12.1.1 PROTOCOL AND PROTOCOL AMENDMENTS

This appendix includes the following approved original protocol and protocol amendments

- Original Protocol – [redacted]

Clinical Trial Protocol: PT003005-00

Study Title:	A Randomized, Double-Blind, (Test Products), Chronic Dosing (7 Days), Four-Period, Eight-Treatment , Incomplete Block, Cross-Over, Multi-Center Study to Assess Efficacy and Safety of Five Doses of PT003, One Dose of PT001 and One Dose of PT005 in Patients With Moderate to Severe COPD, Compared With Spiriva® Handihaler® (Tiotropium Bromide 18 µg, Open-Label) as Active Control
Study Number:	PT003005-00
Study Phase:	IIb
Product Name:	Glycopyrrolate and Formoterol Fumarate Inhalation Aerosol; PT003 Formoterol Fumarate Inhalation Aerosol; PT005 Glycopyrrolate Inhalation Aerosol; PT001
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/Formoterol Fumarate Inhalation Aerosol; PT003
Formoterol Fumarate Inhalation Aerosol; PT005
Glycopyrrolate Inhalation Aerosol; PT001
Spiriva® Handihaler®; Spiriva

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

Study Title:
A Randomized, Double-Blind, (Test Products), Chronic Dosing (7 Days), Four-Period, Eight-Treatment , Incomplete Block, Cross-Over, Multi-Center Study to Assess Efficacy and Safety of Five Doses of PT003, One Dose of PT001 and One Dose of PT005 in Patients With Moderate to Severe COPD, Compared With Spiriva® Handihaler® (Tiotropium Bromide 18 µg, Open-Label) as Active Control

Study Number: PT003005-00

Study Phase: IIb

Study Objective(s):

For combination drug development, a study is required to demonstrate superiority of the combination [Glycopyrrolate/Formoterol Fumarate metered dose inhaler (MDI) (GFF MDI)] to individual components [Glycopyrrolate MDI (GP MDI) and Formoterol Fumarate MDI (FF MDI)]. In addition, GFF MDI, GP MDI and FF MDI will be compared to a marketed product, Spiriva (18 µg, open-label)

Primary objective:
The primary objective of this study is to assess the efficacy of GFF MDI relative to individual components (GP MDI and FF MDI) in subjects with moderate to severe COPD within the range of doses evaluated in this protocol. To this end, the primary efficacy endpoint, FEV_1 AUC_{0-12}, will be compared for each dose of GFF MDI administered twice daily (BID) relative to GP MDI (18µg ex-actuator, BID) and FF MDI (9.6 µg ex-actuator, BID).

Secondary Objective:
The secondary objective of the study is to characterize the dose-response curve for GFF MDI. The primary and secondary endpoints identified in Section 3.1 will be assessed for

GFF MDI given as a twice-daily administration as compared to GP MDI, FF MDI and Spiriva (18 µg, open-label).

Safety Objective:
The safety objective is to evaluate the safety of GFF MDI (18/9.6, 9/9.6, 4.6/9.6, 2.4/9.6 and 1.2/9.6 µg ex-actuator, BID) in subjects with moderate to severe COPD compared with GP MDI (18 µg ex-actuator, BID), FF MDI (9.6 µg ex-actuator, BID) and Spiriva (18 µg, open-label, QD). Safety will be assessed by adverse events (AEs and SAEs), physical examination findings, dry mouth, tremor, paradoxical bronchospasm, vital signs, electrocardiograms (ECGs), and laboratory assessments.

Study Design:

This is a randomized, double-blind (test products), chronic dosing (7 days), four-period, eight-treatment, incomplete block, cross-over, multi-center study to assess efficacy and safety of five doses of GFF MDI (18/9.6, 9/9.6, 4.6/9.6, 2.4/9.6 and 1.2/9.6 µg ex-actuator, BID), one dose of FF MDI (9.6 µg ex-actuator, BID), and one dose of GP MDI (18 µg ex-actuator, BID) in subjects with moderate to severe COPD, compared with Spiriva (18 µg, open-label, QD) as an active control.

This multi-center study will be conducted at approximately 16-20 sites, contributing approximately 8 to 10 subjects per site in the United States. Across these sites, it is planned that approximately 160 subjects with moderate to severe COPD will be randomized into the study to provide approximately 110 subjects to complete the study.

The entire study period is scheduled to take a maximum of 19 weeks for each individual subject. The study is anticipated to run for approximately 9 months and should not exceed 18 months.

Study Population:
Approximately 160 subjects with moderate to severe COPD will be enrolled to provide approximately 110 subjects to complete the study.

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

Product Name & Potency	Dosage Form	Comments
Glycopyrrolate/Formoterol Fumarate 18/9.6 µg ex-actuator	MDI	Taken as 2 inhalations of the 9/4.8 µg per actuation strength MDI
Glycopyrrolate/Formoterol Fumarate 9/9.6 µg ex-actuator	MDI	Taken as 2 inhalations of the 4.5/4.8 µg per actuation strength MDI
Glycopyrrolate/Formoterol Fumarate 4.6/9.6 µg ex-actuator	MDI	Taken as 2 inhalations of the 2.3/4.8 µg per actuation strength MDI
Glycopyrrolate/Formoterol Fumarate 2.4/9.6 µg ex-actuator	MDI	Taken as 2 inhalations of the 1.2/4.8 µg per actuation strength MDI
Glycopyrrolate/Formoterol Fumarate 1.2/9.6 µg ex-actuator	MDI	Taken as 2 inhalations of the 0.6/4.8 µg per actuation strength MDI
Glycopyrrolate 18 µg ex-actuator	MDI	Taken as 2 inhalations of the 9 µg per actuation strength MDI
Formoterol Fumarate 9.6 µg ex-actuator	MDI	Taken as 2 inhalations of the 4.8 µg per actuation strength MDI
Tiotropium inhalation powder† 18 µg	Dry Powder Inhaler (DPI)	US source: (Spiriva Handihaler) Taken as 1 capsule containing 18 µg of tiotropium via the Handihaler DPI *Supplies are open-label.*
Albuterol Sulfate inhalation aerosol§ 90 µg	MDI	US source: (Ventolin® HFA) Each inhalation contains 108 µg corresponding to 90 µg albuterol base from the mouthpiece *Supplies are open-label.*
Ipratropium Bromide HFA inhalation aerosol* 34 µg ex-actuator	MDI	US source: (Atrovent HFA) Taken as 2 inhalations of the 17 µg per actuation strength MDI *Supplies are open-label.*

† Active control

§ Rescue medication and reversibility testing.

* Used for COPD maintenance therapy during screening and washout periods.

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

The 18/9.6, 9/9.6, 4.6/9.6, 2.4/9.6 and 1.2/9.6 µg ex-actuator delivery of GFF MDI are equivalent to 20.6/11.0, 10.3/11.0, 5.3/11.0, 2.7/11.0, and 1.4/11.0 µg ex-valve of GFF MDI, respectively. The 18 µg ex-actuator delivery of GP MDI is equivalent to 20.6 µg ex-valve of GP MDI. The 9.6 µg ex-actuator delivery of FF MDI is equivalent to 11.0 µg ex-valve of FF MDI.

Duration of Treatment:
Each subject will receive 7 days of study treatment with each of their assigned treatments for a total of 4 separate treatment periods. A washout period of at least 7 days (up to 21 days) will occur between each treatment period. The entire study is scheduled to take a maximum of 19 weeks for each individual subject from the time of screening (see Figure 1).

Efficacy Assessments:
All efficacy assessments, except for the mean number of puffs of rescue medication, are relative to baseline. Since pre-dose values are known to be variable, and an isolated time-point may not accurately reflect the true baseline, the following baseline will be used for statistical analyses unless otherwise specified: the mean of available pre-dose values on the first day of each treatment cycle, i.e., the mean of pre-dose values at Visits 2, 4, 6 and 8, where the mean of the -60 and -30 minute value for each visit day is averaged and then the average of all visit means are averaged. Previous studies showed that this average baseline was more robust than the mean of pre-dose values at the start of each treatment period, or the mean of pre-dose values during Visit 2 alone, and that it gave more precise estimates of treatment means.

Primary Efficacy Endpoint Evaluated on Treatment Day 7 (Visits 3 5, 7, and 9, following chronic dosing):

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

Secondary Efficacy Endpoints:

Secondary Endpoints Evaluated on Treatment Day 1 (Visits 2, 4, 6 and 8) relative to baseline:

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

Secondary Endpoints Evaluated on Treatment Day 7 (Visits 3, 5, 7 and 9, following chronic dosing):

- Change from baseline in morning pre-dose trough FEV_1, (defined as the average of the 60 and 30 minute pre-dose values on Treatment Day 7 minus the baseline).

- Peak change from baseline in FEV_1 (defined as the change at the highest value of FEV_1 post-dose).
- Change from baseline for mean morning pre-dose trough IC (mean of 60 and 30 minute pre-dose assessments minus the baseline).
- Peak change from baseline in IC (mean of 1 and 2 hours post-dose assessments minus the baseline).
- Change from baseline in 12-hour post-dose trough FEV_1 (12-hour post-dose trough FEV_1 is defined as the mean of the FEV_1 assessments taken at 11.5 and 12 hours post-dose).
- Change from baseline in mean morning pre- and post-dose daily peak flow readings taken by subjects and recorded in subject diaries, during each treatment period (excluding reading taken pre- dose on Treatment Day 1).
- Change from baseline in mean evening pre- and post-dose daily peak flow readings taken by subjects and recorded in subject diaries, during each treatment period (Subjects taking Spiriva will perform a single evening assessment).
- Mean number of puffs of rescue medication recorded in subject diaries, during each treatment period and by treatment and number of days treated.

Exploratory Endpoints Evaluated on Treatment Day 7 (Visits 3, 5, 7 and 9, following chronic dosing):

- Peak expiratory flow rate (PEFR) morning pre-dose trough and peak change from baseline on Day 7. PEFR AUC_{0-12} and change from baseline by post-dose time point. AUC will be normalized by dividing by time (12 hours) so that unit of AUC will be L.
- Forced vital capacity (FVC) morning pre-dose trough and peak change from baseline on Day 7. FVC AUC_{0-12} and change from baseline by post-dose time point. AUC will be normalized by dividing by time (12 hours) so that the units of AUC will be L.
- Change from baseline for mean evening 12 hour post-dose trough IC (mean of 11.5 and 12 hours post-dose assessments minus the baseline).

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

Statistical Methods:

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

The standard error of each contrast was calculated, assuming a generalized least squares analysis in which the ratio of between and within subject variance components was known. The generalized least squares estimates also assumed spherical errors. This is an approximation to the standard error of the REML estimates. It was assumed that there are no carryover effects. The non-centrality parameter of the t-test was calculated, assuming the standard error from the generalized least squares analysis, and a difference of 0.080 L. A sample size of 110 subjects achieves approximately 89% power (assuming a significance test at the 5% level, with no multiplicity adjustment). Approximately 160 subjects will be recruited in order to achieve 110 subjects completing.

Efficacy Analyses: In the traditional development approach for a combination product, the optimal dose of the individual components needs to be established and then the combination product is compared to the individual components in order to meet the combination rule as outlined in Title 21 CFR Part 300.50. However, in parallel to the dose ranging studies for the individual components, data with the combination product can also provide useful information to aid in dose selection and in the evaluation of efficacy and safety in further studies. To this end, this study will dose range glycopyrrolate on a fixed background of formoterol fumarate 9.6 µg (GFF MDI 18/9.6, 9/9.6, 4.6/9.6, 2.4/9.6 and 1.2/9.6 µg versus FF MDI 9.6 µg) to assess the incremental benefit offered by each successive dose. Similarly, this study will assess the incremental benefit of each dose of GFF MDI relative to a dose of GP MDI that has previously been shown to be effective (GP MDI 18 µg).

The primary efficacy analysis involves the comparison of the mean primary efficacy endpoint (FEV_1 $AUC_{0\text{-}12}$ relative to baseline) for each combination treatment compared to GP MDI 18 µg ex-actuator and FF MDI 9.6 µg ex-actuator. Baseline will be included in the statistical model as a covariate. Efficacy analysis will be based on a linear mixed model in which treatment and period will be fixed effects, subject will be a random effect, and within subject errors are correlated, but between subject errors are independent. Unstructured, compound symmetry and first order autoregressive error models will be considered, and the appropriate model selected using Akaike's information criterion (Akaike, 1974). Fixed and random effects will be estimated using the REML algorithm (Patterson and Thompson, 1971), which allows for the recovery of inter-block (subject) information.

Secondary and exploratory efficacy analysis will involve the same comparisons between combination and monotherapies, on secondary and exploratory efficacy endpoints. They will also include comparisons between the combination product (GFF MDI) and individual components (GP MDI and FF MDI) with Spiriva (18 μg, open-label). For endpoints other than time to onset, mean number of puffs of rescue medication from diary entries, and percentage of subjects with ≥12% improvement, these comparisons will be performed using the same mixed model and the same algorithms as for the primary efficacy objective. Hierarchical testing will not be imposed for secondary endpoints. For time to onset, comparisons will be based on Murray's method for weighted Kaplan-Meier statistics for paired data (Murray, 2001). The mean number of puffs of rescue medication will be analyzed using a generalized linear mixed model with a Poisson family, and random effects representing patients and periods within patients. The percentage of subjects with ≥12% improvement FEV_1 on Treatment Day 1 will be compared using a generalized linear mixed model for incompletely paired data (with a binomial family and random effects for patients and periods wihin patients).

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 subjects with adverse events.

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 SAS (Version 9.2 or higher). Graphs may also be produced using R.

