i.e.	*Id est*, that is
ICD	Implantable cardioverter defibrillator
ICF	Informed consent form
ICH	International Conference on Harmonization
ICMJE	International Committee of Medical Journal Editors
ICS	Inhaled Corticosteroid
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITT	Intention-to-treat
IUD	Intrauterine device
IV	Intravenous
IWRS	Interactive Web Response System
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
PEF	Peak expiratory flow
PEFR	Peak expiratory flow rate
PFT	Pulmonary function test
PK	Pharmacokinetics
PP	Per Protocol
PRN	pro re nata
PVC	premature ventricular contraction
Rx	Treatment
QID	quater in die; four times a day
QTcF	QT corrected using Fridericia's formula ($QT/(RR^{1/3})$)
SAE	Serious Adverse Event
SBP	Systolic blood pressure
SOP	Standard operating procedure
TLC	Total Lung Capacity
TNFα	Tumor necrosis factor α
US	United States
VPB	ventricular premature beats
VT	ventricular tachycardia

TRADEMARK INFORMATION

Trademarks Not Owned By Pearl Therapeutics

Aerolizer

Atrovent

Dulera

Foradil

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 monotherapy 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

was 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 death, 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 (36/9.6 and 72/9.6 µg); all references to doses of FF MDI will be to the ex-actuator or "delivered" doses (2.4, 4.8, 7.2 and 9.6 µg); all references to doses of GP MDI will be to the ex-actuator or "delivered" doses (18, 36, 72, and 144 µg); all references to the Foradil Aerolizer dose will be to the capsule content of 12 µg (corresponds to approximately 10 µg delivered dose); and all references to Spiriva (tiotropium bromide, 18 µg) will be to the capsule content of 18 µg (delivered via the Handihaler); all references to doses of Ventolin HFA (albuterol sulfate inhalation aerosol) will be to the ex-actuator or "delivered" doses (90 µg); all references to doses of Atrovent HFA (ipratropium bromide) will be to the ex-actuator or "delivered" doses (17 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 monotherapy 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.

A cardiovascular safety study provides additional safety assurance prior to proceeding into a longer-term chronic Phase III program. The doses selected for evaluation in this study are based on the prior clinical studies and represent the highest doses likely to be used in the Phase III program.

The duration of exposure to GFF MDI 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 the porous particles 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

This study is primarily a safety study. The primary and secondary endpoints are based on 24-hour Holter monitor assessments obtained on Day 14 relative to baseline (Visit 2).

2.1 Primary Objective

The primary safety objective of this study is to compare the change in mean heart rate averaged over 24 hours post-dose, following twice daily dosing over 14 days with GFF MDI, FF MDI, GP MDI or Foradil Aerolizer compared to heart rate averaged over 24 hours at baseline in patients with moderate to severe COPD.

2.2 Secondary Objectives

The secondary objective of the study is to further characterize additional cardiovascular safety parameters of all treatment groups including the maximum 24-hour heart rate, mean night-time [22:00 to 06:00) and day-time [06:00 to 22:00)[2] heart rate, ventricular ectopic events (including a single premature ventricular contraction [PVC]), ventricular couplets (defined as two PVCs preceded or followed by regular beats), ventricular runs (defined as three or more PVCs preceded or followed by regular beats), the number of supraventricular runs, and sustained ventricular tachycardia (VT) [defined as PVCs lasting > 30 s at a rate > 120 beats/min], supraventricular ectopic events, and other clinically relevant arrhythmias (such as atrial fibrillation).

2.3 Additional Safety Assessments

The additional safety objectives are to evaluate the safety of GFF MDI, FF MDI, and GP MDI in patients with moderate to severe COPD compared with Foradil Aerolizer (12 µg). Safety will be assessed by adverse events (AEs), vital signs, electrocardiograms (ECGs), and laboratory assessments.

2.4 Efficacy Objective

The key efficacy objective of this study is to compare the change in pre-dose morning trough FEV_1 averaged over Day 7 and Day 14, relative to the mean of pre-dose values at baseline (Day 1).

[2] Note the use of open and closed interval notation to specify endpoint relationships. $[a,b) = \{x \in \mathbb{R} | a \leq x < b\}$.

3 STUDY ENDPOINTS

3.1 Safety Endpoints

The safety assessments include AE and SAE assessments, Holter monitoring, ECGs, physical examination findings, vital signs, and clinical laboratory tests.

Primary Safety Endpoint:
The primary safety objective of this study is to compare the change in mean heart rate averaged over 24 hours post-dose, following twice daily dosing over 14 days with Glycopyrrolate and Formoterol Fumarate Metered Dose Inhaler (GFF MDI), Formoterol Fumarate MDI (FF MDI), Glycopyrrolate MDI (GP MDI) or Foradil Aerolizer compared to heart rate averaged over 24 hours at baseline in patients with moderate to severe chronic obstructive pulmonary disease (COPD).

Secondary Safety Endpoints

Based on Holter assessment at baseline and on Day 14: the maximum 24-hour heart rate, mean night-time (22:00 to 06:00) and day-time (06:00 to 22:00)[3] heart rate, ventricular ectopic events (including a single premature ventricular contraction [PVC]), ventricular couplets (defined as two PVCs preceded or followed by regular beats), ventricular runs (defined as three or more PVCs preceded or followed by regular beats), the number of supraventricular runs and sustained ventricular tachycardia (VT) [defined as PVCs lasting > 30 s at a rate > 120 beats/min], supraventricular ectopic events, and other clinically relevant arrhythmias (such as atrial fibrillation).

3.2 Efficacy Endpoints

Forced expiratory spirometry for derivation of FEV_1, FVC and PEFR will be assessed. The key efficacy endpoint will be average change in pre-dose morning trough FEV_1 on Day 7 and Day 14 relative to the mean of pre-dose values at baseline (Day 1, Visit 3 randomization).

[3] Note the use of open and closed interval notation to specify endpoint relationships. $[a,b) = \{x \in \mathbb{R} | a \leq x < b\}$.

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

This is a randomized, multi-center, double-blind, chronic dosing (14 days), parallel group study to assess the safety of twice-daily (BID) dosing of GFF MDI (36/9.6 μg), GP MDI (36 μg), and FF MDI (9.6 μg) compared to Foradil Aerolizer (12 μg) in patients with moderate to severe COPD.

This multi-center study will be conducted at approximately 20 sites, contributing approximately 10 to 15 patients per site, in Australia, New Zealand, and the US. Across these sites, it is planned that approximately 220 patients with moderate to severe COPD will be randomized into the study to provide approximately 200 patients to complete the study.

The entire study period is scheduled to take approximately 5-7 weeks for each individual patient. The study is anticipated to run for approximately 9 months and should not exceed 18 months.

Study Design

← Screening Period →		←——— Treatment Period ———→			Follow-up
Screening Visits		Randomization		End of Treatment Final Visit	Follow-up Telephone Call
Days -28 to - 1		Day 1	Day 7 (±2)	Day 14 (-3)	Day 21 (+7)
Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	

All patients will sign an informed consent form prior to the conduct of any screening assessments (Visit 1). The Investigator will obtain a medical history, physical examination, and any required documentation in order to determine eligibility for participation (inclusion/exclusion criteria). Reversibility of FEV_1 30 minutes following 4 puffs of Ventolin® HFA will be assessed at Screening to characterize the patient population but will not be used to determine eligibility to participate in the study.

Patients who meet all entry criteria will have their inhaled bronchodilator medication switched to Atrovent q.i.d. and Ventolin p.r.n. as rescue medication (see Section 5.4).

All patients will undergo a washout period of at least 1 week (≥2 weeks if taking tiotropium or phosphodiesterase inhibitors), but not greater than 3 weeks prior to returning to the clinic for Visit 2.

Patients will receive a study medication diary in which they will be asked to maintain a daily record of their study medication dosing and rescue medication. The next visit will be scheduled and the patient will be discharged.

Patients will return to the clinic at least 1 week (≥2 weeks if taking tiotropium or phosphodiesterase inhibitors) after screening for Visit 2. At Visit 2, a Holter monitor will be applied and patients will undergo 24-hour Holter monitoring to provide a baseline. During Holter monitoring, patients will complete a specific Holter monitoring diary.

When the patient returns to the clinic for Holter monitor removal the following day, the quality of the recordings will be assessed at the site. If the Holter monitor recordings fail to meet adequate quality criteria (acceptable tracings for a minimum of 18 hours), the Holter Monitor will be reconnected for another 24 hours using a new Holter hook-up kit. The patient will be instructed to continue his/ her medications as per study protocol and complete all necessary assessments on the patient diaries. The patient will return the following day for removal of the Holter Monitor. If the Holter monitoring quality remains unacceptable on the second attempt, the patient will be considered a screen-failure.

Once an acceptable (i.e. acceptable tracings for a minimum of 18 hours) baseline Holter monitor test is obtained, patients can proceed with Visit 3 (Randomization) provided no clinically significant findings are reported following review of the Holter monitoring report by [redacted]. The screening period of 7 to 28 days will be followed by randomization to one of the four treatment groups, with patients being allocated in approximately equal numbers to each group. Eligibility will be determined on the basis of their medical history, physical examination, clinical tests, and adequacy of 24-hour Holter monitoring at Screening.

For all treatment visits (Visits 3, 4 and 5), patients should withhold all study medications on the morning of their visit and should not take Ventolin HFA within 6 hours prior to their visit.

At Visit 3 (Randomization Visit; Treatment Day 1), patients will return to the clinic before 10:00 a.m. Patients who continue to meet entry inclusion/exclusion criteria and remain eligible for participation in the study will be randomized to treatment.

Randomization will be performed centrally, using an interactive web response system (IWRS).