Date of Original Approved Protocol: [redacted]

Prepared in: Microsoft Word 2007

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATS	American Thoracic Society
AUC	Area under the curve
AV	Atrioventricular block
BID	bis in die, twice daily
BMP	Basic Metabolic Panel
BP	Blood Pressure
BPM	Beats per minute
BTPS	Body Temperature and Pressure Saturated
BUN	Blood urea nitrogen
$CaCl_2$	Calcium chloride
CFR	Code of Federal Regulations
CIR	Cumulative incidence ratio
CMP	Comprehensive Metabolic Panel
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case report form
CRO	Contract Research Organization
CT	Computerized Tomography
DBP	Diastolic blood pressure
DPI	Dry Powder Inhaler
DSPC	Distearoylphophatidylcholine
e.g.	Exempli gratia, for example
ECG	Electrocardiogram
ERS	European Respiratory Society
EV	Back extrapolation volume
ex-actuator	dose delivered from the actuator (i.e., mouthpiece) of the MDI

FDA	Food and Drug Administration
FEV_1	Forced Expiratory Volume in 1 second
FF MDI	Formoterol Fumarate MDI
FRC	Functional Residual Capacity
FVC	Forced Vital Capacity
GCP	Good clinical practice
GFF MDI	Glycopyrrolate and Formoterol Fumarate MDI
GP MDI	Glycopyrrolate MDI
HCG	Human chorionic gonadotropin
HR	Heart Rate
HFA	Hydrofluroalkane
i.e.	*Id est,* that is
IC	Inspiratory Capacity
ICF	Informed consent form
ICH	International Conference on Harmonization
ICMJE	International Committee of Medical Journal Editors
ICS	Inhaled Corticosteroid
IEC	Independent Ethics Committee
IM	Intramuscular
IRB	Institutional Review Board
ITT	Intention-to-treat
IUD	Intrauterine device
IV	Intravenous
IWRS	Interactive Web Response System
L	Liter
LABA	Long-acting beta agonist
LAMA	Long-acting antimuscarinic agents
LTOT	Long Term Oxygen Therapy
MAO	Monoamine oxidase inhibitor

MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MDI	Metered Dose Inhaler
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified ITT
mL	Milliliter
Msec (ms)	Millisecond
NHANES III	Third National Health and Nutrition Examination Survey
OTC	Over-the-counter
PEFR	Peak expiratory flow rate
PFT	Pulmonary function test
PP	Per protocol
PRN	pro re nata
REML	Residual or restricted maximum likelihood
Rx	Treatment
QTcF	QT corrected using Fridericia's formula ($QT/(RR^{1/3})$)
SABA	Short-acting beta agonist
SAE	Serious Adverse Event
SBP	Systolic blood pressure
SOP	Standard operating procedure
SVC	Slow Vital Capacity
TLC	Total Lung Capacity
TNFα	Tumor necrosis factor α
US	United States

TRADEMARK INFORMATION

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Aerolizer

Atrovent

Dulera

Foradil

Handihaler

PulmoSphere

Robinul

Robinul Forte

Spiriva

Symbicort

Ventolin

1 INTRODUCTION

Chronic obstructive pulmonary disease (COPD), a common preventable disease and treatable disease is characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases. Exacerbations and comorbidities contribute to the overall severity in individual patients (GOLD, 2011). To date, none of the existing medications for COPD have been shown conclusively to modify the long-term decline in lung function that is the hallmark of this disease. Therefore, pharmacotherapy for COPD is used to reduce COPD symptoms, reduce the frequency of and severity of exacerbations, and improve health status and exercise tolerance (GOLD, 2011).

Bronchodilator medications are central to the symptomatic management of COPD. The principal bronchodilator treatments are β2-agonists, anticholinergics, and methylxanthines used as monotherapy or in combination. Treatment with long-acting bronchodilators is more conveinient and more effective at producing maintained symptom relief than treatment with short-acting bronchodilators. Combining bronchodilators from different pharmacological classes may improve efficacy and decrease the risk of side effects compared to increasing the dose of a single bronchodilator (GOLD, 2011). Long acting muscarinic antagonists (LAMAs) and long-acting β2-agonists (LABAs) reduce bronchoconstriction through different mechanisms and there is a long history of combination therapy for COPD with short-acting agents in these classes.

Pearl Therapeutics is developing a combination product comprised of 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.

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 short acting β_2-agonists (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 subjects demonstrated that formoterol fumarate is effective and well tolerated in subjects 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 subjects 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 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. Spiriva 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, subjects with COPD, and subjects with asthma that support its safety. Inhaled glycopyrrolate has been safely administered to over 550 subjects 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 completed clinical studies with its LABA/LAMA formulation (GFF MDI: Studies PT0030901, PT0031002, PT003003 and PT003004) as well as Phase IIa dose-ranging studies in subjects with COPD with each of the individual component products (Formoterol Fumarate MDI [FF MDI] and Glycopyrrolate MDI [GP MDI]; Studies PT0050801, PT005003, PT001002 and PT0010801).

A summary of the trials Pearl Therapeutics has completed with its LABA/LAMA formulation (GFF MDI) is presented below.

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 subjects 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. In Study PT0031002, comparable efficacy results were demonstrated for GFF MDI 36/9.6 µg and GFF MDI 72/9.6 µg administered twice daily. The results from Study PT0031002 also demonstrated that both FF MDI doses (7.2 and 9.6 µg) were non-inferior to Foradil Aerolizer 12 µg for the primary endpoint, FEV_1 AUC_{0-12} at Day 7, with only FF MDI 9.6 µg demonstrating bioequivalence from a PK perspective with Foradil Aerolizer 12 µg. No substantial differences were noted between any of the active treatments and placebo in terms of common AEs, SAEs, and AEs leading to withdrawal. The most commonly reported AEs (≥ 5% of subjects) overall were dry mouth, headache, COPD worsening, cough, and tremor. No deaths were reported in the study. Five subjects reported a total of 6 SAEs, none of which were attributed to study treatment: inhaled foreign body, COPD exacerbation (for which the subject was withdrawn), ruptured appendix, atypical chest pain (for which the subject was withdrawn), and gastritis and abdominal aortic aneurysm reported in one subject. A total of 11 subjects were withdrawn from the study due to AEs: 8 subjects experienced COPD (increase/exacerbation); 2 subjects experienced lower respiratory tract infection (chest infection); and 1 subject experienced chest pain. All AEs leading to subject discontinuation from the study were considered unrelated to study treatment with the exception of one event of lower respiratory tract infection reported in 1 subject considered possibly due to treatment with FF MDI 9.6 µg. No clinically significant changes were noted in QTc values, vital signs, laboratory values, or serum potassium values.

Study PT003003 was a randomized, multi-center, double-blind, chronic dosing (14 days), parallel group study that evaluated the cardiovascular safety (as assessed by 24-hour Holter monitoring) of GFF MDI (36/9.6 µg), GP MDI (36µg), and FF MDI (9.6 µg) compared to Foradil Aerolizer (12 µg) administered BID in subjects with moderate to severe COPD. This was primarily a safety study. A total of 237 subjects were randomized. The response in trough FEV_1 with GFF MDI 36/9.6 µg was significantly greater than GP MDI 36 µg, FF MDI 9.6 µg and Foradil Aerolizer 12 µg ($p<0.002$) on Day 2, Day 7 and Day 14. These data suggest that little incremental benefit is attained in morning pre-dose trough FEV_1 beyond Day 7 across all treatment groups.

None of the treatment groups showed a clinically relevant change in mean heart rate from baseline on Day 1 or Day 14. The 95% CI of these differences were contained within 1 beat per minute (bpm). A total of 5 subjects were withdrawn from the study due to AEs. Two of the AEs leading to subject discontinuation from the study were considered unrelated to study treatment including one event of COPD exacerbation with Foradil Aerolizer 12 µg (which was considered a serious adverse event) and one event of ventricular asystole with GFF MDI 36/9.6 µg). Three AEs leading to subject discontinuation from the study were possibly or probably related to study treatment and included one event of atrioventricular block (probably related, GP MDI 36 µg), one event of ventricular asystole (possibly related, GFF MDI 36/9.6 µg), and one event of dyspnea (probably related, Foradil Aerolizer 12 µg). All AEs that lead to withdrawal from the study resolved.

Study PT003004 was a randomized, double-blind, chronic dosing (7 days), two-period, six-treatment, balanced incomplete block, crossover, multi-center study to assess efficacy and safety of four doses of GFF MDI (36/7.2, 36/9.6, 18/9.6, and 9/9.6 µg BID) in subjects with moderate to severe COPD, compared with its individual components, GP MDI (36 µg BID) and FF MDI (9.6 µg BID), as active controls that was conducted at 15 clinical sites in the US.

All doses of GFF MDI were superior to GP MDI 36 µg for the primary endpoint FEV_1 AUC_{0-12} on Day 7. All doses of GFF MDI were numerically greater compared to FF MDI 9.6 µg for FEV_1 AUC_{0-12} on Day 7, but the differences did not reach statistical significance. However, the FEV_1 AUC_{0-12} response observed in the FF MDI 9.6 µg treatment arm was larger than that observed in prior Pearl Therapeutics clinical trials while the response to GFF MDI 36/9.6 µg and GP MDI 36 µg was similar to previous studies. Overall, there was a flat dose response seen across the GFF MDI treatment arms with GFF MDI 9/9.6 µg providing a comparable response to higher doses of GFF MDI.

The most frequently reported AEs were dry mouth (16 subjects, 8.6%), COPD (9 subjects, 4.9%), and tremor (8 subjects, 4.3%). A total of 14 subjects were withdrawn from the study due to AEs: 7 subjects experienced a COPD exacerbation; 3 subjects experienced worsening hypertension (hypertension); and 1 subject each experienced a herniated disc (intervertebral disc protrusion), dyspnea, dry mouth, and acute renal failure (which was reported as an SAE)

There were three treatment-emergent SAEs pyelonephritis (GP MDI 36 µg), hypokalemia (GFF MDI 36/7.2 µg) and acute renal failure (GP MDI 36 µg). With the exception of hypokalemia, the events were deemed not related to study drug. The SAE of hypokalemia (GFF MDI 36/7.2 µg) was judged to be possibly related to study drug.

As a result of the information provided by the comprehensive Phase I/II development program with GFF MDI, further studies assessing efficacy and safety of GFF MDI with lower doses of glycopyrrolate are required.

Note: Unless otherwise indicated, throughout this document all references to doses of GFF MDI will be to the ex-actuator or "delivered" doses (18/9.6, 9/9.6, 4.6/9.6, 2.4/9.6, and 1.2/9.6 µg); all references to the FF MDI dose will be to the ex-actuator or "delivered" doses (9.6 µg); all references to the GP MDI dose will be to the ex-actuator or "delivered" doses (18 µg); all references to Spiriva® (tiotropium bromide, 18 µg) will be to the capsule content of 18 µg (delivered via the Handihaler®); all references to Atrovent HFA MDI will be to the ex-actuator or "delivered" doses of 34 µg; all references to Ventolin® HFA (albuterol sulfate inhalation aerosol) will be 108 µg corresponding to 90 µg albuterol base from the mouthpiece.

1.1 Study Rationale

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. In the development of a combination product, the optimal dose of the individual

components needs to be established and then the combination product is compared to the individual components in order to meet the combination rule as outlined in Title 21 CFR Part 300.50.

Formoterol is a well-established and extensively tested LABA that is clinically indicated for the management of COPD. Pearl has performed dose-ranging studies with FF MDI. The most recent was Study PT005003. This randomized, double-blind, single dose, crossover study assessed the efficacy, safety and PK of three doses of FF MDI (7.2, 9.6 and 19.2 µg) compared to Foradil Aerolizer 12 and 24 µg in subjects with moderate to severe COPD with demonstrated reversibility to albuterol. Both FF MDI 7.2 and 9.6 µg were non-inferior to Foradil Aerolizer 12 µg, however only the FF MDI 9.6 µg dose demonstrated PK bioequivalence to Foradil Aerolizer 12 µg.

Glycopyrrolate is under clinical investigation for patients with COPD. Pearl Therapeutics has performed dose-ranging studies with GP MDI. Study PT001002 is the most recently completed study. Study PT001002 was a randomized, double-blind, chronic-dosing (7 day), three-period, six-treatment, placebo-controlled, incomplete block, crossover study that evaluated the efficacy and safety of GP MDI 36, 18, 9 and 4.6 µg administered BID compared to Placebo MDI administered BID and Atrovent HFA Inhalation Aerosol 34 µg (Atrovent) administered four times daily (QID) in patients with moderate to severe COPD. All doses of GP MDI demonstrated statistically significant improvements compared to Placebo MDI ($p<0.0001$). However, the dose response for GP MDI was flat, with a similar response noted with the lowest dose of GP MDI (4.6 µg) when compared with higher doses of GP MDI (18 and 36 µg).

As a result of the information provided by the comprehensive Phase I/II development program, FF MDI 9.6 µg twice daily will be carried forward in combination development with five doses of glycopyrrolate (18, 9, 4.6, 2.4 and 1.2 µg) in the proposed study. To this end, this study will dose range glycopyrrolate on a fixed background of FF MDI 9.6 µg (GFF MDI 18/9.6, 9/9.6, 4.6/9.6, 2.4/9.6 and 1.2/9.6 µg ex-actuator) versus FF MDI 9.6 µg to assess the incremental benefit offered by each successive dose of glycopyrrolate after 7 days of treatment. Similarly, this study will assess the incremental benefit of each dose of GFF MDI relative to a dose of GP MDI that has previously been shown to be effective (GP MDI 18 µg) and Spiriva (18 µg) as an active control.

2 STUDY OBJECTIVES

For combination drug development, a study is required to demonstrate superiority of the combination [Glycopyrrolate/Formoterol Fumarate metered dose inhaler (MDI) (GFF MDI)] to individual components [Glycopyrrolate MDI (GP MDI) and Formoterol Fumarate MDI (FF MDI)]. In addition, GFF MDI, GP MDI and FF MDI will be compared to a marketed product, Spiriva (18 µg, open-label).

2.1 Primary Objective

The primary objective of this study is to assess the efficacy of GFF MDI relative to individual components (GP MDI and FF MDI) in subjects with moderate to severe COPD within the range of doses evaluated in this protocol. To this end, the primary efficacy endpoint, FEV_1 AUC_{0-12}, will be compared for each dose of GFF MDI administered twice daily (BID) relative to GP MDI (18 µg ex-actuator, BID) and FF MDI (9.6 µg ex-actuator, BID).

2.2 Secondary Objectives

The secondary objective of the study is to characterize the dose-response curve for GFF MDI. The primary and secondary endpoints identified in Section 3.1 will be assessed for GFF MDI given as a twice-daily administration as compared to GP MDI, FF MDI and Spiriva (18 µg, open-label).

2.3 Safety Objective

The safety objective is to evaluate the safety of GFF MDI (18/9.6, 9/9.6, 4.6/9.6, 2.4/9.6 and 1.2/9.6 µg ex-actuator, BID) in subjects with moderate to severe COPD compared with GP MDI (18 µg ex-actuator, BID), FF MDI (9.6 µg ex-actuator, BID) and Spiriva (18 µg, open-label). Safety will be assessed by adverse events (AEs and SAEs), physical examination findings, dry mouth, tremor, paradoxical bronchospasm, vital signs, electrocardiograms (ECGs), and laboratory assessments.

3 STUDY ENDPOINTS

3.1 Efficacy Endpoints

All efficacy assessments, except for the mean number of puffs of rescue medication, are relative to baseline. Since pre-dose values are known to be variable, and an isolated time-point may not accurately reflect the true baseline, the following baseline will be used for statistical analyses unless otherwise specified: the mean of available pre-dose values on the first day of each treatment cycle, i.e., the mean of pre-dose values at Visits 2, 4, 6 and 8, where the mean of the -60 and -30 minute value for each visit day is averaged and then the average of all visit means are averaged. Previous studies showed that this average baseline was more robust than the mean of pre-dose values at the start of each treatment period, or the mean of pre-dose values during Visit 2 alone, and that it gave more precise estimates of treatment means.

3.1.1 Primary Efficacy Endpoint

Primary Efficacy Endpoint Evaluated on Treatment Day 7 (Visits 3, 5, 7 and 9, following chronic dosing):

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

3.1.2 Secondary Efficacy Endpoints

Secondary Endpoints Evaluated on Treatment Day 1 (Visits 2, 4, 6 and 8) relative to baseline:

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

Secondary Endpoints Evaluated on Treatment Day 7 (Visits 3, 5, 7 and 9, following chronic dosing):

- Change from baseline in morning pre-dose trough FEV_1, (defined as the average of the 60 and 30 minute pre-dose values on Treatment Day 7 minus the baseline).
- Peak change from baseline in FEV_1 (defined as the change at the highest value of FEV_1 post-dose).

- Change from baseline for mean morning pre-dose trough IC (mean of 60 and 30 minute pre-dose assessments minus the baseline).
- Peak change from baseline in IC (mean of 1 and 2 hours post-dose assessments minus the baseline).
- Change from baseline in 12-hour post-dose trough FEV_1 (12-hour post-dose trough FEV_1 is defined as the mean of the FEV_1 assessments taken at 11.5 and 12 hours post-dose).
- Change from baseline in mean morning pre- and post-dose daily peak flow readings taken by subjects and recorded in subject diaries, during each treatment period (excluding reading taken pre- dose on Treatment Day 1).
- Change from baseline in mean evening pre- and post-dose daily peak flow readings taken by subjects and recorded in subject diaries, during each treatment period (Subjects taking Spiriva will perform a single evening assessment).
- Mean number of puffs of rescue medication recorded in subject diaries, during each treatment period and by treatment and number of days treated.

3.1.3 Other/Exploratory Endpoints

Exploratory Endpoints Evaluated on Treatment Day 7 (Visits 3, 5, 7 and 9, following chronic dosing):

- Peak expiratory flow rate (PEFR) morning pre-dose trough and Peak change from baseline on Day 7. PEFR AUC_{0-12} and change from baseline by post-dose time point. AUC will be normalized by dividing by time (12 hours) so that unit of AUC will be L.
- Forced vital capacity (FVC) morning pre-dose trough and Peak change from baseline on Day 7. FVC AUC_{0-12} and change from baseline by post-dose time point. AUC will be normalized by dividing by time (12 hours) so that the units of AUC will be L.
- Change from baseline for mean evening 12 hour post-dose trough IC (mean of 11.5 and 12 hours post-dose assessments minus the baseline).

3.2 Safety Endpoints

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

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

This is a randomized, double-blind (test products), chronic dosing (7 days), four-period, eight-treatment, incomplete block, cross-over, multi-center study to assess efficacy and safety of five doses of GFF MDI (18/9.6, 9/9.6, 4.6/9.6, 2.4/9.6 and 1.2/9.6 µg), one dose of FF MDI (9.6 µg), and one dose of GP MDI (18 µg) in subjects with moderate to severe COPD, compared with Spiriva (18 µg, open-label) as an active control.

This multi-center study will be conducted at approximately 16-20 sites, contributing approximately 8 to 10 subjects per site in the United States. Across these sites, it is planned that approximately 160 subjects with moderate to severe COPD will be randomized into the study to provide approximately 110 subjects to complete the study (see Study Flow Diagram). The entire study period is scheduled to take a maximum of 19 weeks for each individual subject (see Figure 1). The study is anticipated to run for approximately 9 months and should not exceed 18 months.

At the Screening Visit (Visit 1a), all subjects are to sign an informed consent form prior to the conduct of any screening assessments. 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 60 minutes following 4 puffs of Ventolin HFA will be assessed at Screening to characterize the subject population but will not be used to determine eligibility to participate in the study. Subjects who are not using a prohibited medication and meet all other entry criteria will return to the clinic at least 7 days (≥14 days if taking tiotropium) after screening for Visit 2 (Randomization).

Subjects will complete a COPD Assessment Test (CAT) at Screening. The CAT will be used to assess symptoms to characterize the subject population only and will not be used to determine eligibility to participate in the study.

A blinded study drug diary will be issued at the Screening Visit for use as a practice diary (Note: the blinded study drug diary is different from the **Spiriva diary,** see section 7.1.2). Site personnel will use the practice diary to assess the subject's compliance and understanding of how to use the diary. A sponsor-provided peak flow meter and appropriate training on the proper use of the device will be provided to the subject at the Screening Visit.

Subjects who meet all entry criteria but are using certain prohibited COPD medications (e.g., oral β_2 agonists, LABAs, corticosteroid/LABA combination products, phosphodiesterase inhibitors (e.g. theophylline, roflumilast), cromoglycate or nedocromil inhalers, leukotriene antagonists [e.g., zafirlukast, montelukast, zileuton], or tiotropium) will discontinue these medications for the duration of the trial and be switched to sponsor-provided Atrovent HFA (see Section 5.4).

In order to allow for an adequate washout of previous maintenance medications, subjects will undergo a washout period of at least 7 days (at least 14 days if taking tiotropium or

phosphodiesterase inhibitors), but not greater than 28 days duration prior to returning to the clinic for Visit 2 (Randomization).

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

At Visit 2 (Randomization Visit; Treatment [Rx] 1, Day 1), subjects will return to the clinic before 10:00 am. Subjects who continue to meet entry inclusion/exclusion criteria and remain eligible for participation in the study will be randomized into one of the pre-defined treatment sequences.

Subjects will be randomized to a treatment sequence in order to receive 4 treatments (all possible treatment sequences to which a subject can be randomized are shown in Appendix 8). Each sequence will include exactly 4 of the 8 treatment groups [GFF MDI (18/9.6, 9/9.6, 4.6/9.6, 2.4/9.6 and 1.2/9.6 µg), FF MDI (9.6 µg), GP MDI (18 µg) and Spiriva (18 µg)] included in this study. The subject, clinical site personnel and Pearl Therapeutics will be unaware of the treatment dose assigned to a subject when the treatment is GFF MDI, GP MDI or FF MDI. If a subject is assigned GFF MDI, GP MDI or FF MDI, it will not be possible to differentiate between these three treatments since they will be identical in all aspects. Blinding with regard to the active comparator (Spiriva) will not be performed in order to avoid 'dummy/dummy' allocations

Randomization will be centralized, through the use of an IWRS (Interactive Web Response System). GFF MDI, GP MDI and FF MDI will be administered twice daily; Spiriva will be administered once per day. Each of the 4 treatments will be administered for 7 days with a washout period of at least 7 days (up to 21 days) in between treatments.

During Visit 2 (Rx 1, Day 1), subjects will be dispensed study medication and will administer their first dose at the clinic under site personnel supervision. Before sites dispense first dose and prior to any study procedures being performed, site staff must confirm the subject met all protocol specific requirements and ensure adequate washout (6 hours or longer) of short acting bronchodilators.

Subjects will be required to remain at the clinic until completion of all protocol-defined assessments up to and including 2-hour post-dose time point (see Table 5). Subjects will then be discharged from the clinic and will continue to administer study medication for 1 week at home until Visit 3 (Rx 1, Day 7). Subjects will receive a diary in which they will be asked to maintain a daily record of their study medication dosing, rescue medication use, and collection of daily peak flow rates using a sponsor-provided portable peak flow meter while in clinic and at home.

At Visit 3 (Rx 1, Day 7) the subject will return to the clinic at approximately the same time as Visit 2 (± 2 hours) but not to exceed 10:00 AM. On Day 7, Site Personnel must review diary data prior to dosing study medication in the clinic and will return the diary to subject for

recording pre- and 30 minute post-dose peak flow values and time of dosing while in the clinic (See Table 6). Site Personnel will collect completed subject diary after subject has recorded 30 minute post-dose PEFR. Subjects will receive their last dose of Rx 1 study medication that morning under site personnel supervision and will be required to remain at the clinic until completion of all protocol-defined assessments up to and including the 12-hour post-dose time point (see Table 6). Following discharge, subjects will undergo a study medication washout period of at least 1 week but no more than 3 weeks duration, on sponsor-provided Atrovent HFA MDI, prior to initiating the next treatment in their assigned treatment sequence.

Following the washout period, subjects will repeat a similar pattern of visits and assessments for the next three treatments in their assigned sequence, as follows:

Visit 4 (Rx 2, Day 1): Subjects will be dispensed study medication and will administer their first dose of Rx 2 study medication in clinic under site personnel supervision, undergo all protocol-defined assessments up to and including 2-hour post-dose assessments (see Table 5), be discharged and continue daily administration until Visit 5.

Visit 5 (Rx 2, Day 7): Subjects will administer their last dose of Rx 2 study medication in clinic under site personnel supervision, undergo all protocol-defined assessments up to and including 12-hour post-dose assessments (see Table 6), be discharged and undergo washout for at least 1 week (up to 3 weeks) on sponsor-provided Atrovent HFA MDI.

Visit 6 (Rx 3, Day 1): Subjects will be dispensed study medication and will administer their first dose of Rx 3 study medication in clinic under site personnel supervision, undergo all protocol-defined assessments up to and including 2-hour post-dose assessments (see Table 5), be discharged and continue daily administration until Visit 7.

Visit 7 (Rx 3, Day 7): Subjects will administer their last dose of Rx 3 study medication in clinic under site personnel supervision, undergo all protocol-defined assessments up to and including 12-hour post-dose assessments (see Table 6), be discharged and undergo washout for at least 1 week (up to 3 weeks) on sponsor-provided Atrovent HFA MDI.

Visit 8 (Rx 4, Day 1): Subjects will be dispensed study medication and will administer their first dose of Rx 4 study medication in clinic under site personnel supervision, undergo all protocol-defined assessments up to and including 2-hour post-dose assessments (see Table 5), be discharged and continue daily administration until Visit 9.

Visit 9 (Rx 4, Day 7): Subjects will administer their last dose of Rx 4 study medication in clinic under site personnel supervision, undergo all protocol-defined assessments up to and including 12-hour post-dose assessments (see Table 6), be discharged and return to pre-study or appropriate inhaled COPD maintenance medication(s).

Visit 10 will serve as the final/follow-up visit. Subjects will complete all post-study assessments, including a final physical examination and recording of any AEs, and will then be discharged from the study.

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

During Treatment Visits 2 through 9 (in clinic):

- At the start of each treatment visit, prior to any study procedures being performed, site personnel must confirm the subject withheld all COPD medications, including study medication, rescue medications (e.g. albuterol), and ICS for at least 6 hours, by confirming the last time of dosing for all COPD medication(s). Note: Subjects who inadvertently took COPD medication(s) within 6 hours of the start of study procedures must be rescheduled as soon as is practical but within the specified visit window. In addition, before the in-clinic dose is administered, the site must confirm the subject met all other protocol specified requirements (e.g. Reproducibility).
- Subjects must not ingest xanthine-containing foods and beverages for at least 6 hours prior to each study visit and for the duration of each study visit and 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.
- Subjects will be required to return to the clinic at approximately the same time as Visit 2 for all treatment visits (± 2 hours) but not to exceed 10:00 AM and will be required to remain at the clinic until completion of all protocol-defined assessments.
- Site personnel will instruct subjects not to take any COPD medications, without site personnel permission, during a visit until all study procedures have been completed and the subject is discharged. Site personnel should take every precaution to prevent use of COPD medications during test day. Site personnel may request the subject to surrender all COPD medications prior to start of the visit before performing any study procedures and return to subject at end of the visit when all study procedures are completed.
- If a subject is experiencing severe symptoms and requires Ventolin HFA for relief of COPD symptoms at any time during a test day, site personnel must note the time and justification of use in the subject's chart and all subsequent spirometry assessments should be stopped. However, safety asssessments should be continued at the discretion of the Investigator.

At Visits 1, 2, 4, 6, and 8, subjects will receive a diary in which they will be asked to maintain a daily record of their study medication dosing, rescue medication use, and collection of daily peak flow rates using a sponsor-provided portable peak flow meter during the treatment period while in the clinic and at home. **Note:** Diary data will not be collected during the washout periods (between Visits 3 and 4, Visits 5 and 6, and Visit 7 and 8).

At all treatment visits (Visits 2-9), subjects will record pre- and 30 minute post-dose peak flow values and the time of study medication dosing in their diary while in the clinic (See Section 7.1.4).