During the treatment phase, all treatments will be administered twice daily. Each of the 4 treatments will be administered for 14 (-3) days. In addition, patients will be supplied by the investigator with open-label Ventolin HFA (90 µg emitted dose per puff) to be used when required as rescue medication throughout the trial.

At Visit 3, a Holter monitor will be placed for continuous 24-hour Holter monitoring and patients will receive a Holter monitoring diary. Patients will be dispensed study medication and a study medication diary 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 to the 2-hour post-dose time point, and be discharged. Patients will return to the clinic after 24 hours (Treatment Day 2) for removal of the Holter monitor and to return the Holter monitoring diary. **Note: If the Holter monitoring assessment collected on Treatment Day 1 is unacceptable, a repeat assessment will not be performed.**

Upon return of the Holter monitor and Holter monitoring diary, patients will be discharged from the clinic and will continue to administer study medication twice daily for 7 (±2) days at home until they return for Visit 4.

Patients will return to the clinic for Visit 4 (Treatment Day 7) at approximately the same time as Visit 3 (± 2 hours). 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). Patients will undergo all protocol-defined pre-dose assessments. Patients will have their final visit (Visit 5) scheduled approximately 1 week later and then be discharged.

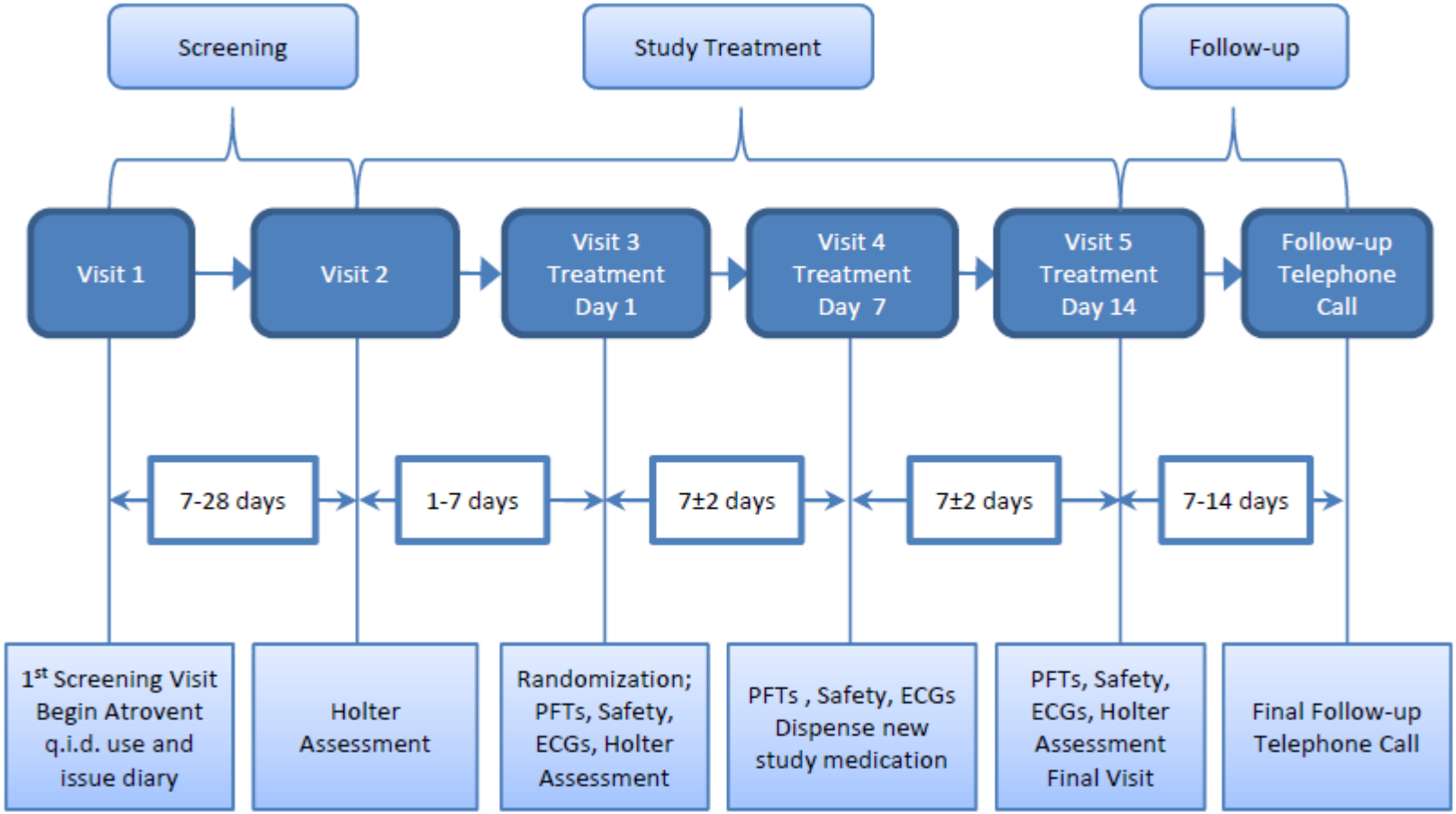
Patients will return to the clinic for Visit 5 (Treatment Day 14) at approximately the same time as Visit 3 (± 2 hours). To accommodate scheduling conflicts a window of 11-14 days is permitted (i.e., Treatment Day 14 procedures must be done within a minimum of 11 days and a maximum of 14 days). Patients will undergo all protocol defined pre-dose assessments. A Holter monitor will be placed and the Holter monitoring diary will be given to the patient. Patients will take their morning dose of study medication at the clinic. Patients will undergo all protocol-defined post-dose assessments. Patients will be discharged and instructed to return to the clinic the following day for removal of the Holter monitor and to return the Holter monitoring diary.

When the patient returns to the clinic the following day, i.e. Day 15 (-3), an ECG will be obtained prior to removal of the Holter monitoring equipment and the quality of the Holter monitor recordings will be assessed at the site. Provided the Holter monitor recording meets protocol defined criteria for acceptability, the patient will undergo a final physical examination, final laboratory assessments, and recording of any AEs. The patient will then be discharged from the study. Study staff will make a follow-up telephone call approximately 7 days later to ensure all post-study AEs (if any) have been captured.

If the Holter monitor recordings fail to meet adequate quality criteria (acceptable tracings for a minimum of 18 hours), the Holter Monitor will be reconnected for another 24 hours using a new Holter hook-up kit and no additional assessments (i.e. physical examination and laboratory assessments) will be perfomed. The patient will be instructed to continue his/ her medications as per study protocol and complete all necessary assessments on the patient diaries. The patient will return the following day for removal of the Holter Monitor and an ECG will be obtained prior to removal of the Holter monitoring equipment. Quality of the recordings will not be assessed at this repeat visit. Patients will undergo a final physical examination, final laboratory assessments, and recording of any AEs. The patient will then be discharged from the study. Study staff will make a follow-up telephone call approximately 7 days later to ensure all post-study AEs (if any) have been captured. **Note: It is advised that patients schedule their visit ahead of Day 14 because 14 days of dosing cannot be exceeded (i.e. if a subject returns for Holter placement on Day 14 and it is noted on Day 15 that the Holter assessment is inadequate, then a repeat Holter assessment will not be possible).**

A Study Flow Diagram is displayed in Figure 1.

Figure 1. Study Flow Diagram



PFT = pulmonary function test, Rx = treatment

Holter monitoring: 24-hour continuous monitoring during screening (Visit 2) and at Visit 3 and Visit 5. Patients are to return the morning following Visits 2, 3 and 5 to return the Holter monitor recorder and Holter monitoring diary.

5 STUDY POPULATION SELECTION AND WITHDRAWAL CRITERIA

5.1 Inclusion Criteria

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

1. Give their signed written informed consent to participate.
2. Are between 40-80 years of age at Visit 1.
3. A female is eligible to enter and participate in the study if she is of:
   - Non-child bearing potential (i.e., physiologically incapable of becoming pregnant, including any female who is 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 8):
     - Complete abstinence from intercourse from screening until 2 weeks after Visit 8 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 3), 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 Atrovent HFA q.i.d. with or without inhaled corticosteroid (ICS) as maintenance treatment for their COPD and Ventolin HFA p.r.n. for relief of COPD symptoms for at least 1 week prior to randomization.
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.
10. Acceptable baseline (Visit 2) Holter monitor recording (see Section 7.2.4).

5.2 Exclusion Criteria

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

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

7. Hospitalization: Patients who have been hospitalized due to poorly controlled COPD within 3 months of Screening (Visit 1).
8. Poorly Controlled COPD: Patients who have poorly controlled COPD, defined as acute worsening of COPD that requires treatment with corticosteroids or antibiotics in the 6-week interval prior to Screening (Visit 1), or between Screening and Randomization (Visit 3).
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 3acceptable 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), 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)]. **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 (Type 2) or third degree atrioventricular (AV) block).
      Note: Isolated right bundle branch block does not constitute an exclusion criteria.
    - Clinically significant arrhythmias (e.g., sick sinus syndrome, current or prior history of atrial fibrillation, atrial flutter, 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).
    - Bradycardia with rate <45 bpm.
    - Pathological Q waves of 1 year or less
    - Significant ST-T wave abnormalities (excluding non-specific ST-T wave abnormalities)

13. Clinically significant abnormal findings during the baseline Holter recording defined as (but not limited to) any of the following:
    - Average heart rate ≤ 40 beats per minute for any one hour
    - Second-degree Atrioventricular (AV) block (Type 2) or third-degree AV block. Transient type 1 second degree AV block lasting for more than 60 minutes.
    - Ventricular asystole of 2.5 seconds duration
    - Any run of ventricular ectopic beats associated with symptoms (hypotension or syncope), regardless of the rate.
    - Any episode of ventricular flutter and/or ventricular fibrillation.
    - Any episode of sustained ventricular tachycardia (VT)
        - VT is defined as a run of 3 or more ventricular premature beats (VPB's) with a rate >120 beats per minute. Sustained VT is defined as VT lasting > 30 seconds or > 60 beats. Nonsustained VT is a run of 3 or more VPB's with a rate > 120 beats per minute which does not fulfill the criteria for sustained VT.
    - Five or more events of non-sustained VT / 24 hours or any episode of non-sustained VT with > 15 VPB's in a row.
    - > 200 VPB/HR
    - Paroxysmal supraventricular tachycardia
14. Patients with a pacemaker or ICD/CRT/CRT_D devices
15. Uncontrolled Hypertension: Patients who have clinically significant uncontrolled hypertension.
16. 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.
17. 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.
18. 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 and/or constituents of the dry powder product (lactose).
19. Substance Abuse: Patients with a known or suspected history of alcohol or drug abuse within the last 2-year period prior to Screening.
20. 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.
21. 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.