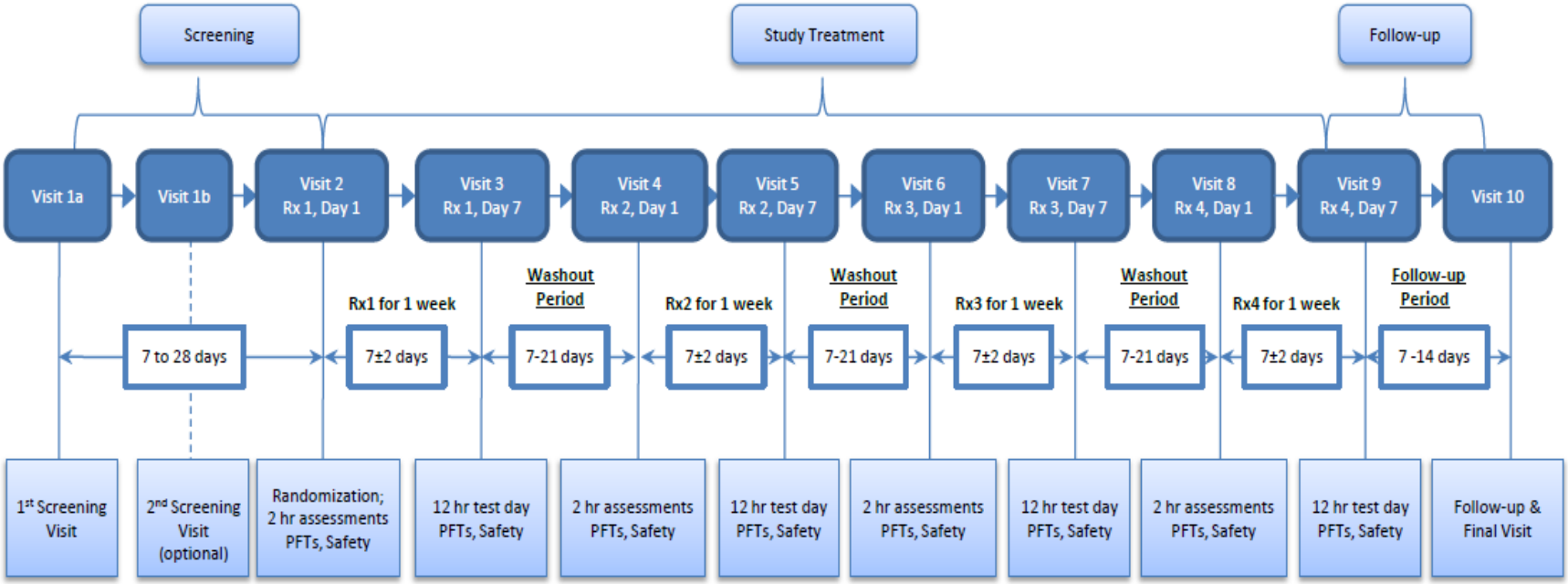
During the treatment periods (between Visits 2 and 3, Visits 4 and 5, Visits 6 and 7 and Visits 8 and 9), subjects will be permitted to use sponsor-provided Ventolin HFA on an as needed basis for relief of COPD symptoms.

During the washout period when subjects are not taking study drug (between Visits 3 and 4, Visits 5 and 6 and Visits 7 and 8), subjects will use the sponsor-provided short-acting bronchodilator (Atrovent HFA) administered QID and may use rescue albuterol as needed.

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

A Study Flow Diagram is displayed in Figure 1.

Figure 1. Study Flow Diagram



PFT = pulmonary function test, Rx = treatment

5 STUDY POPULATION SELECTION AND WITHDRAWAL CRITERIA

5.1 Inclusion Criteria

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

1. Give their signed written informed consent to participate.
2. Are between 40-80 years of age at Visit 1.
3. A female is eligible to enter and participate in the study if she is of:
   - Non-child bearing potential (i.e., physiologically incapable of becoming pregnant, including any female who is 2 years post-menopausal); or
   - Child bearing potential, has a negative serum pregnancy test at screening, and agrees to one of the following acceptable contraceptive methods used consistently and correctly (i.e., in accordance with the approved product label and the instructions of the physician for the duration of the study - Screening until 14 days after Visit 10):
     - Complete abstinence from intercourse from screening until 14 days after Visit 10 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: Subjects with an established clinical history of COPD as defined by the American Thoracic Society (ATS)/European Respiratory Society (ERS) (Celli, 2004) characterized by:
   - Airflow limitation that is not fully reversible. Progressive airflow limitation associated with an abnormal inflammatory response of the lungs to noxious particles or gases, primarily caused by cigarette smoking.

5. Tobacco Use: Current or former smokers with a history of at least 10 pack-years of cigarette smoking. [Number of pack years = (number of cigarettes per day / 20) x number of years smoked (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: Subjects with an established clinical history of COPD and severity defined as:
   - Pre- and post-bronchodilator FEV_1/FVC ratio of <70%.
   - At Screening (Visit 1), post-bronchodilator FEV_1 must be greater than or equal to 30% and <80% predicted normal value calculated using the Third National Health and Nutrition Examination Survey (NHANES III) reference equations, and must also be greater than or equal to 750 mL.
   - At Baseline (Visit 2), pre-bronchodilator FEV_1 must be <80% predicted normal value calculated using NHANES III reference equations.
7. Subject 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 MDI with or without ICS for maintenance therapy of COPD and as needed rescue albuterol 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.
9. Chest X-ray or CT scan within 6 months prior to Screening must be acceptable to the investigator. Subjects who have a chest X-ray (or CT scan) that reveals clinically significant abnormalities not believed to be due to the presence of COPD should not be enrolled. 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).
10. Compliance: Subjects must be willing to remain at the study center as required per protocol to complete all visit assessments.

5.2 Exclusion Criteria

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

1. Pregnancy: Women who are pregnant or lactating.
2. Asthma: Subjects who have a current diagnosis of asthma.
3. Alpha-1 Antitrypsin Deficiency: Subjects who have alpha-1 antitrypsin deficiency as the cause of COPD.
4. Other Respiratory Disorders: Subjects who have other active pulmonary disease such as active tuberculosis, lung cancer, bronchiectasis, sarcoidosis, lung fibrosis, primary pulmonary hypertension, interstitial lung disease and sleep apnea. Allergic rhinitis is not exclusionary.
5. Lung Resection: Subjects who have undergone lung volume reduction surgery or lobectomy within 1 year of visit 1.

6. Use of nocturnal positive pressure (e.g., continuous positive airway pressure or bi-level positive airway pressure).
7. Hospitalization: Subjects who have been hospitalized due to poorly controlled COPD within 3 months of Screening (Visit 1).
8. Poorly Controlled COPD: Subjects who have poorly controlled COPD, defined as acute worsening of COPD that requires treatment with corticosteroids or antibiotics in the 6-week interval prior to Screening (Visit 1), or between Screening and Visit 2.
9. Lower Respiratory Tract Infection: Subjects who had lower respiratory tract infections that required antibiotics within 6 weeks prior to Screening (Visit 1).
10. Spirometry Performance: Subjects who cannot perform acceptable spirometry (at least 3 acceptable flow-volume curves with 2 or more meeting ATS reproducibility criteria).
11. Subjects with uncontrolled glaucoma. Subjects with previously diagnosed glaucoma who have intraocular pressure controlled with medication(s) are eligible. All medications approved for control of intraocular pressures are allowed including topical ophthalmic non-selective beta-blockers such as betaxolol, carteolol, levobunolol, metipranolol, timolol.
12. Subjects with symptomatic prostatic hypertrophy (if treated and asymptomatic, the subject is eligible for enrollment).
13. Other Diseases: Subjects who have clinically significant medical conditions , as deemed by the Investigator including but not limited to cardiovascular, neurological, psychiatric, hepatic, gastrointestinal, renal (calculated creatinine clearance ≤ 50 mL/minute by the CKD-EPI formula), immunological, endocrine (including uncontrolled diabetes, hypokalemia or thyroid disease), hematological medical problems, and urinary retention problems [including bladder-neck obstruction (e.g., difficulty passing urine, painful urination]). Significant is defined as any disease that, in the opinion of the investigator, would put the safety of the subject at risk through study participation or would affect the efficacy analysis if the disease/condition exacerbated during the study.
14. Subjects with documented myocardial infarction within a year from screening visit are to be excluded. Subjects with a recent history of acute coronary syndrome, or who have undergone percutaneous coronary intervention or coronary artery bypass graft within three months of screening visit are to be excluded.
15. Clinically significant abnormal ECG: Subjects who in the opinion of the investigator have a clinically significant abnormal 12-lead ECG. A clinically significant abnormal ECG is defined as (but not limited to) any of the following:

    - Clinically significant conduction abnormalities (e.g., left bundle branch block, Wolff-Parkinson-White syndrome or evidence of second degree (Mobitz Type II) or third degree atrioventricular (AV) block)
    - Clinically significant arrhythmias (e.g., atrial fibrillation, ventricular tachycardia)
    - A mean corrected QT interval using Fridericia's correction factor (QTcF) value at screening >450 ms for males and >470 ms for females or an ECG that is not suitable for QT measurements (e.g., poorly defined termination of the T wave).

- Bradycardia with rate <45 bpm.
- Pathological Q waves of 1 year or less
- ST-T wave abnormalities (excluding non-specific ST-T wave abnormalities)

16. Uncontrolled Hypertension: Subjects who, in the opinion of the investigator, have clinically significant uncontrolled hypertension.
17. Subject with abnormal liver function tests defined as AST, ALT, alkaline phosphatase or total bilirubin ≥ 1.5 times upper limit of normal on repeat testing.
18. Cancer: Subjects who have cancer that has not been in complete remission for at least 5 years. Note: Subjects with squamous cell carcinoma and basal cell carcinoma of the skin that have been resected for cure are not considered exclusionary. Subjects with localized prostate cancer that in the opinion of the investigator has been adequately worked up, is clinically controlled and the subject's participation in the study would not represent a safety concern, are eligible
19. Drug Allergy: Subjects who have a history of hypersensitivity to any β_2-agonists, glycopyrrolate or other muscarinic anticholinergics, lactose/milk protein or any component of the MDI or DPI.
20. Substance Abuse: Subjects with a known or suspected history of alcohol or drug abuse within the last 2-year period prior to Screening.
21. Medication Prior to Spirometry: Subjects who are medically unable to withhold their short-acting bronchodilators for the 6-hour period required prior to spirometry testing at each study visit will be excluded.
22. Prohibited COPD Medications: Subjects 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: Subjects requiring chronic maintenance therapy with oral corticosteroids are excluded from participation in this study.
    - 6 weeks: antibiotics administered for a COPD exacerbation
    - 4 weeks: use of ICS at a dose of >1,000 µg/day of fluticasone propionate or equivalent within 30 days of Visit 1. Initiation or discontinuation of ICS within 30 days of Visit 1
23. 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).
- Systemic calcineurin inhibitors, systemic antifungal agents, protease inhibitors and cimetidine.
- Note: Benzodiazepines are not exclusionary

24. Oxygen: Subjects 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.
25. Pulmonary Rehabilitation: Subjects 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. Subjects who are in the maintenance phase of a Pulmonary Rehabilitation program are not to be excluded.
26. Non-compliance: Subjects 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.
27. 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.
28. Questionable Validity of Consent: Subjects with a history of psychiatric disease, intellectual deficiency, poor motivation, substance abuse (including drug and alcohol), or other conditions that will limit the validity of informed consent to participate in the study.
29. 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.
30. A subject who requires the use of a spacer device to compensate for poor hand-to-breath coordination with a MDI.
31. Subjects who were previously enrolled in Pearl Therapeutics PT001 (GP MDI), PT005 (FF MDI) and/or PT003 (GFF MDI) studies.

5.3 Subject Identification

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

5.4 Prior, Concomitant, and Prohibited Medications

All prescription and over-the-counter (OTC) medications taken by the subject 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. Subjects should also be instructed to contact the investigator if they develop any illnesses.

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

Prohibited COPD Medications:

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)

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

- Subjects taking the above listed COPD medications at Screening (Visit 1) will discontinue these medications for the duration of the trial and be switched to sponsor-provided Atrovent HFA MDI administered QID.
- Subjects 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 must have been on the ICS component for at least 4 weeks prior to screening and maintained on a stable dose for at least 4 weeks prior to screening. These subjects will be switched to the corresponding dose of fluticasone, mometasone or budesonide administered as a single agent BID, with sponsor-provided Atrovent HFA MDI administered QID.
- Subjects receiving a maintenance dose of an ICS that is not administered as a fixed dose combination together with a LABA will be permitted to continue the ICS provided they have been maintained on a stable dose for at least 4 weeks prior to screening.

- All subjects 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 sponsor-provided Atrovent HFA MDI administered QID.

Note: During the screening phase and washout periods (i.e., between Visits 1 and 2, Visit 3 and 4, Visit 5 and 6, and Visit 7 and 8), sponsor-provided Atrovent HFA MDI is to be used as maintenance medication administered QID, but must be withheld for at least 6 hours before each study visit.

Note: During study treatment (i.e., between Visits 2 and 3, Visits 4 and 5, Visits 6 and 7, and Visits 8 and 9), subjects will receive study drug and are allowed sponsor provided Ventolin HFA to be used as needed for relief of symptoms.

5.5 Other Restrictions, Illicit Drugs or Drugs of Abuse

Illicit drugs or drugs of abuse will not be allowed from the start of Screening (Visit 1) to the end of Visit 10 or to whenever the subject discontinues the study. If any illicit drugs or drugs of abuse are used by the subject during the study, the dates of use and the amount will be documented.

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

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

Subjects will be required to refrain from **smoking** for at least 4 hours prior to each study visit and throughout the duration of each study visit. 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 Subject 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 subjects, to assign drug to subjects and to manage the distribution of clinical supplies. Clinical supplies will be packaged according to a component schedule generated by the Sponsor. Each person accessing the IWRS system must be assigned an individual unique PIN. They must use only their assigned PIN to access the system and they must not share their assigned PIN with anyone.

6.2 Product Descriptions

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

Table 1. Product Descriptions

Product Name & Potency	Dosage Form	Comments
Glycopyrrolate/Formoterol Fumarate 18/9.6 µg ex-actuator	MDI	Taken as 2 inhalations of the 9/4.8 µg per actuation strength MDI
Glycopyrrolate/Formoterol Fumarate 9/9.6 µg ex-actuator	MDI	Taken as 2 inhalations of the 4.5/4.8 µg per actuation strength MDI
Glycopyrrolate/Formoterol Fumarate 4.6/9.6 µg ex-actuator	MDI	Taken as 2 inhalations of the 2.3/4.8 µg per actuation strength MDI
Glycopyrrolate/Formoterol Fumarate 2.4/9.6 µg ex-actuator	MDI	Taken as 2 inhalations of the 1.2/4.8 µg per actuation strength MDI
Glycopyrrolate/Formoterol Fumarate 1.2/9.6 µg ex-actuator	MDI	Taken as 2 inhalations of the 0.6/4.8 µg per actuation strength MDI
Glycopyrrolate 18 µg ex-actuator	MDI	Taken as 2 inhalations of the 9 µg per actuation strength MDI
Formoterol Fumarate 9.6 µg ex-actuator	MDI	Taken as 2 inhalations of the 4.8 µg per actuation strength MDI
Tiotropium bromide inhalation powder† 18 µg	Dry Powder Inhaler (DPI)	US source: (Spiriva® delivered via the Handihaler®) *Supplies are open-label.*
Albuterol Sulfate inhalation aerosol§ 90 µg	MDI	US source: (Ventolin® HFA) Each inhalation contains 108 µg corresponding to 90 µg albuterol base from the mouthpiece *Supplies are open-label.*
Ipratropium Bromide HFA inhalation aerosol† 34 µg ex-actuator*	MDI	US source: (Atrovent HFA) Taken as 2 inhalations of the 17 µg per actuation strength MDI *Supplies are open-label.*

† Active controls
§ Rescue medication and reversibility testing.
* Used for COPD maintenance therapy during screening and washout periods.
Note: All study drugs will be administered by oral inhalation.

For open-label Spiriva Handihaler (tiotropium bromide, 18 µg), bulk commercial DPIs will be provided. Manufacturer's instructions for study drug administration will be provided.

For open-label Atrovent HFA (ipratropium bromide, 34 µg), bulk commercial MDIs 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 MDIs 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 Pearl Therapeutics as summarized in

Table 2. Spiriva supplies will be supplied as open-label DPI. Atrovent HFA and Ventolin HFA supplies will be supplied as open-label MDIs.

Table 2. Packaging of Clinical Supplies

Product Name and Potency	Product Strength	Fill Count	Dosing Instructions
GFF MDI 18/9.6 µg ex-actuator	GFF MDI 9/4.8 µg per actuation	1 MDI 120 actuations	Take 2 inhalations as directed in the morning and evening.
GFF MDI 9/9.6 µg ex-actuator	GFF MDI 4.5/4.8 µg per actuation	1 MDI 120 actuations	Take 2 inhalations as directed in the morning and evening.
GFF MDI 4.6/9.6 µg ex-actuator	GFF MDI 2.3/4.8 µg per actuation	1 MDI 120 actuations	Take 2 inhalations as directed in the morning and evening.
GFF MDI 2.4/9.6 µg ex-actuator	GFF MDI 1.2/4.8 µg per actuation	1 MDI 120 actuations	Take 2 inhalations as directed in the morning and evening
GFF MDI 1.2/9.6 µg ex-actuator	GFF MDI 0.6/4.8 µg per actuation	1 MDI 120 actuations	Take 2 inhalations as directed in the morning and evening
GP MDI 18 µg ex-actuator	GP MDI 9 µg per actuation	1 MDI 120 actuations	Take 2 inhalations as directed in the morning and evening
FF MDI 9.6 µg ex-actuator	FF MDI 4.8 µg per actuation	1 MDI 120 actuations	Take 2 inhalations as directed in the morning and evening
Tiotropium Bromide inhalation powder[†] 18 µg ex-actuator[†]	Tiotropium Bromide inhalation powder[†] 18 µg	N/A	Take one capsule as directed in the morning.
Albuterol Sulfate inhalation aerosol[§] 90 µg ex-actuator	US source: (Ventolin HFA) Each inhalation contains 108 µg corresponding to 90 µg albuterol base per actuation	1 MDI 60 or 200 actuations	Use only as directed.
Ipratropium Bromide HFA inhalation aerosol 34 µg ex-actuator[*]	Ipratropium bromide inhalation aerosol 34 µg ex-actuator*	1 MDI 200 actuations	Take two inhalations as directed four times a day.

[†] Active control
[§] Rescue medication and reversibility testing.
*Used for COPD maintenance therapy during screening and washout periods.

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

Open-label Supplies: Open-label Spiriva (18 µg) will be provided as individually labeled DPIs with bulk commercial blister packs containing individually sealed capsules. The foil pouch will be labeled with a two-part label.

Open-label Atrovent HFA and Ventolin HFA will be provided as individually labeled MDIs. Each MDI will contain a single label. The foil pouch will be labeled with a two-part 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 will be packaged in boxes as outlined in Table 3. Open-label Spiriva, 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
Spiriva HandiHaler	1 DPI Plus Blister Packs
Atrovent HFA	1 MDI
Ventolin HFA	1 MDI

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

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

6.5 Unblinding Procedures

The IWRS should be used in order to unblind subjects 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.

Spiriva supplies: Store at 25ºC (77°F). Brief storage between between 59° and 86°F (15° and 30°C) is permitted. Do not expose the capsules to extreme temperatures or moisture. Avoid freezing. Do not store capsules in the HandiHaler device. Once the blister is opened, the capsule should be used immediately.

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.

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.

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, GP and FF MDIs

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

All 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 subject treatment area. Since the MDI is primed in a separate room before dosing, there is a possibility that there may be a delay between priming and dosing, and therefore to ensure consistency in the administration for all subjects, the MDIs are to be gently shaken (5-10 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. Subjects will be dispensed the MDI and instructed to continue taking study medication twice daily, 2 puffs in the morning and 2 puffs in the evening approximately 12 hours apart, until subject returns to the clinic. The MDI should be stored at room temperature by the subject, avoiding temperature extremes and storage in direct sunlight. See Appendix 3 for instructions on the administration of GFF, GP and FF MDIs.

Spiriva Handihaler (tiotropium bromide)

Spiriva Handihaler device and blister packs 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 subject number and treatment visit number on each of the two-part labels. The 'tear-off' part of the label is to be placed onto the IWRS confirmation report.

In addition, bulk commercial blister packs containing individually sealed tiotropium bromide (18 μg) capsules will be provided for emergency resupply needs.

On Treatment Day 1, if the study day treatment box is opened and contains a Spiriva Handihaler device with accompanying blister packs, then one of the capsules will be used for the in clinic dosing.

Subjects will be dispensed the Handihaler device and blister pack(s) containing the remaining tiotropium bromide 18 µg capsules to continue taking study medication once a day until the subject returns to the clinic. The contents of 1 capsule will be inhaled in the morning approximately 24 hours apart. See Appendix 4 for the manufacturer's instructions on the administration of Tiotropium.

Atrovent HFA MDI (ipratropium bromide)

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

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

As needed, subjects will be dispensed the MDI for COPD maintenance therapy during screening (between Visit 1 and 2) and washout periods (between Visits 3 and 4, Visits 5 and 6, Visits 7 and 8) per the manufacturer's instruction, 2 puffs with each administration four times a day, approximately 6 hours apart. The MDI should be stored at room temperature by the subject, avoiding temperature extremes and storage in direct sunlight. See Appendix 5 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 subject. Ventolin HFA should be primed per manufacturer's instructions prior to dispensing to subject. See Appendix 4 for the manufacturer's instructions on the administration of Ventolin HFA. Study personnel will record number on the dose counter at the time of dispensing (following priming) and upon return.

6.8 Drug Accountability/Return of Clinical Supplies

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

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

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

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

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

7 STUDY PROCEDURES

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

All assessments during Visits 2 through 9 will be conducted in the following order: dry mouth and tremor assessments, vital signs, ECGs, clinical laboratory assessments, and spirometry (IC, when conducted should be obtained prior to all other spirometry assessments).

7.1 Efficacy Assessments

Both forced expiratory spirometry for derivation of FEV_1, FVC and PEFR, and Slow Vital Capacity (SVC) maneuvers for IC determination will be assessed using a spirometer that meets or exceeds minimum performance recommendations of the ATS (See Appendix 1).

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

On Day 1 of each treatment period (Visits 2, 4, 6, and 8), spirometry will be conducted 60 minutes and 30 minutes prior to study drug administration. The average of these two assessments will be used to establish test-day baseline FEV_1, FVC and PEFR. Following study drug administration, spirometry will be obtained at 15 and 30 minutes, and 1 and 2 hours post-dosing of study drug.

At Visits 4, 6 and 8 (Day1 of Rx 2, Rx 3 and Rx 4 respectively) subjects must meet the Reproducibility Criteria (see below) prior to dosing.

<u>Reproducibility Criteria:</u> The baseline FEV_1 at Visits 4, 6 and 8 ideally will be within ±15% and/or 150 ml of the baseline FEV_1 obtained at the Randomization Visit (Visit 2). Provided reproducibility is within ±15% and/or 150 mL of the baseline FEV_1 obtained at the Randomization Visit (Visit 2) the subject will be permitted to proceed. If on initial assessment the subject fails to meet the reproducibility criteria, but the 30 minute pre-dose assessment is within 20% of the baseline FEV_1 obtained at Randomization, another assessment may be conducted 30 minutes later. If the last 2 assessments meet the reproducibility requirements (i.e. within ±15% and/or 150 mL), the initial 60 minute pre-dose assessment will <u>not</u> be used and the last 2 assessments will be used to establish the eligibility criteria. If the test day FEV_1 is not within ± 15% or 150 mL, the visit may be rescheduled (for a maximum of 3 attempts) at the investigator's discretion (e.g., within one week), or the subject discontinued.

On Day 7 of each treatment period (Visits 3, 5, 7, and 9), spirometry will be conducted 60 and 30 minutes prior to study drug administration. Following study drug administration, spirometry will be obtained at 15 and 30 minutes, and 1, 2, 4, 6, 8, 10, 11.5, and 12 hours post-dosing of study drug. Specifically, FEV_1, FVC and PEFR data will be analyzed for primary and secondary assessments.

On Day 1 of each treatment period (Visits 2, 4, 6, and 8), IC assessments will be obtained at 60 and 30 minutes prior to study drug and at 1 and 2 hours after study drug

On Day 7 of each treatment period (Visits 3, 5, 7, and 9), IC assessments will be obtained at 60 and 30 minutes prior to study drug and at 1, 2, 11.5, and 12 hours after study drug. IC assessments are to precede spirometry assessments.

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

7.1.1 Pulmonary Function Tests

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

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

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

7.1.2 Subject Diary

The study coordinator will be responsible for explaining to the subject the proper methods for completing the diary. The diary contains questions concerning actual time of dosing, rescue Ventolin HFA use, and collection of home peak flow measurements using a sponsor-provided home peak flow meter. Two types of diaries will be provided – one for use during Spiriva® (18 μg) study treatment and the other for use with all other treatments.

Beginning with the Screening Visit (Visit 1) and at Visits 2, 4, 6 and 8, the subject will be given a diary in which they will be asked to maintain a daily record of their study medication dosing, rescue medication use, and collection of daily peak flow rates using a sponsor-provided portable peak flow meter during the treatment period while in the clinic and at home. **Note:** Diary data will not be collected during the washout periods (between Visits 3 and 4, Visits 5 and 6, and Visit 7 and 8).

Before giving the diary to the subject, the study coordinator will be responsible for entering the subject's identification (screening number [Visit 1] and randomization number [Visits 2, 4, 6 and 8]), and dates of the week(s) the diary is to be completed.

A blinded study drug diary will be issued at the Screening Visit for use as a practice diary (Note: this is not the same as a **Spiriva** Diary). Site personnel will use the practice diary to assess the subject's compliance and understanding of how to use the diary.

At or prior to Visit 2 (randomization), subjects should demonstrate acceptable use of the diary by recording the time of dosing for Atrovent HFA, rescue Ventolin HFA use, and home peak flow measurements data on the diary provided at screening on at least 4 different days. Subjects who fail to demonstrate proper diary use must be retrained prior to randomization.

On Day 1 of each treatment period (Visits 2, 4, 6 and 8), site personnel will provide the subject with an appropriate diary based on their assigned treatment (i.e. Spiriva or blinded study drug).

On Day 7 (Visits 3, 5, 7 and 9), Site Personnel must review diary data prior to dosing study medication in the clinic and will return the diary to subject for recording pre- and 30 minute post-dose home peak flow values and time of dosing while in the clinic. Site Personnel will collect the completed subject diary after the subject has recorded 30 minute post-dose PEFR on Day 7.

Note: At all treatment visits (Visits 2-9), subjects will record pre- and 30 minute post-dose home peak flow values and the time of study medication dosing in their diary while in the clinic.

The study coordinator will be responsible for reviewing the diary for completeness and accuracy with the subject. All data fields should be completed by the subject. The subject 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 subject**, not the study coordinator, should make the corrections. The subject should draw a single line through the error and initial and date all corrections. The subject 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 subject binder*.

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

7.1.3 Rescue Ventolin HFA Use

The subject will record the total number of "puffs" of rescue Ventolin HFA used on a daily basis. The number of "puffs" of rescue Ventolin HFA to be recorded is the number of actuations of the canister. For example, when rescue Ventolin HFA is required and 2 actuations are inhaled, this should be recorded as 2 "puffs." In the event the subject requires 4 actuations, this should be recorded as 4 "puffs." Subjects requiring more than 8 puffs per day on 3 or more consecutive days with worsening symptoms should contact the site.

7.1.4 Home Peak Expiratory Flow Rate

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

The peak flow meter will be used by all subjects for home measurements of pre- and post-dose morning and evening assessments. At each study visit, the investigator will review the PEFR readings and any findings will be discussed with the subject and clinical relevance determined. Subjects will bring their peak flow meter to the clinic at each visit.