22. 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.
23. 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.
24. 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.
25. 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.
26. 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.
27. 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.
28. 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.
29. A patient who requires the use of a spacer device to compensate for poor hand-to-breath coordination with a MDI.
30. Patients who were previously enrolled in a Pearl Therapeutics PT001 (GP MDI), PT005 (FF MDI) or PT003 (GFF MDI) studies.

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 3 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 Atrovent HFA qid as maintenance therapy of their COPD and Ventolin HFA prn as rescue medication. During the treatment period (Visit 3 – Visit 5), patients will discontinue use of Atrovent HFA qid and continue use of Ventolin HFA prn as rescue medication. All short acting bronchodilators should be withheld for at least 6 hours before Visits 3, 4 and 5.
- 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 (Atrovent HFA q.i.d. for maintenance of COPD and Ventolin HFA p.r.n. as rescue medication during the screening period) per the protocol provided they have been maintained on a stable dose for at least 4 weeks.
- Patients receiving a maintenance dose of an ICS that is not administered as a fixed dose combination together with a LABA will be permitted to continue the ICS provided they have been maintained on a stable dose for at least 4 weeks.
- All patients treated with either a LABA (salmeterol, formoterol) or long-acting anti-muscarinic agent (LAMA) (tiotropium) administered alone or as a loose combination will have these medications discontinued and replaced with short-acting bronchodilators (Atrovent HFA q.i.d. for maintenance of COPD and Ventolin HFA p.r.n. as rescue medication during the screening period) per the protocol.

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) until the patient completes or discontinues from 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 Pearl Therapeutics. Each person accessing the IWRS system must be assigned an individual unique PIN. They must use only their assigned PIN to access the system and they must not share their assigned PIN with anyone.

6.2 Product Descriptions

Investigational materials will be provided by the Sponsor as summarized in Table 1.

Table 1. Product Descriptions

Product Name & Potency	Dosage Form	Comments
Formoterol 9.6 µg ex-actuator (FF MDI)	MDI	Taken as 2 inhalations of the 4.8 µg per actuation strength MDI
Glycopyrrolate 36 µg ex-actuator (GP MDI)	MDI	Taken as 2 inhalations of the 18 µg per actuation strength MDI
Glycopyrrolate 36 µg /Formoterol 9.6 µg ex-actuator combination (GFF MDI)	MDI	Taken as 2 inhalations of the Glycopyrrolate 18 µg / Formoerol 4.8 µg per actuation strength MDI
Formoterol Fumarate Inhalation Powder 12 µg[†]	DPI	US source: (Foradil Aerolizer) Taken as 1 capsule. Each capsule contains 12 µg corresponding to 10 µg formoterol fumarate dehydrate delivered from the mouthpiece *Supplies are open-label.*
Ipratropium Bromide inhalation aerosol 17 µg ex-actuator	MDI	US source: (Atrovent HFA) Each inhalation contains 21 µg corresponding to 17 µg ipratropium bromide per actuation *Supplies are open-label.*
Albuterol Sulfate inhalation aerosol[§] 90 µg ex-actuator	MDI	US source: (Ventolin HFA) Each inhalation contains 108 µg corresponding to 90 µg albuterol base per actuation *Supplies are open-label.*
[†] Active control [§] Rescue medication **Note: All study drugs will be administered by oral inhalation.**		

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

For open-label Atrovent HFA (ipratropium bromide, 17 µg), bulk commercial metered dose inhalers with dose counters will be provided. Manufacturer's instructions for study drug administration will be provided.

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

6.3 Primary Packaging and Labeling Information

Investigational materials will be packaged by the Sponsor as summarized in Table 2 below. Atrovent HFA and Ventolin HFA supplies will be supplied as open-label MDIs.

Table 2. Packaging of Clinical Supplies

Product Name and Potency	Fill Count	Dosing Instructions
Formoterol Fumarate 9.6 µg ex-actuator (FF MDI)	1 MDI 120 actuations	Take two inhalations as directed in the morning and evening.
Glycopyrrolate 36 µg ex-actuator (GP MDI)	1 MDI 120 actuations	Take two inhalations as directed in the morning and evening.
Glycopyrrolate 36 µg /Formoterol 9.6 µg ex-actuator combination (GFF MDI)	1 MDI 120 actuations	Take two inhalations as directed in the morning and evening.
Formoterol Fumarate Inhalation Powder 12 µg[†]	N/A	Take one capsule as directed in the morning and evening.
Ipratropium Bromide inhalation aerosol 17 µg ex-actuator[†]	1 MDI 200 actuations	Take two inhalations as directed four times a day.
Albuterol Sulfate inhalation aerosol[§] 90 µg ex-actuator	1 MDI 60 or 200 actuations	Use only as directed.
[†] Active control [§] Rescue medication		

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

Open-label Supplies: Open-label Foradil Aerolizer supplies will be provided as individually labeled DPIs and bulk labeled commercial blister packs packaged in sets of 4 blister pack per patient within a foil overwrap labeled with a two-part label. Each Foradil Aerolizer will have a single label.

Open-label Atrovent HFA and 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 the study will be packaged in boxes as outlined in Table 3. Open-label Atrovent HFA and 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
Foradil Aerolizer Device	1 DPI
Bulk Foradil Aerolizer Capsule	1 Foil Pouch Containing 4 Blister Packs Each
Ventolin HFA	1 MDI
Atrovent HFA	1 MDI

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

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

6.5 Unblinding Procedures

The IWRS should be used in order to unblind patients and to unmask drug identity. Pearl Therapeutics will not provide a disclosure envelope with the clinical supplies. The investigator or treating physician may unblind a subject's treatment assignment **only in the case of an emergency**, when knowledge of the study treatment is essential for the

appropriate clinical management or welfare of the subject. Whenever possible, the investigator must first discuss options with the Medical Monitor or appropriate study personnel **before** unblinding the subject's treatment assignment. If this is impractical, the investigator must notify Pearl Therapeutics as soon as possible, but without revealing the treatment assignment of the unblinded subject, unless that information is important for the safety of subjects currently in the study. The date and reason for the unblinding must be recorded in the appropriate data collection tool.

6.6 Storage Requirements

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

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

Atrovent HFA supplies: Store at 25°C (77°F). Brief storage between between 59 and 86°F (15 and 30°C) is permitted. Do not puncture. Do not use or store near heat or open flame. Exposure to temperatures above 120°F may cause bursting. Never throw the inhaler into a fire or incinerator. Avoid spraying in eyes.

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

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

6.7 Instructions for Preparation of Treatments for Administration and Dispensing

GFF MDI, GP MDI, and FF MDI

Individual 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 (puff).

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

Each dose will consist of 2 puffs from the MDI. 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, , until patient returns to the clinic. The MDI should be stored at room temperature by the patient, avoiding temperature extremes and storage in direct sunlight. See Appendix 4 for instructions on the administration of GFF MDI, GP MDI, and FF MDI.

Foradil Aerolizer

Individual Foradil Aerolizer devices will be packaged in a foil overwrap contained in an individual visit treatment carton. Both the visit treatment carton and the foil overwrap will have a label with a component ID number. Confirm that the identifier given by IWRS and the component ID number written on the label are the same. The foil overwrap is labeled with a two-part label. Write the patient number and treatment visit number on each of the two-part labels. The 'tear-off' part of the label is to be placed onto the IWRS confirmation report.

For open-label Foradil Aerolizer drug supplies, the bulk commercial blister packs will be stored refrigerated in a secured location within the clinic or pharmacy facilities. To ensure adequate time for equilibration (minimum 2 hours) to room temperature prior to administration, one foil pouch (containing 4 blister packs) should be kept in a secure location at room temperature. If a patient is randomized to Foradil Aerolizer, the equilibrated supplies will be dispensed and at an appropriate time following study drug administration, study staff will obtain new foil pouch (containing 4 blister packs) from the refrigerated bulk supplies. Retain new foil pouch at the site, stored at room temperature in a secured location for use with a subsequent patient.

The contents of 1 capsule each will be inhaled in the morning and in the evening approximately 12 hours apart, until patient returns to the clinic. See Appendix 5 for the manufacturer's instructions on the administration of Foradil Aerolizer.

Atrovent HFA (ipratropium bromide)

Individual Atrovent HFA MDIs will be contained in an individual visit treatment box. Both the visit treatment box and the foil overwrap will have a label with a component ID number. Confirm that the identifier given by IWRS and the component ID number written on the label are the same. The 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.

Atrovent HFA is a solution aerosol that does not require shaking. However, as with any other MDI, some coordination is required between actuating the canister and inhaling the medication. Atrovent HFA should be primed per manufacturer's instructions prior to dispensing to patient (i.e. "prime" or actuate Atrovent HFA before using for the first time by releasing 2 test sprays into the air away from the face). In cases where the inhaler has not been used for more than 3 days, prime the inhaler again by releasing 2 test sprays into the air away from the face. Patients should avoid spraying Atrovent HFA into their eyes.

Patients will be dispensed the MDI at Visit 1 to continue taking study medication four times a day (approximately 6 hours apart) during the run in period between Visits 1 to 3, 2 puffs with each administration. The MDI should be stored at room temperature by the patient, avoiding temperature extremes and storage in direct sunlight. See Appendix 6 for the manufacturer's instructions on the administration of Atrovent HFA.

Ventolin HFA (albuterol sulfate inhalation aerosol)

Bulk supplies of open-label Ventolin HFA will be provided by Pearl Therapeutics and stored in a secured location within the clinic or pharmacy facilities. 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 7 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 or destroyed as directed by Pearl Therapeutics.

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

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

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

7 STUDY PROCEDURES

A time and events schedule is provided in Table 4.

All assessments during Visits 2 through 5 will be conducted in the following order: ECGs, vital signs, clinical laboratory assessments, and spirometry.

7.1 Efficacy Assessments

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

The volume accuracy of the spirometer is to be checked daily using a 3 L syringe across 3 flow ranges e.g., 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).

At each visit during the treatment period (Visits 3, 4 and 5), spirometry will be conducted 60 minutes and 30 minutes prior to study drug administration. The average of the two pre-dose assessments will be used to establish a baseline FEV_1 at Visit 3 and a corresponding pre-dose trough value at Visits 4 and 5.

7.1.1 Pulmonary Function Tests

All pulmonary function tests including FEV_1, FVC and PEFR as defined in ATS/ERS guidelines (Miller, 2005) and will be performed in accordance with ATS criteria (Miller, 2005).

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

Refer to Section 7.3 for specific FEV_1 criteria that prompt patients to be discontinued from the study.

7.1.2 Patient Diaries

7.1.2.1 Study Medication 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 and rescue Ventolin HFA use. Two types of diaries will be provided – one for use during the screening period (between Visits 1 and 3) when patients are taking Atrovent HFA (17 μg) q.i.d. and Ventolin HFA p.r.n. as rescue medication and the other for use during the treatment period (between Visits 3 and 5) when patients are taking study medication b.i.d. and Ventolin HFA p.r.n. as rescue medication.

Beginning with the Screening Visit (Visit 1), the patient will be given a diary to be completed daily and returned at the next visit. Before giving the diary to the patient, the study coordinator will be responsible for entering the patient's identification (screening number for Visits 1 and 2, and randomization number for all other Study Visits), 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 a study visit, patients will return the diary provided at the previous visit.

At Visit 3, patients should demonstrate acceptable use of the diary. Patients who fail to demonstrate proper diary use should be retrained prior to randomization.

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.

7.1.2.2 Holter Monitoring Diary

Patients will complete a Holter Monitor Diary during the 24-hour collection period for holter monitoring. The diary will be in the form of a checklist and will ask patients to confirm whether certain predetermined events occurred during the 24-hour monitoring period.

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 Medication Compliance

Time of dosing with study medication will be recorded in the patient study medication 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 AE and SAE assessments, Holter monitoring, ECGs, physical examination findings, vital signs, and clinical laboratory tests.

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 3). A complete physical examination will be performed at Screening and the Final Visit (Visit 5). A complete physical examination will include the following: general appearance, skin, head, eyes, ears, nose, throat, neck (including thyroid), lymph nodes, chest, heart, abdomen, extremities, and nervous system. Weight, assessed in ordinary indoor clothing with shoes off, and height (Screening) will be recorded at the specified visits.

7.2.2 Vital Sign Measurements

Heart rate, systolic and diastolic blood pressure ('vital signs') will be assessed at each visit; assessments will be obtained after being supine for 10 minutes. 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, systolic and diastolic blood pressure readings that prompt patients to be discontinued from the study. When vital signs assessment are scheduled at the same time point as ECGs, blood draws and/or spirometry, the sequence of events should be: ECG, vital signs, laboratory assessments and spirometry.

Systolic and diastolic blood pressures, heart rate will be obtained 60 and 30 minutes prior to study drug administration on Days 1, 7 and 14 as well as 30 minutes and 2 hours after study drug on Days 1 and 14. On Days 2 and 15 systolic and diastolic blood pressures, heart rate will be obtained immediately after ECG assessment. Temperature will be obtained at Screening and once at each visit as part of the initial vital sign assessment (i.e. Once on Day 1, 2, 7, 14 and 15), and will not be repeated at subsequent time points unless clinically indicated.

7.2.3 12-Lead Electrocardiogram (ECG)

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.

ECGs will be obtained at:

- Screening (Visit 1)
- Treatment Day 1 (Visit 3): between 1 to 2 hours and 30 minutes to 1 hour prior to study drug and at 30 minutes and 2 hours after study drug.
- Treatment Day 2 prior to removal of the Holter monitor
- Treatment Day 7 (Visit 4): within 60 minutes prior to study drug administration.
- Treatment Day 14 (Visit 5): between 1 to 2 hours and 30 minutes to 1 hour prior to study drug and at 30 minutes and 2 hours after study drug.
- Day 15 prior to removal of the Holter monitor (Study drug not to be administered beyond Day 14)

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 manually calculated QTcF 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, a repeat ECG is to be recorded. If the prolonged QTc intervals are confirmed on review by the investigator (or designated ECG reviewer), the Investigator will make a

determination on the suitability of continuing the patient in the study. If QTcF interval prolongation exceeding these limits is verified during treatment, the patient's medical background should be examined closely for risk factors that may have contributed to the event, including genotyping for hereditary long QT syndromes, if appropriate. Refer to Section 7.3 for specific criteria for QTcF (Fridericia's Formula) that prompt patients to be discontinued from the study.

Additional ECGs will be obtained if the patient's resting 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 at Visit 3). Refer to Section 7.3 for specific criteria for heart rate that prompt patients to be discontinued from the study.

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 24-hour continuous electrocardiography (Holter monitoring)

The designated CRO for Holter monitoring will be [redacted]. All Holter monitor recordings will be assessed for cardiac arrhythmias by an independent cardiologist appointed by [redacted].

Continuous 12-lead ECGs (Holter assessment) will be obtained at Visit 2 (screening), Visit 3 (baseline) and Visit 5 [Day 14(-3); end of treatment]. The Visit 2, Visit 3 and Visit 5 Holter monitor recordings are to be initiated in the morning at approximately the same time (+/- 2 hours). The Visit 3 and Visit 5 Holter monitoring will be initiated 15-30 minutes prior to the administration of the morning dose of trial medication.

Continuous Holter monitor recording will be collected for a minimum of 24 hours. Holter monitor recordings should contain a minimum of 18 hours of acceptable quality recording in a 24-hour period to be deemed an acceptable Holter assessment.

The Holter recording obtained at Visit 2 will be used to determine the patient's eligibility for the study and will serve as the baseline for all comparisons. If the initial Holter monitor assessment at Visit 2 is unacceptable, the Holter Monitor will be reconnected for another 24 hours using a new Holter hook-up kit. The patient will be instructed to continue his/her

medications as per study protocol and complete all necessary assessments on the patient diaries. The patient will return the following day for removal of the Holter Monitor. If the second attempt is unacceptable, the patient will not be allowed to continue in the study and considered a screen-failure.

The Holter monitor assessment at Visits 3 will not be repeated even if it is unacceptable.

At Visit 5, the Holter monitor can be placed on Day 11, 12, 13 or 14. If the initial Holter monitor assessment at Visit 5 is unacceptable, the Holter monitor will be reconnected for another 24 hours using a new Holter hook-up kit provided that the initial Holter was placed on Day 11, 12 or 13. The patient will be instructed to continue his/her medications as per study protocol and complete all necessary assessments on the patient diaries. The patient will return the following day for removal of the second Holter Monitor. No further attempts are allowed if the second attempt is unacceptable. **If the initial Holter monitor is placed on Day 14 a repeat assessment is not allowed regardless of acceptability.**

Each patient will receive a Holter monitoring diary. Patients will record cardiovascular-related symptoms which occurred during the Holter monitor recording (e.g., chest pain, shortness of breath). Every effort must be made to instruct the patient to consistently record entries in the Holter monitoring diary. The information in the Holter monitoring diary may be used by [redacted] in the interpretation of the Holter monitor recordings. The patient's Holter monitoring diary will also be reviewed by the investigator to identify symptoms which the investigator considers to be appropriate for recording in the eCRFs as adverse events.

Data for analysis will include:

- General trends including heart rate
- Hourly rhythm comments
- Ventricular ectopy summary
- Ventricular run summary
- Supraventricular ectopy summary
- Supraventricular run summary
- Any other clinically relevant arrhythmias, including atrial fibrillation and pronounced bradycardia.

Manual summary interpretation of the data is sent as a report to the site and to Pearl Therapeutics.

7.2.5 Clinical Laboratory Tests

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

Hematology (Complete Blood Count) and chemistry (Comprehensive Metabolic Panel) will be obtained at Screening, within 60 minutes prior to dosing on Treatment Day 1, Treatment Day 2, and on Day 15 when patients return to have their Holter monitor removed.

Serum pregnancy testing will be performed at Screening and at the Final Visit (Visit 5) 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)
Alkaline phosphatase	Calcium
Bilirubin, total	Chloride
Gamma-glutamyl transferase	Cholesterol
	Bicarbonate
	Creatinine
	Glucose
	Magnesium
	Potassium
	Phosphate
	Protein, total
	Sodium
	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.

7.2.6 Adverse Events

7.2.6.1 Performing Adverse Events Assessments

The investigator is responsible for promptly documenting and reporting all AEs observed during the study in the subject's case report form and on the AE Reporting Form. If the AE is "alarming", the investigator must report the AE immediately to Pearl Therapeutics. In addition, certain AEs (as described in Section 7.2.6.7) are classified as "serious" and must be reported no later than 24 hours after the investigator recognizes/classifies the event as a serious adverse event to Pearl Therapeutics or its designee (Sponsor).