At each treatment visit (Visits 2-9) subject will measure, in clinic, PEFR immediately before and 30 minutes after dosing with study medication and must record pre and post peak flow values and time of dosing in their diary. Note: The in clinic 30 minute post-dose PEFR at each treatment visit (Visits 2-9) (Days 1 and 7 of each treatment period) should be obtained after spirometry assessments allowing enough time for the subject to recover from the pulmonary function test maneuvers. The subject will be instructed to forcefully exhale from total lung capacity 3 times into the peak flow meter and confirm the collection of PEFR measurements on the diary card. These PEFR measurements will continue from day 1 to day 7 of each treatment period.

Subjects taking double-blind study medication will perform peak flow home measurements immediately before and 30 minutes after dosing with study medication in the morning and in the evening.

Subjects in the open-label Spiriva cohort will perform peak flow home measurements immediately before and 30 minutes after dosing with study medication in the morning. A single PEFR assessment will be performed in the evening approximately 12 hours after the morning dosing, preferably without influence of rescue albuterol.

7.1.5 Medication Compliance

Time of dosing with study medication will be recorded in the subject 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.

7.1.6 COPD Assessment Test (CAT)

The COPD Assessment Test (CAT, http://www.catestonline.org/) is a short and simple, self-administered questionnaire designed to assess the condition of subjects and overall impact of COPD. It has been proven that the CAT has good repeatability and discriminative properties which suggest that it is sensitive to treatment effects at a group level. Since the CAT is designed to assess the impact of COPD on the subject by measuring overall impairment, it has better correlations with other instruments, such as the MRC (Medical Research Council) dyspnea scale, St George's Respiratory Questionnaire (SGRQ),and the 6-minute walk test. However, it does not correlate well with FEV_1. The CAT is the only validated, short and simple assessment test which can provide a holistic measure of the impact of COPD on subjects.

Subjects will complete a CAT at the Screening visit (see Appendix 7). CAT will be used to assess symptoms to characterize the subject population only and will not be used to determine eligibility to participate in the study.

7.2 Safety Assessments

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

7.2.1 Medical/Surgical History and Physical Examination

Medical history will be taken at Screening (Visit 1) and updated at the Randomization Visit (Visit 2). History of COPD exacerbation within 12 months of screening will also be collected. A complete physical examination will be performed at Screening and the Final/Follow-up Visit (Visit 10). A complete physical examination will include the following: general appearance, skin, head, eyes, ears, nose, throat, neck (including thyroid), lymph nodes, chest, heart, abdomen, extremities, and nervous system (including assessment

of tremor pre-albuterol use). Weight, assessed in ordinary indoor clothing with shoes off, and height (Screening) will be recorded at the specified visits.

7.2.2 Vital Sign Measurements

Heart rate and systolic and diastolic blood pressure ('vital signs') will be assessed at each visit; assessments will be obtained after being supine for 5 minutes for the first 2 hours after study drug and thereafter measurements may be obtained in the supine or seated position. If in the opinion of the investigator a clinically significant vital sign change occurs, then the measurement will be repeated at medically appropriate intervals until the value returns to within an acceptable range**.** Refer to Section 7.3 for specific criteria for heart rate and systolic and diastolic blood pressure readings that prompt subjects to be discontinued from the study.

Systolic and diastolic blood pressures and heart rate will be obtained at the same times as indicated for spirometry (i.e., 60 and 30 minutes prior to study drug (all visits); 15 and 30 minutes, and 1 and 2 hours after study drug [Visits 2, 4, 6 and 8]; 15 and 30 minutes, and 1, 2, 4, 6, 8, 10, 11.5, and 12 hours after study drug on Day 7 of each treatment period [Visits 3, 5, 7 and 9]) Temperature will be obtained at Screening and at pre-dose and 2 hours post-dose on all test days and will not be repeated at subsequent time points unless clinically indicated.

7.2.3 12-Lead Electrocardiogram (ECG)

An ECG will be obtained at Screening. At Visits 2, 4, 6 and 8 (on Day 1), ECGs will be obtained between 1 to 2 hours and 30 minutes to 1 hour prior to study drug and at 15 and 30 minutes, and 1, and 2 hours after study drug. On Day 7 of each treatment period (Visits 3, 5, 7 and 9), ECGs will be obtained between 1 to 2 hours and 30 minutes to 1 hour prior to study drug and at 15 and 30 minutes, and 1, 2, 4, and 12 hours after study drug.

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

The ECG parameters that will be assessed include heart rate, RR interval, PR interval, QRS axis, QRS interval, and QT/QTcF (Fridericia's Formula) interval.

QT intervals and calculated QTcF (Fridericia's Formula) intervals will be reviewed and checked for gross inaccuracies by the investigator or designated ECG reviewer. If the calculated QTcF intervals are greater than 500 msec, and have increased by 60 msec or more

over baseline value, the investigator will make a determination on the suitability of continuing the subject in the study. Refer to Section 7.3 for specific criteria for QTcF that prompt subjects to be discontinued from the study. If QTcF interval prolongation exceeding these limits is verified during treatment, the subject's medical background should be examined closely for risk factors that may have contributed to the event, including genotyping for hereditary long QT syndromes, if appropriate.

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

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

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

7.2.4 Clinical Laboratory Tests

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

On Day 1 of each treatment period (Visits 2, 4, 6 and 8), hematology (Complete Blood Count) and chemistry (Comprehensive Metabolic Panel) will be obtained within 60 minutes prior to dosing. A basic metabolic panel (BMP) with focus on potassium and glucose parameters will be obtained at 2 hours post-dosing on all subjects (see Table 5).

On Day 7 of each treatment period (Visits 3, 5, 7 and 9), hematology (Complete Blood Count) and chemistry (Comprehensive Metabolic Panel) will be obtained within 60 minutes prior to dosing and collect a BMP at 30 minutes and a CMP at 2 hours post-dosing (see Table 6).

Serum pregnancy testing will be performed at Screening and at the Final Visit (Visit 10) with Urine HCG testing occurring prior to the start of each treatment period (Visits 2, 4, 6 and 8) in women of child-bearing potential.

The following clinical laboratory parameters will be assessed:

Hematology	
Hemoglobin	Mean corpuscular hemoglobin (MCH)
Hematocrit	Mean corpuscular hemoglobin concentration (MCHC)
White Blood Cell count with differential	Mean corpuscular volume (MCV)
Red Blood Cell count	
Platelet Count	
Clinical Blood Chemistry	
Liver Enzyme and Other Function Tests	**Other Clinical Blood Chemistry**
Alanine aminotransferase (ALT)	Albumin
Aspartate aminotransferase (AST)	Blood urea nitrogen (BUN)[a]
Alkaline phosphatase	Calcium[a]
Bilirubin, total	Chloride[a]
Gamma-glutamyl transferase	Cholesterol
	Bicarbonate
	Creatinine[a]
	Glucose[a]
	Magnesium
	Potassium[a]
	Phosphate
	Protein, total
	Sodium[a]
	Triglycerides
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 visits 2, 4, 6 and 8.	
Creatinine clearance will be estimated by the CKD-EPI published formula.	

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

7.2.5 Adverse Events

7.2.5.1 Performing Adverse Events Assessments

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

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

7.2.5.2 Adverse Event Definitions

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

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

Adverse events include, but are not limited to:

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

An AE does **not** include:

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

7.2.5.3 Pre-Randomization Adverse Events

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

7.2.5.4 Severity

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

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

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

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

7.2.5.5 Relationship

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

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

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

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

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

7.2.5.6 Clinical Laboratory Adverse Events

Many laboratory abnormalities observed during the course of a study will be included under a reported AE describing a clinical syndrome (e.g., elevated BUN and creatinine in the setting of an adverse event of renal failure, or decreased hemoglobin in a case of bleeding esophageal varices). In such cases, the laboratory abnormality itself (e.g., elevated creatinine in a setting of renal failure) does not need to be recorded as an AE. However, isolated

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

Criteria for a "clinically significant" laboratory abnormality are:

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

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

7.2.5.7 Serious Adverse Events

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

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

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

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

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

Reporting Serious Adverse Events

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

Post-study SAEs following the last dose of study drug must be reported to Pearl Therapeutics as described in Section 7.2.5.10.

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

7.2.5.8 Supplemental Investigations of SAEs

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

7.2.5.9 Post-Study Follow-Up of Adverse Events

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

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

7.2.5.10 Notification of Post-Study Serious Adverse Events

Investigators are not obligated to actively follow subjects after the completion of the study. However, if the investigator becomes aware of a post-study SAEs occurring up to 14 days following the last dose of study drug must be reported to Pearl Therapeutics, whether or not the event is attributable to study drug. All SAEs must be reported to Pearl Therapeutics no later than 24 hours after the investigator recognizes/classifies the event as a serious adverse event.

7.2.5.11 IRB/IEC Notification of Serious Adverse Events

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

7.2.5.12 Health Authority Safety Reports

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

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

7.2.6 AEs of Interest

Paradoxical bronchospasm may occur following inhalation from an MDI. Dry Mouth is a known side effect following administration of a LAMA. Tremor is a known side effect following administration of a LABA.

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

Subjects will be specifically asked about the presence of dry mouth at baseline and at specified intervals (pre-dose and at 1 and 2 hours post-dose on Day 1 and on Day 7). On Day 7 if dry mouth persists at 2 hours additional assessments will be conducted every 2 hours until resolution of symptoms or completion of the test day (see Table 5 and Table 6) and if present, the severity (mild, moderate, and severe) of dry mouth symptoms will be assessed.

If dry mouth is not noted at 2 hours post study drug administration, further dry mouth assessments do not need to be collected. All reports of dry mouth exceeding baseline will be recorded as AEs.

Instructions for Recording Dry Mouth AE:

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

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

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

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

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

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

Subjects will be asked about symptoms of tremor at baseline and at specified intervals (pre-dose and at 1 and 2 hours post-dose at treatment Visits. If tremor persists at 2 hours post-dose additional assessments will be conducted every 2 hours until resolution of symptoms or completion of the test day (see Table 5) and if present, the severity (mild, moderate, severe and very severe) of tremor symptoms will be assessed. If tremor is not noted at 2 hours post study drug administration, further tremor assessments do not need to be collected. All reports of tremor exceeding baseline will be recorded as AEs.

Instructions for Recording Tremor AEs:

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

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

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

    b. Subject has no history of tremor at screening.

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

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

7.2.7 Overdose

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

7.2.8 Pregnancy

Any pregnancy that occurs from screening until study completion must be reported to Pearl Therapeutics. To ensure subject safety, each pregnancy must be reported to Pearl Therapeutics within 14 days (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

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

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

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

All subjects who prematurely discontinue the study after being randomized, regardless of the cause, should undergo only the assessments outlined in Section 8.6 on the date of discontinuation.

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

- QTcF prolongation increase of >60 msec from test day baseline (QTc interval obtained from test day baseline ECGs corrected using Fridericia's correction formula) and QTcF >500 msec at any time after taking study drug.
- Heart rate increase of >40 bpm from test day baseline (before taking study drug) and >120 bpm at any time within the 12-hour interval after taking study drug.
- Systolic BP (SBP) increase of >40 mmHg from test day baseline (before taking study drug) and SBP >180 mmHg at any time within the 12-hour interval after taking study drug.
- FEV_1 decrease by more than 20% from test day baseline (before taking study drug) on two consecutive spirometry assessments obtained at least 15 minutes apart with associated symptoms of dyspnea at any time within the first 2-hour interval after taking study drug.

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

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 subjects' 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 subjects have been randomized; or

2. 9 or more deaths from any cause at any time during the course of the study.

Stopping criteria based on deaths from any source were based on estimates of instantaneous rates of mortality taken from the TORCH (Calverley, 2007) and UPLIFT (Tashkin, 2008)

studies. These criteria imply a 1% chance of placing the study on hold if there is no true increase in mortality.

8 STUDY ACTIVITIES

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

Table 4. Schedule of Events

Procedures	Screening[a]		Treatment Period 1[a]		Treatment Period 2[a]		Treatment Period 3[a]		Treatment Period 4[a]		Follow-Up/ Final
	Visit 1a	Visit 1b (optional)	Visit 2 Randomization (Rx 1, Day 1)	Visit 3 (Rx 1, Day 7)	Visit 4 (Rx 2, Day 1)	Visit 5 (Rx 2, Day 7)	Visit 6 (Rx 3, Day 1)	Visit 7 (Rx 3, Day 7)	Visit 8 (Rx 4, Day 1)	Visit 9 (Rx 4, Day 7)	Visit 10 Final Visit
Study Day[a]	**-28 to -7[a]**		**1[a]**	**7±2[a]**	**14[a]**	**21±2[a]**	**28[a]**	**35±2[a]**	**42[a]**	**49±2[a]**	**63[a]**
Informed Consent	X										
Eligibility Criteria	X	X	X								
Verify Continued Eligibility				X	X	X	X	X	X	X	
Reversibility to Ventolin HFA[b]	X	X									
Demographics & Medical/Surgical History	X	X									
COPD Asessment Test (CAT)[c]	X										
Prior/Concomitant Medications[d]	X	X	X	X	X	X	X	X	X	X	X
Spirometry[e]	X	X	X	X	X	X	X	X	X	X	
Physical Examination[f]	X										X
Vital Signs[g]	X		X	X	X	X	X	X	X	X	X
12-Lead ECG[h]	X		X	X	X	X	X	X	X	X	X
Pregnancy Test[i]	X		X		X		X		X		X
Clinical Laboratory Testing[i]	X		X	X	X	X	X	X	X	X	X
Adjust COPD Medications[j]	X									X	
Adverse Events	X	X	X	X	X	X	X	X	X	X	X
Inhalation Device Training	X		X								
Study Drug Administration[k]			X	X	X	X	X	X	X	X	
Dispense Peak Flow Meter	X										
Dispense Subject Diary	X		X		X		X		X		
Collect/Review Subject Diary			X	X		X		X		X	
Study Drug Dispensing			X		X		X		X		
Study Drug Collection				X		X		X		X	
Dry Mouth Assessment	X		X	X	X	X	X	X	X	X	
Tremor Assessment	X		X	X	X	X	X	X	X	X	
Paradoxical Bronchospasm[l]			X	X	X	X	X	X	X	X	