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

7.2.6.2 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).

7.2.6.3 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.

7.2.6.4 Severity

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

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

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

Severe: Associated with inability of 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.

7.2.6.5 Relationship

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

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

Probably: A reaction that follows a reasonable temporal sequence from administration of study drug; that follows a known or expected response pattern to the study drug; and/or that

could not be reasonably explained by other factors such as underlying disease, complications, concomitant drugs, or concurrent treatments.

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

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

7.2.6.6 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.

7.2.6.7 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 the 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 may include copies of hospital records, case reports, and autopsy reports, and other pertinent documents.

Post-study SAEs following the last dose of study drug must be reported to Pearl Therapeutics as described in Section 7.2.6.10.

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

7.2.6.8 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.

7.2.6.9 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.

7.2.6.10 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.

7.2.6.11 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.

7.2.6.12 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.

7.2.7 AEs of Interest

Syncope and atrial fibrillation are considered to be AEs of interest, and will be tabulated separately.

7.2.8 Overdose

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

7.2.9 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 Therpeutics 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.

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 rest as recorded on ECG 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 2-hour interval after taking study drug.
- Symptoms of dyspnea at any time within the 2-hour interval after taking study drug, that in the opinion of the investigator or designee requires additional spirometry assessments, which demonstrates a decrease in FEV_1 of more than 20% from test day baseline (before taking study drug) on two consecutive assessments obtained at least 15 minutes apart.

Holter monitoring criteria for discontinuation:

- Average heart rate ≤ 40 beats per minute for any one hour
- Development of transient or fixed complete heart block
- Development of type 2 second degree AV block
- Development of type 1 second degree AV block lasting more than 60 minutes
- Ventricular asystole of ≥ 2.5 seconds duration
- Development of Holter monitoring criteria for proarrhythmia (see Appendix 3)
  Other clinically relevant findings that the Investigator deems should lead to the subject being discontinued.

Other valid reasons for removing a patient from the study include:

- The patient does not adhere to study rules and procedures;
- The patient wishes to withdraw from the study;
- Continuation of the patient is in violation of the inclusion and exclusion criteria;
- The investigator feels it is in the patient's best interest to terminate participation;
- The study is terminated by Pearl Therapeutics.

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.

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. 7 or more deaths from any cause at any time during the course of the study.

Stopping criteria for 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 an approximately 99% chance of each patient surviving 50 days on study. Assuming that 220 patients are randomized, the probability of placing the study on hold if mortality is no greater than background is 0.3%. Should the criterion for study hold be reduced to 6 or more deaths, the probability of inappropriate hold increases to 1.25%.

8 STUDY ACTIVITIES

A time and events schedule is provided in Table 4.

Table 4. Schedule of Events

	Screening[a]		Treatment Period[a]					Follow-Up
	Visit 1	Visit 2	Visit 3 Randomization		Visit 4	Visit 5		Telephone Contact
Procedures	Day -7 to -28	Day -1 to -7	Day 1	Day 2	Day 7 (±2)	Day14 (-3)	Day15 (-3)	Day 21(+7)
Informed Consent	X							
Eligibility Criteria	X	X	X					
Verify Continued Eligibility		X	X	X	X	X	X	
Reversibility to Ventolin HFA[b]	X							
Demographics & Medical/Surgical History	X							
Concomitant Medications[c]	X		X		X	X		
Spirometry[d]	X		X	X	X	X		
Physical Examination[e]	X						X	
Vital Signs[f]	X	X	X	X	X	X	X	
12-Lead ECG[g]	X		X	X	X	X	X	
24-Hour Holter Monitoring[h]		X	X			X		
Pregnancy Test[i]	X		X				X	
Clinical laboratory testing[i]	X		X	X			X	
Adjust COPD Medications Per Protocol[j]	X							
Resume pre-study COPD medications as appropriate[k]							X	
Adverse Events	X	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			X		
Collect/Review Patient Diary		X	X		X	X		
Follow-up Telephone Call to assess Adverse Events and Safety								X

Table 4. Schedule of Events (continued)

[a] Screening period of at least 7 days and up to 28 days. Patients are required to take Atrovent HFA q.i.d. and Ventolin HFA p r n. and complete the patient study medication diary during the screening period. An acceptable baseline Holter monitoring assessment is required before patients can proceed to Visit 3.

[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, patients should withold short-acting bronchodilator and other COPD medications at least 6 hours prior to the start of visit procedures.

[d] Spirometry (FEV_1, FVC, and PEFR) will be assessed at Screening and Visits 3, 4, and 5. During the treatment period (Visits 3, 4 and 5), spirometry will be conducted 60 minutes and 30 minutes prior to study drug administration.

[e] Includes evaluation of height and weight at Screening.

[f] Vital signs will be obtained at each visit. Assessments will be obtained after being supine for 10 minutes. SBP, DBP and HR will be obtained in the supine position. On Days 2 and 15 systolic and diastolic blood pressures, heart rate will be obtained immediately after ECG assessment. Temperature will be obtained at Screening and once at each visit as part of the initial vital sign assessment (i.e. Once on Day 1, 2, 7, 14 and 15), and will not be repeated at subsequent time points unless clinically indicated.

[g] ECGs will be collected at Screening (Visit 1) and Treatment Days 1, 2, 7 and 14. A final ECG will be collected on Day 15 prior to removal of the Holter monitoring equipment. On Days 1 and 14 ECGs will be collected at 60 minutes (between 60 to 120 minutes) and 30 minutes (between 30 to 60 minutes) prior to dosing and 30 minutes and 2 hours post dosing. On Day 7 an ECG will only be conducted at 60 minutes (between 30 to 60 minutes) prior to dosing. An ECG should be collected prior to removal of the Holter monitoring equipment on Days 2 and 15.

[h] Holter monitoring: 24-hour continuous monitoring during screening (Visit 2) and at Visit 3 and Visit 5. Patients are to return the morning following Visits 2, 3 and 5 to return the Holter monitor recorder and Holter monitoring diary.

[i] All clinical laboratory tests will be obtained at Screening, Visit 3 (Treatment Day 1 and 2) and Visit 5 (Day 15). Pregnancy test (women of child-bearing potential only): serum [human chorionic gonadotropin (HCG)] at Screening and Visit 5 only and Urine HCG at all other visits.

[j] 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).

[k] At the end of the Visit 5, return patient to pre-study or other appropriate inhaled maintenance COPD medications.

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

8.1 Screening Visit (Visit 1)

- Obtain informed consent.
- Check inclusion/exclusion criteria.
- Obtain demographic data, including age, race, smoking history, and medical/surgical history including glaucoma and age of onset of COPD.
- Obtain medication history, including COPD medications.
- 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 a 12-lead ECG after being supine for 10 minutes.
- Obtain vital signs (heart rate and blood pressure in a supine position and oral or tympanic temperature), height and weight.
- Obtain laboratory samples (hematology and chemistry).
    - Perform 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 baseline spirometry assessments.
- Dispense Ventolin HFA and instruct patient on its use (See package insert for Ventolin HFA for proper inhaler use)
- 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).
- Complete an eye examination for glaucoma if not performed within the last 2 years (New Zealand Sites Only)
- 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). Dispense Atrovent HFA to be used as maintenance medication for COPD during the screening period. Instruct patients

on the proper use of Atrovent HFA and Ventolin HFA during the screening period (see Section 5.4).

- Complete Screening Log (basic demographics, spirometry, medications and reasons for screen failure) for patients who do not meet eligibility criteria.

- Record 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 as medical history and not as a study adverse event unless the event meets the definition of an SAE

- Dispense patient study medication diary and provide instructions on diary completion.

- Arrange date of Visit 2 as appropriate.

8.2 Screening Visit for Baseline Holter Assessment (Visit 2)

- Collect and review patient diary (if diary is not completed correctly, re-train patient).

- Review inclusion/exclusion criteria to confirm protocol eligibility.

- Review of clinical laboratory results from Visit 1. Please note whether the results are clinically significant and include comments where applicable.

- Obtain vital signs (heart rate and blood pressure in a supine position and oral or tympanic temperature)

- Record 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 as medical history and not as a study adverse event unless the event meets the definition of an SAE.

- Review concomitant medications to ensure adherence to COPD regimen.

- Note time of last dose of short-acting bronchodilator and other COPD medications in the source documents.

- Perform Holter Monitoring for 24 hours – see Section 7.2.4. Record the start time of Holter monitor recording in the eCRF. Dispense Holter monitoring diary and instruct patient regarding its use. The patient must return the next morning with the device, study medication and diaries.

24-hours post dose assessments

- After completion of the 24-hour Holter monitor recording determine acceptability of Holter monitor recording (see Section 7.2.4). If 24-hour Holter monitor

recording is unacceptable, see Section 7.2.4 for instructions. **Note: Patients should not be randomized unless an acceptable Holter monitor recording has been obtained.**

- Obtain vital signs (heart rate and blood pressure in a supine position and oral or tympanic temperature)
- Record adverse events, if any
- Instruct patient to continue Atrovent qid and Ventolin HFA prn as rescue medication until Visit 3
- Instruct patient to continue completion of the study medication diary until Visit 3 (re-train patient on diary completion if necessary)
- Schedule Visit 3, if appropriate, or record patient status as screen failure.
- Remind patients scheduled for Visit 3 to withhold all study medications on the morning of Visit 3 and instruct them to not take Atrovent HFA or Ventolin HFA within 6 hours prior to their visit.

8.3 Randomization Visit (Visit 3; Day 1)

- Check to see if the patient has received rescue medication within 6 hours prior to the start of the visit. Note time of last dose of short-acting bronchodilator and other COPD medications on the source documents.
- Collect and review patient study medication diary (if diary is not completed correctly, re-train patient).
- Review inclusion/exclusion criteria to confirm protocol eligibility.
- Record 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 as medical history and not as a study adverse event unless the event meets the definition of an SAE.
- Review concomitant medications to ensure adherence to COPD regimen.
- Perform urine pregnancy test (women of child-bearing potential only).
- Perform all pre-dose assessments.
- Attach and initiate 24-hour Holter Monitor 15-30 minutes prior to dosing (see Section 7.2.4). Dispense Holter monitoring diary and instruct patient regarding its use. This test to be performed for approximately 24 hours. Obtain patient treatment assignment information from IWRS. At this point the patient is randomized.

- At 15-30 minutes prior to dosing, the seal around the study day treatment box is to be opened and the instructions for administration of study drug on the inner flap of the study day treatment box are to be followed.
    - Refer to Section 6.7 for detailed instructions for preparation of treatments for administration. These instructions are to be adhered to and are relevant to all study treatment visits.
- Patient will administer first dose of study drug at the clinic.
- Record adverse events (if any).
- Enter Time of first dose of study medication into study medication diary
- Perform all post-dosing assessments.
- The patient should be instructed to take the evening dose of study medication while wearing the Holter. The patient must return the next morning with the device, which is to be removed prior to taking the next morning's dose of study medication. The Holter monitoring diary is to be collected at that time. The time of dosing with study medication and Ventolin HFA rescue medication during the Holter monitor recording will be recorded by the patient in the study medication diary and by the site personnel in the eCRF.

24-hours post dose assessments

- Collect ECG prior to removal of Holter monitor
- Remove Holter monitor. **Note: At this visit, the 24-hour Holter monitor recording will not be repeated regardless of whether or not it meets acceptability criteria**
- Obtain vital signs (heart rate and blood pressure in a supine position and oral or tympanic temperature)
- Perform spirometry assessments (prior to AM dosing)
- Obtain laboratory samples (hematology and chemistry)
- Record adverse events, if any
- Instruct patient to continue taking study medication twice daily and Ventolin HFA prn as rescue medication until Visit 4
- Instruct patient to continue completion of the study medication diary until Visit 4 (re-train patient on diary completion if necessary)
- Schedule Visit 4.
- Remind patients to withhold all study medications on the morning of Visit 4 and instruct them to not take Ventolin HFA within 6 hours prior to their visit.

8.4 Visit 4 (Day 7)

- Collect and review patient study medication diary.
- Note time of last dose of short-acting bronchodilator and other COPD medications on source documents.
- Review concomitant medications and ensure adherence to COPD regimen.
- Confirm eligibility to continue.
- Record adverse events (if any).
- Perform all pre-dose assessments.
- Patient will administer dose of study drug at the clinic under supervision.
- **For patients taking double-blind study medication**: Previously dispensed study medication will be collected and a new supply of study medication will be dispensed.
- **For patients taking open-label Foradil**: Previously dispensed study medication will be collected and a new supply of blister packs will be dispensed. Patients will continue to use their existing Aerolizer device for the remainder of the trial.
- Schedule Visit 5 and ensure patient has adequate supply of study drug and rescue Ventolin HFA.

8.5 Visit 5 (Day 14)

- Collect and review patient study medication diary.
- Confirm eligibility to continue.
- 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 source documents.
- Perform all pre-dose assessments.
- Attach and initiate 24-hour Holter Monitor 15-30 minutes prior to dosing (see Section 7.2.4).

- Dispense Holter monitoring diary and instruct patient regarding its use. This test to be performed for 24 hours.
- Patient will administer dose of study drug at the clinic under supervision.
- Perform all post-dosing assessments.
- Redispense study medication and instruct patient to take the evening dose of study medication, **but not to take a dose the following morning.**
- Redispense patient study medication diary and provide instructions on diary completion if appropriate.
- The patient must return the next morning with the Holter device, study medication and diaries.

24-hours post dose assessments

- Collect ECG prior to removing Holter
- After completion of the 24-hour Holter monitor recording determine acceptability of Holter monitor recording (see Section 7.2.4). If 24-hour Holter monitor recording is unacceptable, see Section 7.2.4 for instructions.
- Collect previously dispensed study medications
- Obtain vital signs (heart rate and blood pressure in a supine position and oral or tympanic temperature)
- 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 laboratory samples (hematology and chemistry).
    - Perform serum pregnancy test (women of child-bearing potential only).
- Record adverse events
- Record usage of COPD and other concomitant medications
- At completion of all Visit 5 assessments, return patient to pre-study or appropriate inhaled COPD medication(s).

8.6 Follow-Up Telephone Call (7-14 days post Visit 5)

- Study site staff will contact the patient via telephone and record adverse events (if any).
- 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 CRF. The following categories should be used to describe these events in the CRF:

- Patient discretion (document reason)
- Investigator considers it to be in the best interest of the patient
- Adverse events(s)
- Administrative reasons (e.g., early termination of the study)
- Patient lost-to-follow-up
- Major protocol violation (with approval by Pearl Therapeutics)
- 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 parallel group 4-treatment, randomized design evaluating the following 4 treatments in approximately 50 completing patients for each treatment:

- Formoterol Fumarate MDI 9.6 µg ex-actuator
- Glycopyrrolate MDI 36 µg ex-actuator
- Glycopyrrolate MDI 36 µg /Formoterol 9.6 µg ex-actuator combination
- Formoterol Fumarate Inhalation Powder 12 µg

The primary objective of this study is to assess the safety of the Glycopyrrolate 36 µg /Formoterol 9.6 µg ex-actuator combination relative to the component treatments (Formoterol Fumarate 9.6 µg ex-actuator and Glycopyrrolate 36 µg ex-actuator) and the active comparator (Formoterol Fumarate Inhalation Powder 12 µg) in patients with moderate to severe COPD.

9.2 Protocol Variables

9.2.1 Efficacy Endpoints

All efficacy assessments will be expressed as change from baseline, where baseline is defined as mean of the pre-dose assessments on Day 3.

9.2.1.1 Key Efficacy Endpoint

The key efficacy endpoint is mean change from baseline FEV_1 trough over Day 7 and Day 14 relative to the mean of pre-dose values at Visit 3.

9.2.1.2 Secondary Efficacy Endpoints

There are no secondary endpoints for which hypothesis testing will be performed. Change from baseline in FEV_1, FVC and PEFR on Days 2, 7, and 14 will be captured and characterized using descriptive statistics only.

9.2.2 Safety Endpoints

The safety endpoints for this study include:

9.2.2.1 Holter monitor summary data:

- 24 hour mean heart rate (primary safety endpoint)
- 24 hour maximum heart rate
- 24 hour minimum heart rate
- The total number of beats
- The proportion of ventricular ectopics

- The proportion of supraventricular ectopics
- The proportion of paced beats
- The number of ventricular couplets
- The number of ventricular runs
- The number of isolated ventricular events
- The number of supraventricular couplets
- The number of supraventricular runs
- The number of isolated supraventricular events
- The number of bradycardia episodes
- The number of tachycardia episodes

9.2.2.2 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.

9.2.2.3 Paradoxical Bronchospasm and Tremor

Will be regarded as adverse events of special significance, and tabulated separately.

9.2.2.4 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 on Day 1 (Visit 3).

9.2.2.5 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.

9.2.2.6 Clinical Laboratory Testing:

Full clinical laboratory testing at every sample time including hematology and clinical chemistry, characterized by change from baseline, where the baseline is defined as the value prior to dosing on Day 1 (Visit 3).

9.2.2.7 Vital Sign Measurements:

Change from baseline values where baseline is defined as the average of the values prior to dosing on Day 1 (Visit 3).

9.3 Analysis

9.3.1 Key Efficacy Analysis

Efficacy analysis will be based on a linear model in which Treatment will be a fixed effect using baseline as a covariate.

The key efficacy analysis will involve *a priori* comparisons between the combination treatment and Formoterol Fumarate MDI 9.6 µg and Glycopyrrolate MDI 36 µg for the primary endpoint: mean pre-dose FEV_1 on Visit 5 compared to pre-dose values at Visit 3. The comparisons will comprise:

- Glycopyrrolate 36 µg /Formoterol Fumarate 9.6 µg ex-actuator combination vs Formoterol Fumarate 9.6 µg ex-actuator. This is a superiority comparison.
- Glycopyrrolate 36 µg /Formoterol Fumarate 9.6 µg ex-actuator combination vs Glycopyrrolate 36 µg ex-actuator. This is a superiority comparison.

9.3.2 Other Efficacy Analysis

No other efficacy comparisons will be performed. Descriptive statistics (mean, median, range and standard deviation) will be presented for mean pre-dose FEV_1 n Day 1 and on Day 7, and for FVC and PFER on Days 1, 7 and 14.

9.3.3 Safety Analysis

9.3.3.1 Holter Monitor Results

The change from baseline (Visit 2) mean heart rate will be analysed using a linear model. The mean heart rate during the baseline period (Visit 2) will be used as a covariate.

The proportions of the following beats will be analysed using a generalized linear model with a quasi-binomial family (Wedderburn 1974):

- Ventricular ectopics
- Supraventricular ectopics
- Paced beats.

Extra-binomial variation will be accommodated by inflating the variance covariance matrix by the sum of squared Pearson residuals divided by the residual degrees of freedom (Venables and Ripley, 2002 page 208). For each proportion, the logit-transformed equivalent proportion during the baseline period (Visit 2) will be used as a covariate. Where the observed proportion is zero, the logit will be calculated assuming 1 event out of twice the total number of QRS complexes.

The numbers of the following events will be analysed using a generalized linear model with a quasi-Poisson family:

- Ventricular couplets
- Total ventricular runs
- Isolated ventricular events
- Supraventricular couplets
- Total supraventricular runs
- Isolated supraventricular events
- Bradycardia episodes
- Tachycardia episodes.