Table 4. Schedule of Events (continued)

a. Screening period of at least 7 days and up to 28 days. Subjects are to return to the clinic within 7 days following initiation of each treatment arm. There must also be at least 7 days (not to exceed 21 days) between Visits 3 and 4, Visits 5 and 6 and Visits 7 and 8 to allow for appropriate washout of study drug. The indicated Study Days are estimates calculated based on a 7-day treatment period and a 7-day washout period.

b. Assess reversibility of FEV_1 at 60 minutes following 4 puffs of Ventolin HFA (to characterize the subject population only; not to be used to determine eligibility to participate in the study).

c. Subjects will complete CAT at Screening. CAT will be used to assess symptoms to characterize the subject population only and not to be used to determine eligibility to participate in the study.

d. At all visits beyond Screening, note time of last dose of short-acting bronchodilator and other COPD medications (if <6 hours, visit should be rescheduled).

e. Spirometry (FEV_1, FVC, and PEFR) will be assessed at Screening. See Table 5 and Table 6 for spirometry assessments and specific time points to be performed on Day 1 and 7 respectively.

f. Includes evaluation of height and weight at Screening.

g. All vital signs will be obtained at Screening and Final Visit. SBP, DBP and HR will be obtained in the supine position at all time points preceding and including the 2 hours time point post-dose. SBP, DBP and HR measurements obtained after the first 2 hours post-dose may be obtained in either the supine or the seated position. See Table 5 and Table 6 for SBP, DBP, and HR assessments and specific time points to be performed on Day 1 and 7 respectively. At Visits 2-9, oral and/or tympanic temperature will be obtained at pre-dose and 2 hours post-dose and will not be repeated at subsequent time points unless clinically indicated.

h. An ECG will be conducted at Screening and Final Visit. See Table 5 and Table 6 for ECG assessments and specific time points to be performed on treatment Day 1 and 7 respectively.

i. All clinical laboratory tests will be obtained at Screening and Follow-up. At Visits 2 through 9, hematology (Complete Blood Count) and chemistry (Comprehensive Metabolic Panel) will be obtained within 60 minutes prior to dosing. At Visits 2, 4, 6, and 8 (Treatment Day 1), BMP with focus on potassium and glucose parameters will be obtained at 2 hour post-dose on all subjects (see Table 5). On Treatment Day 7 (Visits 3, 5, 7, and 9), BMP with focus on potassium and glucose parameters will be obtained at 30 minutes and a CMP at 2 hour post-dose (see Table 6). Pregnancy test (women of child- bearing potential only): serum [human chorionic gonadotropin (HCG)] at Screening and Final Visit only and Urine HCG at visits 2, 4, 6 and 8.

j. At Screening, stop prohibited COPD medications and change COPD medications as specified in protocol Section 5.4 (i.e., Sponsor-provided Atrovent HFA with or without ICS). At the end of the Visit 9, return subject to pre-study or other appropriate inhaled maintenance COPD medications.

k. At the start of each treatment visit, subject must withhold all COPD medications, including study medication, rescue medications (Albuterol) and ICS for at least 6 hours prior to start of test day procedures

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

Table 5. Visit Procedures on Day 1 of Each Treatment Period (Visits 2, 4, 6, and 8)

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

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

b. If no dry mouth or tremor is noted at the 2-hour time point, no further assessment is required. If dry mouth or tremor persists at 2 hours additional assessments will be conducted every 2 hours until resolution of symptoms or completion of the test day.

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

d. Two Baseline ECGs should be conducted, one between 60 to 120 minutes and another between 30 to 60 minutes prior to dosing. If >30 ms difference in QTcF observed between the two baseline ECGs then the investigator will make a determination as to the suitability of the subject to proceed. If the subject does proceed in the study, a third baseline ECG is to be obtained prior to dosing.

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

f. The baseline FEV_1 at Visit 4 must be within ±15% or 150 mL of the baseline FEV_1 obtained at the Randomization Visit (Visit 2). On initial assessment if the subject fails to meet the reproducibility criteria, but the 30 minute pre-dose assessment is within 20% of the baseline FEV_1 obtained at Randomization, another assessment may be conducted 30 minutes later. If the last 2 assessments meet the reproducibility requirements, the initial 60 minute pre-dose assessment will not be used and the last 2 assessments will be used to establish the eligibility criteria. If the test day FEV_1 is not within ± 15% or 150 mL, the visit may be rescheduled **(for a maximum of 3 attempts)** at the investigator's discretion (e.g., within one week), or the subject discontinued.

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

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

i. Subject must record pre- and post-home peak flow values and time of dosing in their diary while in the clinic (See Section 7.1.4).

j. See Section 6.7 for Instructions for Preparation of Treatments for Administration and Dispensing.

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

Table 6. Visit Procedures on Day 7 of Each Treatment Period (Visits 3, 5, 7 and 9)

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

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

b. If dry mouth or tremor is noted at the 2-hour time point, no further assessment is required. If dry mouth or tremor persists at 2 hours additional assessments will be conducted every 2 hours until resolution of symptoms or completion of the test day.

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

d. Two Baseline ECGs should be conducted, one between 60 to 120 minutes and another between 30 to 60 minutes prior to dosing. If >30 ms difference in QTcF observed between the two baseline ECGs then the investigator will make a determination as to the suitability of the subject to proceed. If the subject does proceed in the study, a third baseline ECG is to be obtained prior to dosing.

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

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

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

h. Site Personnel will review diary data prior to dosing study medication in the clinic and will return the diary to subject for recording pre- and 30 minute post-dose home peak flow values and time of dosing while in the clinic. Site Personnel will collect the completed subject diary after the subject has recorded 30 minute post-dose PEFR on Day 7 (See Section 7.1.4).

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

8.1 Screening Visit (Visit 1)

- Obtain informed consent.
- Register subject in IWRS to obtain subject screening number.
- Obtain demographic data, including age, race, smoking history, medical/surgical history including dry mouth, glaucoma and age of onset of COPD.
- Obtain history of COPD exacerbation within 12 months of Screening Visit (Visit 1).
- Check inclusion/exclusion criteria.
- Obtain medication history, including COPD medications.
- Obtain COPD Assessment Test (CAT).
- Conduct a serum pregnancy test for all female subjects unless it is documented in the medical history that the subject has been irreversibly surgically sterilized (hysterectomy, oophorectomy or bilateral tubal ligation) or they are at least 2 years post-menopausal.
- Conduct a complete physical examination (general appearance, skin, head, eyes, ears, nose, throat, neck [including thyroid], lymph nodes, chest, heart, abdomen, extremities, and nervous system).
- Obtain height, weight, and vital signs (heart rate and blood pressure after being supine for 5 minutes, and oral or tympanic temperature).
- Obtain a 12-lead ECG.
- Conduct baseline spirometry assessments.
- Administer 4 puffs of Ventolin HFA. **Note:** The administration of Ventolin HFA for reversibility characterization should be within 15 minutes of pre-bronchodilator spirometry:
    - Confirm subject's ability to use MDI correctly (provide coaching as needed).
    - Repeat spirometry assessments 60 minutes following 4 puffs Ventolin HFA (to characterize the subject population only; not to be used to determine eligibility to participate in the study).
- Obtain laboratory samples (hematology and chemistry).
- Complete Chest X-ray or CT scan if not performed within the last 6 months.

- Stop prohibited COPD medications and change concurrent COPD medications as specified in protocol (see Section 5.4).

- Arrange date of Visit 1b or Visit 2 as appropriate.

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

- Adverse events must be recorded during the screening period, that is, from the time of consent to the start of study treatment. Adverse events that occur between the time the subject signs the informed consent form for the study and the time when that subject is randomized will be summarized as medical history and not as a study adverse event unless the event meets the definition of an SAE (See Section 7.2.5.7).

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

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

- Collect and review subject practice diary (if diary is not completed correctly re-train subject).

- Note time of last dose of short-acting bronchodilator and other COPD medications on the CRF (if <6 hours, Visit 2 must be rescheduled).

- Review inclusion/exclusion criteria to confirm subject eligibility.

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

- Record adverse events (if any).

- Review concomitant medications to ensure adherence to COPD regimen.

- Perform urine pregnancy test (women of child-bearing potential only).

- Perform all pre-dose assessments (refer to Table 5).

- Dispense subject diary and provide instructions on diary completion if appropriate.

- Obtain subject treatment assignment information from IWRS.

- At 15-30 minutes prior to dosing, the seal around the study day treatment box is to be opened and the instructions for administration of study drug on the inner flap of the study day treatment box are to be followed.

- Refer to Section 6.7 for detailed instructions for preparation of treatments for administration. These instructions are to be adhered to and are relevant to all study treatment visits.

- Subject will administer first dose of newly assigned study drug at the clinic.
    - The subject is to be considered randomized after receiving study medication.
- Perform all post-dosing assessments (refer to Table 5).
- Schedule Visit 3 and ensure subject has adequate supply of study drug and rescue Ventolin HFA.

8.3 Visit 3 (Rx 1, Day 7)

- Review subject diary.
- Note time of last dose of short-acting bronchodilator and other COPD medications on the source (if <6 hours, reschedule visit).
- Review concomitant medications and ensure adherence to COPD regimen.
- Confirm subject eligibility to continue.
- Record adverse events (if any).
- Perform all pre-dose assessments (refer to Table 6).
- Subject will administer final dose of previously dispensed study drug at the clinic under site supervision.
- Perform all post-dosing assessments (refer to Table 6).
- Collect subject diary.
- Collect previously dispensed study drug.
- Schedule next visit (following a washout period of at least 1 week but no longer than 3 weeks) and ensure subject has adequate supply of COPD medication, including Atrovent HFA.

8.4 Visit 4, 6, and 8 (Day 1 of Rx 2, Rx 3, and Rx 4)

- Note time of last dose of short-acting bronchodilator and other COPD medications on source (if <6 hours, visit must be rescheduled).
- Review inclusion/exclusion criteria to confirm subject eligibility to continue.

- Confirm Reproducibility Criteria was met.
- Review of clinical laboratory results from previous visit. Please note whether the results are clinically significant and include comments where applicable.
- Record adverse events (if any).
- Review concomitant medications and ensure adherence to COPD regimen.
- Perform urine pregnancy test (women of child-bearing potential only).
- Perform all pre-dose assessments (refer to Table 5)
- Dispense subject diary and provide instructions on diary completion if appropriate.
- Obtain subject treatment assignment information from IWRS.
- At 15-30 minutes prior to dosing, the seal around the study day treatment box is to be opened and the instructions for administration of study drug on the inner flap of the study day treatment box are to be followed.
    - Refer to Section 6.7 for detailed instructions for preparation of treatments for administration. These instructions are to be adhered to and are relevant to all study treatment visits.
- Subject will administer first dose of newly assigned study drug at the clinic.
- Perform all post-dosing assessments (refer to Table 5).
- Schedule next visit and ensure subject has adequate supply of study drug and rescue Ventolin HFA.

8.5 Visit 5, 7, and 9 (Day 7 of Rx 2, Rx 3, and Rx 4)

- Review subject diary.
- Note time of last dose of short-acting bronchodilator and other COPD medications on CRF (if <6 hours, reschedule visit).
- Review concomitant medications and ensure adherence to COPD regimen.
- Confirm subject eligibility to continue.
- Record adverse events (if any).
- Perform all pre-dose assessments (refer to Table 6).

- Subject will administer final dose of previously dispensed study drug at the clinic.
- Perform all post-dosing assessments (refer to Table 6).
- Collect subject diary.
- Collect previously dispensed study drug.
- **At Visit 5 and 7 only**: Schedule next visit (following a washout period of at least 1 week but no longer than 3 weeks) and ensure subject has adequate supply of COPD medications, including Atrovent HFA.
- **At Visit 9 only**: Schedule the final/follow-up visit at least 1 week but no longer than 2 weeks from Visit 9. At completion of all Visit 9 assessments, return subject to pre-study or appropriate inhaled maintenance COPD medications.

8.6 Follow-Up (Final) Visit/Premature Discontinuation (Visit 10)

- Record adverse events (if any).
- Review concomitant medications
- Conduct a physical examination, including vital signs.
- Perform ECG and collect blood samples for hematology and chemistry.
- Collect a blood sample for pregnancy test for women of child bearing potential.
- Inform subject about reporting all SAEs up to 14 days following the last dose of study drug.
- If not adjusted following Visit 9, return subject to pre-study or appropriate inhaled maintenance COPD medications.
- Complete study completion page.

8.7 Unscheduled Visits

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

8.8 Completion of the Study

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

- Subject discretion (document reason)
- Investigator considers it to be in the best interest of the subject
- Adverse events(s)
- Administrative reasons (e.g., early termination of the study)
- Subject lost-to-follow-up
- Major protocol violation
- Death
- Completion of the study
- Protocol-specified 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 4-period, 8-treatment, incomplete block cross-over design evaluating the following 8 treatments in approximately 160 subjects:

- GFF MDI 18/9.6 µg BID
- GFF MDI 9/9.6 µg BID
- GFF MDI 4.6/9.6 µg BID
- GFF MDI 2.4/9.6 µg BID
- GFF MDI 1.2/9.6 µg BID
- GP MDI 18 µg BID
- FF MDI 9.6 µg BID
- Spiriva 18 µg QD (open-label)

The primary objective of this study is to assess efficacy of GFF MDI relative to individual components (GP MDI and FF MDI) in subjects with moderate to severe COPD within the range of doses evaluated in this protocol. To this end, the primary efficacy endpoint, FEV_1 $AUC_{0\text{-}12}$, will be compared for each dose of GFF MDI administered twice daily (BID) relative to GP MDI (18µg ex-actuator, BID) and FF MDI (9.6 µg ex-actuator, BID).

9.2 Protocol Variables

9.2.1 Efficacy Endpoints

All efficacy assessments, except for the mean number of puffs of rescue medication, are relative to baseline. Since pre-dose values are known to be variable, and an isolated time-point may not accurately reflect the true baseline, the following baseline will be used for statistical analyses unless otherwise specified: the mean of available pre-dose values on the first day of each treatment cycle, i.e., the mean of pre-dose values at Visits 2, 4, 6 and 8, where the mean of the -60 and -30 minute value for each visit day is averaged and then the average of all visit means are averaged. Previous studies showed that this average baseline was more robust than the mean of pre-dose values at the start of each treatment period, or the mean of pre-dose values during Visit 2 alone, and that it gave more precise estimates of treatment means.