Extra-Poisson variation will be accommodated by inflating the variance covariance matrix by the sum of squared Pearson residuals divided by the residual degrees of freedom. The log-transformed number of the relevant event during the baseline period will be used as a covariate. A constant of 1 will be added to the number of each baseline event before log-transformation.

For each endpoint, the location parameter for the combination treatment will be compared with the location parameter for the other three treatments. No multiplicity adjustment will be imposed.

9.3.3.2 Adverse Events

Adverse events will be summarized by the number of patients experiencing an event for each treatment. They will be tabulated at the level of the MedDRA preferred term, and the MedDRA System Organ Class. The version of MedDRA current at the time the first subject is randomized will be used throughout the study. Tabulations will be broken down by severity and by relationship to study drug. No hypothesis tests will be performed.

9.3.3.3 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 for each treatment. No hypothesis tests will be performed, but a Clopper-Pearson confidence interval may be provided.

9.3.3.4 Clinical Laboratory Measurements

Summary statistics (mean, median, standard deviation and range) of change from baseline values will be tabulated for each treatment and each assessment time. For clinical laboratory measurements, baseline values will be defined by the value prior to dosing on Day 1 (Visit 3). Male and female patients will be tabulated separately.

9.3.3.5 Vital Signs

Summary statistics (mean, median, standard deviation and range) of change from baseline values will be tabulated for each treatment and each assessment time. For vital signs, baseline values will be defined by the value prior to dosing on Day 1 (Visit 3).

9.3.3.6 ECGs

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 on Day 1 (Visit 3).

Summary statistics (mean, median, standard deviation and range) of change from baseline values will be tabulated for each treatment period and each assessment time. For ECG parameters, baseline values will be defined by the value prior to dosing on Day 1 (Visit 3).

The number of subjects with more than a 30 msec change from the pre-dose record on the test day or greater than a 50 msec change from the baseline will be tabulated. These stubjects will be listed, and a detailed narrative provided.

9.4 Randomization

Patients will be randomly assigned to treatment using an IWRS.

9.5 Sample Size Consideration

Stein et al (1998) reported a standard deviation of 10 beats per minute for 24 hour average heart rate in patients with COPD. Takabatake et al (2001) reported a standard deviation of 10.2 bpm, for patients with COPD. Power was calculated assuming that these standard deviations are relevant for this study, and based on a standard deviation opf 10.1 bpm. A sample size of 50 patients per treatment group gives a minimum detectable difference (with approximately 90% power) of 6.5 bpm. Power was calculated assuming a two sided t test at the 5% level. The power to detect a 5 bpm change is approximately 70%.

The ability of the design to detect low frequency cardiac anomalies was also considered. A sample size of 50 patients per group implies that, if no anomalies are detected, the maximum credible value for the true proportion of patients developing the anomaly is approximately 7% (based on the binomial distribution).

Sample size has been determined with respect to the safety objectives, since these form the primary objectives of the study. Nevertheless, power for the key efficacy objective may be evaluated. Previous studies have suggested that the between subject standard deviation of trough FEV_1 is 0.1L. If half of this variability represents variation between long-term averages of subjects, and half represents variation between repeated measurements on the same subject, then the estimated standard deviation of the average of two days' trough FEV_1 is 0.13L. For an effect size of 0.1L, the power is 97%; for an effect size of 0.07L the power is 76%. These power calculations assumed a two sided t test at the 5% level.

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 study unblinding.

9.7 Study Populations

The following analysis populations are defined in this study:

- The Intent-To-Treat (ITT) Population is defined as all subjects who are randomized to treatment, received at least one dose of the study treatment, and had both baseline and post-baseline data for efficacy analysis.
- A Modified ITT (MITT) Population used for analysis of efficacy variables; where subjects must have remained in the study for minimally 2 hours post-dosing on 1 or more test days (Visit 3, 4 or 5). A more detailed description of the MITT Population will be provided in the Statistical Analysis Plan.
- The Per-Protocol (PP) Population is defined as all subjects from the ITT group who completed Visits 3, 4, and 5 of the study with evaluable efficacy data for Visits 3, 4, and 5 as specified in the protocol. The PP Population will be used for sensitivity analyses. The PP Population will exclude any measurements excluded from the MITT Population.
- The Safety Population is defined as all subjects who are randomized to treatment, received at least one dose of the study treatment, and had safety data after starting study treatment.

Analyses will be performed as follows:

- Demographics analyses will be performed for the Safety, ITT, MITT, and PP patient populations, with the Safety Population being considered the primary population for these analyses.
- Efficacy Analyses will be performed for both the MITT and PP patient populations, with the MITT Population being considered the primary population for these analyses.
- Safety Analyses will be performed using the Safety Population.

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 and safety analyses will be based on the dose actually received, rather than the dose scheduled.

9.8 Handling of Missing Data

Missing data will not be imputed. If the spirometry data quality obtained for a patient at any time-point does not meet minimal acceptability requirements per ATS/ERS criteria, as determined during the blinded spirometry over read process, data for that time-point will be considered missing.

9.9 Statistical Software

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

10 ADMINISTRATIVE INFORMATION

10.1 Regulatory Authority Approval

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

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

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

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

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

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

10.3 Patient Information and Consent

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

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

10.4 Confidentiality

10.4.1 Confidentiality of Data

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

10.4.2 Confidentiality of Subject/Patient Records

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

10.5 Quality Control and Assurance

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

10.6 Data Management

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

10.7 Study Monitoring

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

During these contacts, the monitor will:

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

This will be done in order to verify that the:

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

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

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

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

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

10.8 Retention of Data

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

10.9 Financial Disclosure

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

10.10 Investigator's Final Report

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

10.11 Publication Policy

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

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

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Appendix 1 Spirometry Performance Recommendations

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

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

FEV_1 AND FVC MANEUVERS

Equipment Requirements

The spirometer must be capable of accumulating volume for $\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-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

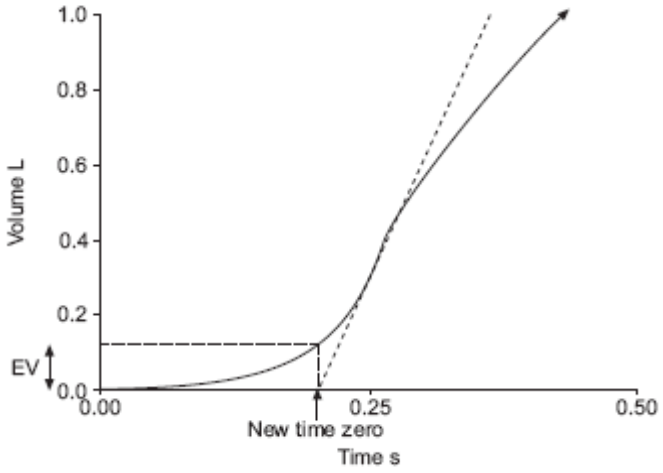
***Acceptable* Tests must meet the following 7 criteria:**

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 Holter Monitoring Criteria for Proarrhythmia

1. The 24-hour Holter monitor recordings obtained after the start of double-blind treatment will be reviewed for the development of or any increase in the incidence of cardiac dysrhythmic events, which could be considered indicative of proarrhythmic drug effects. The definition of proarrhythmia is based on the Morganroth criteria (Morganroth, et al, 1984, 1987). These criteria define proarrhythmia based on the change from the baseline visit in number of ventricular premature beats per hour (VPB/hr) and/or the frequency of ventricular tachycardia (VT) events (nonsustained or sustained) as follows:

BASELINE MEAN VPB/HR	REQUIREMENT FOR DEFINITION OF PROARRHYTHMIA (POSTBASELINE)
0 - 1	$\geq$ 10 Mean VPB/hour
1 - 100	increase of $\geq$ 10 times baseline
Over 100	increase of $\geq$ 3 times baseline

or

BASELINE NONSUSTAINED VT EVENTS*	REQUIREMENT FOR DEFINITION OF PROARRHYTHMIA (POSTBASELINE)
0	$\geq$ 5 events or > 15 beats in events/24 hrs
$\geq$ 1	increase of $\geq$ 10 times baseline events or beats

or

BASELINE SUSTAINED VT EVENTS*	POSTBASELINE SUSTAINED VT EVENTS FOR DEFINITION OF PROARRHYTHMIA*
0	$\geq$ 1

2. Any run of ventricular ectopic beats associated with symptoms (hypotension or syncope), regardless of the rate.

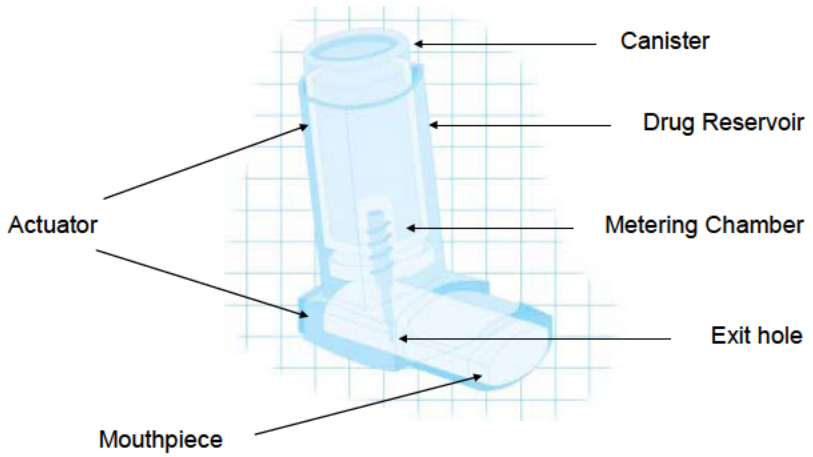
3. Any episode of ventricular flutter and/or ventricular fibrillation.

* Ventricular tachycardia (VT) is defined as a run of 3 or more ventricular premature beats (VPB's) with a rate $\geq$100 beats per minute. Sustained VT is defined as VT lasting $\geq$ 30 seconds or $\geq$ 60 beats. Nonsustained VT is a run of 3 or more VPB's with a rate $\geq$ 100 beats per minute which does not fulfill the criteria for sustained VT.

Appendix 4 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



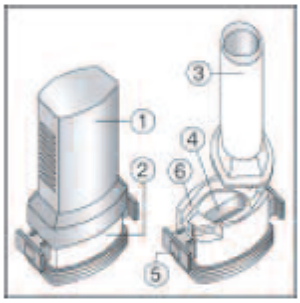
Appendix 5 Instructions for Use of Foradil Aerolizer Device

FORADIL AEROLIZER

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

Aluminum pouch covering the foil blister cards

Foil blister card



The Aerolizer consists of the following parts:
1. A cap to protect the mouth-piece of the base
2. A base that allows the proper release of medicine from the capsule

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

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

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

Taking a dose of FORADIL AEROLIZER requires the following steps:

1. Open the foil pouch containing a blister card of FORADIL capsules. Do not remove a FORADIL capsule until you are ready for a dose.
2. Pull off the AEROLIZER Inhaler cover. (Figure 1)

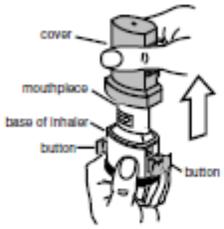


Figure 1

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

Figure 2

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

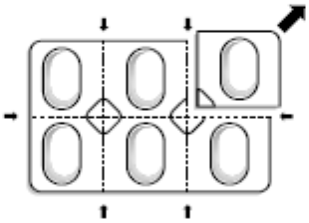


Figure 3

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

Figure 4

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

Figure 5

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

Figure 6

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

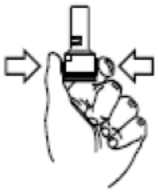


Figure 7

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

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

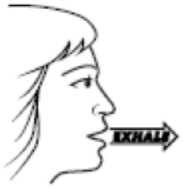


Figure 8

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

Figure 9

Figure 10

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

Figure 11

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

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

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

16. Close the mouthpiece and replace the cover.

Appendix 6 Instructions for Use of Atrovent HFA Inhalation Aerosol MDI Device

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

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

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

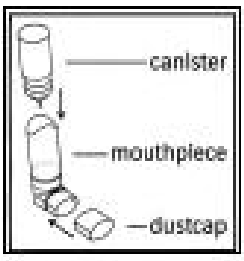


Figure 1

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

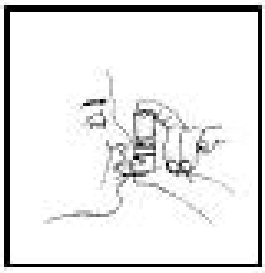


Figure 2

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

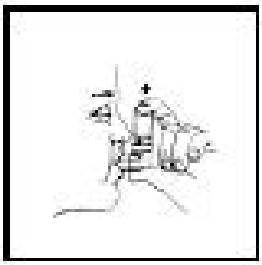


Figure 3

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

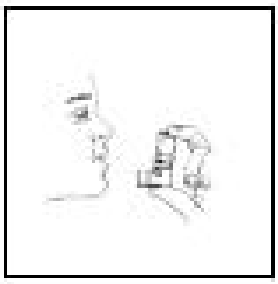


Figure 4

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

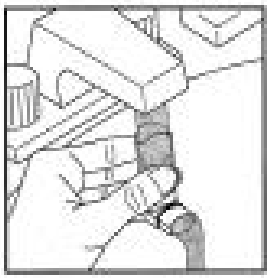


Figure 5

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

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

Appendix 7 Instructions for Use of Ventolin HFA Inhaler

The Parts of Your VENTOLIN HFA Inhaler

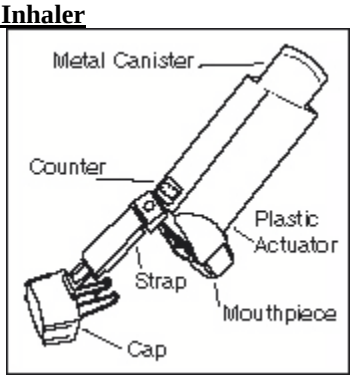


Figure 1

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.

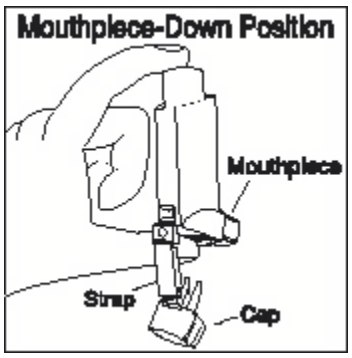


Figure 2

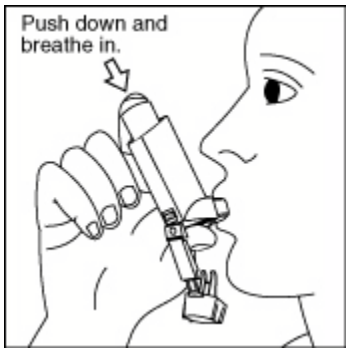


Figure 3

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).

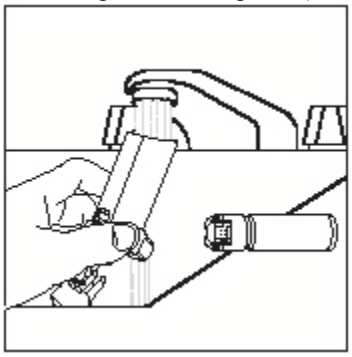


Figure 4

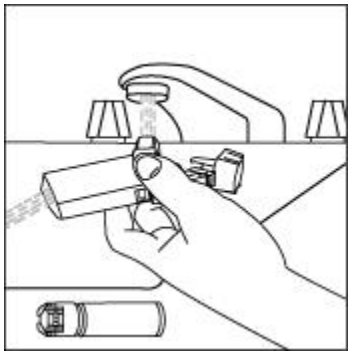


Figure 5

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).

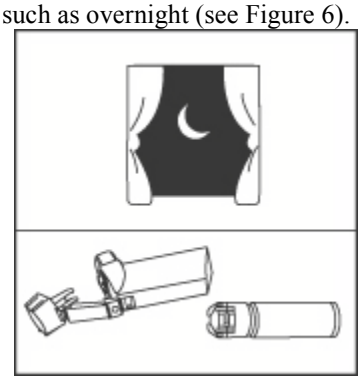


Figure 6

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.

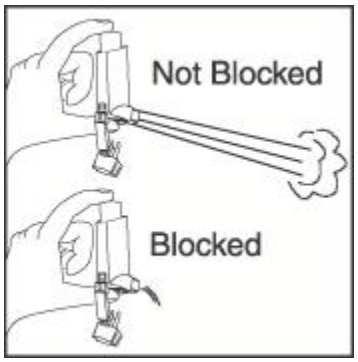


Figure 7

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 8 Sponsor Signatory

Study Title: A Randomized, Double-blind, Parallel Group, 14-day, Multi-Center Study to Evaluate the Safety of PT003, PT005, PT001 and Foradil® Aerolizer® (12 µg, Open-Label) as Evaluated by Holter Monitoring, in Patients with Moderate to Severe Chronic Obstructive Pulmonary Disease (COPD)

Study Number: PT003003-02

Original Protocol Date: [redacted]

Amendment 1 Date [redacted]

Amendment 2 Date: [redacted]

Signature: [redacted] **Date:** [redacted]

Name: [redacted]

Title: [redacted] Pearl Therapeutics, Inc

Appendix 9 Investigator's Agreement and Signature Page

Study Title: A Randomized, Double-blind, Parallel Group, 14-day, Multi-Center Study to Evaluate the Safety of PT003, PT005, PT001 and Foradil® Aerolizer® (12 µg, Open-Label) as Evaluated by Holter Monitoring, in Patients with Moderate to Severe Chronic Obstructive Pulmonary Disease (COPD)

Study Number: PT003003-02

Original Protocol Date: [redacted]

Amendment 1 Date [redacted]

Amendment 2 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 Pearl Therapeutics and prior review and written approval from the IRB/IEC, except where necessary to eliminate an immediate hazard to the subjects, or for administrative aspects of the study (where permitted by all applicable regulatory requirements).
- That I am aware of, and will comply with, good clinical practices (GCP) and all applicable regulatory requirements.
- That I am thoroughly familiar with the appropriate use of the investigational product(s), and other information provided by Pearl Therapeutics including, but not limited to, the following: the protocol and the current Investigators Brochure (IB).
- To ensure that all persons assisting me with the study are qualified, adequately informed about the investigational product(s) and of their study-related duties and functions.
- To supply Pearl Therapeutics with any necessary information regarding ownership interest and financial ties; to promptly update this information if any relevant changes occur during the course of the study and for 1 year following completion of the study; and agree that Pearl Therapeutics may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- I agree to report all information or data in accordance with the protocol and any other study conduct procedures provided by Pearl Therapeutics
- That since the information in this protocol and IB is confidential, I understand that its disclosure to any third parties, other than those involved in approval, supervision or conduct of the study is prohibited.
- To accurately transfer all required data from each patient's source document to the case report forms (CRFs). The CRFs will be provided to Pearl Therapeutics in a timely manner at the completion of the study, or as otherwise specified by Pearl Therapeutics.
- To allow authorized representatives of Pearl Therapeutics or regulatory authority representatives to conduct on-site visits to review, audit and copy study documents. I will personally meet with these representatives to answer any study-related questions.

Signature:_____ Date:_____

Name:_____

Affiliation: _____