For spirometry measurements (peak flow rate) taken with the home instrument, baseline is defined as the average of the pre-dose measurements from Visits 2, 4, 6, and 8.

9.2.1.1 Primary Efficacy Endpoint

Primary Efficacy Endpoint Evaluated on Treatment Day 7 (Visits 3, 5, 7 and 9, following chronic dosing)

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

9.2.1.2 Secondary Efficacy Endpoints

Secondary Endpoints Evaluated on Treatment Day 1 (Visits 2, 4, 6 and 8) relative to baseline:

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

Secondary Endpoints Evaluated on Treatment Day 7 (Visits 3, 5, 7 and 9, following chronic dosing):

- Change from baseline in morning pre-dose trough FEV_1, (defined as the average of the 60 and 30 minute pre-dose values on Treatment Day 7 minus the baseline).
- Peak change from baseline in FEV_1 (defined as the change at the highest value of FEV_1 post-dose).
- Change from baseline for mean morning pre-dose trough IC (mean of 60 and 30 minute pre-dose assessments minus the baseline).
- Peak change from baseline in IC (mean of 1 and 2 hours post-dose assessments minus the baseline).
- Change from baseline in 12-hour post-dose trough FEV_1 (12-hour post-dose trough FEV_1 is defined as the mean of the FEV_1 assessments taken at 11.5 and 12 hours post-dose).
- Change from baseline in mean morning pre- and post-dose daily peak flow readings taken by subjects and recorded in subject diaries, during each treatment period (excluding reading taken pre- dose on Treatment Day 1).
- Change from baseline in mean evening pre- and post-dose daily peak flow readings taken by subjects and recorded in subject diaries, during each treatment period (Subjects taking Spiriva will perform a single evening assessment).
- Mean number of puffs of rescue medication recorded in subject diaries, during each treatment period and by treatment and number of days treated.

9.2.1.3 Exploratory Endpoints Evaluated on Treatment Day 7 (Visits 3, 5, 7 and 9, following chronic dosing)

- Peak expiratory flow rate (PEFR) morning pre-dose trough and peak change from baseline on Day 7. PEFR AUC_{0-12} and change from baseline by post-dose time point. AUC will be normalized by dividing by time (12 hours) so that unit of AUC will be L.
- Forced vital capacity (FVC) morning pre-dose trough and peak change from baseline on Day 7. FVC AUC_{0-12} and change from baseline by post-dose time point. AUC will be normalized by dividing by time (12 hours) so that the units of AUC will be L.
- Change from baseline for mean evening 12 hour post-dose trough IC (mean of 11.5 and 12 hours post-dose assessments minus the baseline).

9.2.2 Safety Endpoints

The safety endpoints for this study include:

1. **Adverse Events:** The safety measurements include both the numbers of adverse events as observed by the investigational team or reported by the subject, and the numbers of subjects 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.
2. **Paradoxical Bronchospasm, Dry Mouth and Tremor** will be regarded as adverse events of special significance and the incidence of subjects with each of these during the scheduled assessment periods on a test day and overall during the treatment period will be tabulated separately.
3. **12 Lead ECG:** Change from baseline heart rate, RR interval, PR interval, QRS axis, QRS interval, QT intervals and QTcF (Fridericia Corrected QT) intervals, where baseline is defined as the average of the values prior to dosing at the start of each treatment sequence.
4. **Concomitant Medications:** All medications (including complementary medicines and other health supplements) that were used to treat acute or chronic conditions will be recorded at screening (Visit 1) and all subsequent visits.
5. **Clinical Laboratory Testing:** Full clinical laboratory testing at every visit including hematology and clinical chemistry, characterized by change from baseline, where the baseline is defined as the value prior to dosing at the start of each treatment sequence.
6. **Vital Sign Measurements:** Change from baseline values where baseline s defined as the average of the values prior to dosing at the start of each treatment sequence.

9.3 Analysis

9.3.1 Primary Efficacy Analysis

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

1. GFF MDI (all doses) vs. GP MDI 18 µg[1]

2. GFF MDI (all doses) vs. FF MDI 9.6 µg.

The analysis of this comparison is therefore **not** sequential. Each comparison will be conducted with a significance level of 0.05. Interpretation of the study will be based on consideration of all comparisons, and no adjustment for multiplicity will be made.

These comparisons will be achieved with a linear mixed effects model, including fixed effect terms for treatment and period. Point and interval estimates will be obtained using the REML algorithm (Patterson and Thompson, 1971), under three models for the within subjects covariance matrix: unstructured (for period), compound symmetry and first order autoregressive (Pinheiro and Bates, 2000). The covariance model yielding the smallest value of Akaike's information criterion (Akaike, 1974) will be selected for tabulation. Testing for unequal carryover effects will be performed.

Two-sided 95% confidence intervals will be tabulated.

9.3.2 Secondary Efficacy Analysis

Secondary efficacy analyses will involve the primary efficacy comparisons applied to secondary efficacy endpoints. They will also include comparisons of combination therapies and monotherapies with Spiriva. For endpoints other than time to onset, the proportion of subjects achieving ≥12% improvement, and the mean number of puffs of rescue medication, these comparisons will be performed using the same mixed model and the same algorithms as for the primary efficacy objective.

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

The proportion of subjects achieving 12% or greater improvement from baseline on Treatment Day 1 will be tabulated by treatment. An analysis using a generalized linear mixed model for incompletely paired data will be used.

The mean number of puffs of rescue mediation will be analyzed using a generalized linear mixed model, with a quasi-Poisson family and treatment and period as fixed, and random effects for patient and periods within patient.

9.3.3 Exploratory Efficacy Analysis

Exploratory efficacy analyses will involve the primary efficacy comparisons applied to exploratory efficacy endpoints. They will also include comparisons between the combination

therapy (GFF MDI) and monotherapies (GP MDI and FF MDI) with Spiriva (18 µg, open-label). For exploratory endpoints, these comparisons will be performed using the same mixed model and the same algorithms as for the primary efficacy objective.

9.3.4 Safety Analysis

9.3.4.1 Adverse Events

Adverse events during each treatment regime will be summarized by the number of subjects experiencing an event. They will be tabulated at the level of the MedDRA preferred term, and the MedDRA System Organ Class. The version of MedDRA 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. Tables will show the overall incidence of adverse events, and the incidence broken down by each of the 8 treatment selections in Part A. That is, adverse events will be tabulated for the entire subject history, rather than for the treatment during which they occurred.

9.3.4.2 Paradoxical Bronchospasm

Paradoxical Bronchospasm will be considered an adverse event of special interest, and will be tabulated separately. Bronchospasm will be summarized by the number of subjects experiencing the event, during scheduled assessment periods on a test day and during the particular treatment period. We note that tabulations for bronchospasms differ from those for general adverse events, since the tabulation involves tabulating the incidence of paradoxical bronchospasm with onset during a treatment period. Bronchospasm with onset outside a treatment period will be listed separately. No hypothesis tests will be performed, but an appropriate confidence interval may be provided.

9.3.4.3 Tremor and Dry Mouth

The incidence of tremor and dry mouth will be summarized by the number of subjects experiencing the event during scheduled assessment periods on a test day and during the particular treatment period. Tremor and dry mouth that occur outside a treatment period will be listed separately. No hypothesis tests will be performed, but an appropriate confidence interval may be provided.

9.3.4.4 Clinical Laboratory Measurements

Summary statistics (mean, median, standard deviation and range) of change from baseline values will be tabulated for each treatment and each assessment time. For clinical laboratory measurements, baseline values will be defined by the value prior to dosing for each treatment period (not including values collected during dosing with an earlier treatment). Male and female subjects will be tabulated separately. Clinically notable change from test day baseline in serum potassium (> 0.5 mmol/L reduction from baseline and serum potassium < 3.5 mmol/L) will be listed and tabulated by treatment. Similarly, clinically notable blood glucose values (> 11.1 mmol/L) will also be listed and tabulated by treatment.

9.3.4.5 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 as the average of the values prior to dosing at the start of each treatment period (not including values collected during dosing with an earlier treatment).

9.3.4.6 ECGs

Summary statistics (mean, median, standard deviation and range) for absolute values and change from baseline values will be tabulated for each treatment and assessment time. For ECG parameters, baseline values will be defined as the average of the value(s) obtained prior to dosing for each treatment period (not including values collected during dosing with an earlier treatment).

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

The percentage and number of subjects with ECG's with > 30 msec increase in QTcF from test day baseline and QTcF intervals greater than 450 msec for males and 470 msec for females will be tabulated. No hypothesis tests will be performed, but a Clopper-Pearson confidence interval may be provided for each group.

9.4 Randomization

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

9.5 Experimental Design

The experimental design was chosen to be balanced with respect to treatments and periods, and nearly first order carry-over balanced. First order carry-over balanced designs based on Williams squares can be generated with multiples of 56 subjects. 112 sequences were generated to show carry-over balance. A further 48 sequences were selected from a 56 sequence Williams design, to maintain treatment and period balance.

The replication of treatment by study period is shown in Table 7.. Treatment sequences are shown in Appendix 8.

Table 7. Treatment Replication By Period

Treatment	Period A	B	C	D
Glycopyrrolate/Formoterol Fumarate 18/9.6 µg ex-actuator	20	20	20	20
Glycopyrrolate/Formoterol Fumarate 9/9.6 µg ex-actuator	20	20	20	20
Glycopyrrolate/Formoterol Fumarate 4.6/9.6 µg ex	20	20	20	20
Glycopyrrolate/Formoterol Fumarate 2.4/9.6 µg ex	20	20	20	20
Glycopyrrolate/Formoterol Fumarate 1.2/9.6 µg ex	20	20	20	20
Glycopyrrolate 18 µg ex-actuator	20	20	20	20
Formoterol Fumarate 9.6 µg ex-actuator	20	20	20	20
Tiotropium inhalation powder[†] 18 µg	20	20	20	20

9.6 Sample Size Consideration

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

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

For the efficacy comparisons, power was calculated as follows:

- Between and within subjects variance components were assumed to have standard deviations of 0.13 L.
- The standard error of each contrast was calculated, assuming a generalized least squares analysis in which the ratio of between and within subject variance components was known. The generalized least squares estimates also assumed spherical errors. This is an approximation to the standard error of the REML estimates. It was assumed that there are no carryover effects.

- The non-centrality parameter of the t-test was calculated, assuming the standard error from the generalized least squares analysis, and a difference of 0.8 L.

Power was calculated under simulation of subject drop-out. From previous studies, the drop-out rate for each period is approximately 9%. 1,000 random realizations of the sequences completing each period were generated, and average power (across all pair-wise treatment comparisons) was calculated for each realization. Power was then averaged across realizations.

Average power to detect effects of 75 mL, 80 mL and 85 mL were 85%, 89% and 93% respectively. The expected number of subjects completing each stage was 145.6, 132.5, 120.6 and 109.7 for treatment cycles 1, 2, 3 and 4 respectively.

9.7 Data Validation and Transformation

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

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

9.8 Analysis Plan

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

9.9 Study Populations

The following analysis populations are defined in this study:

- The **Intent-To-Treat (ITT) Population** is defined as all subjects who are randomized to treatment and receive at least one dose of the study treatment. (Note that a subject who used a study treatment, but took less than one full dose of treatment will qualify for this population).

- A **Modified ITT (MITT) Population** will be used for analysis of efficacy variables, where subjects must have completed at least 2 treatment periods, with baseline and 2 hours post-dosing on Day 7 for each of the treatment periods (i.e., no greater than one missing data-point from 15 minutes to 2 hours inclusive). Any evaluability criteria with a potential impact on efficacy results will be identified in a blinded fashion from review of data listings prior to database lock. Protocol deviations, therefore, can result in exclusion of all (e.g., spirometry) data from a particular subject from the analysis population or require exclusion of data from a specific treatment period or from a particular time point within a treatment period. Protocol deviations for exclusion of data from the MITT Population will be agreed between Pearl Therapeutics and the biostatistician prior to data base lock and will be pre-specified in the Statistical Analysis Plan written prior to database lock.

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

Safety Population

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

Analyses will be performed as follows:

Demographics will be summarized for the ITT, MITT, PP, and Screen Failure Populations. Extent of exposure will be summarized for the ITT population. The Safety Population will be used to summarize safety.

Efficacy Analyses will be performed for the MITT and PP Populations, with the MITT Population being considered the primary population for these analyses. The ITT analyses on the primary parameter and the PP analyses will be used as sensitivity analyses.

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

9.10 Handling of Missing Data

Change from baseline in pre-dose FEV_1 on Day 7 is defined as the average of the 60 and 30 minute pre-dose values on Treatment Day 7 minus baseline. In subjects missing either of these pre-dose assessments, the value will be calculated from the single measurement. In subjects missing both pre-dose values, pre-dose FEV_1 on Day 7 will not be calculated, but other FEV_1 parameters will be calculated provided they meet the requirements below.

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

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

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

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

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

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

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

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

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

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

9.11 Statistical Software

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

10 ADMINISTRATIVE CONSIDERATIONS

10.1 Regulatory Authority Approval

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

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

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

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

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

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

10.3 Subject Information and Consent

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

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

10.4 Laboratory Accreditation

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

10.5 Confidentiality

10.5.1 Confidentiality of Data

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

10.5.2 Confidentiality of Subject/Patient Records

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

10.6 Quality Control and Assurance

Pearl Therapeutics is responsible for implementing and maintaining quality control and quality assurance systems with written standard operating procedures (SOPs) to ensure that trials are conducted and data are generated, documented, and reported in compliance with the protocol,

accepted standards of GCP, and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the clinical study.

10.7 Data Management

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

10.8 Study Monitoring

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

During these contacts, the monitor will:

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

This will be done in order to verify that the:

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

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

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

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

- Review of site study records for completeness.

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

10.9 Retention of Data

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

10.10 Financial Disclosure

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

10.11 Investigator's Final Report

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

10.12 Publication Policy

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

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

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

11 REFERENCE LIST

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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 $\geq$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 $\geq$20 mm-s^{-1}, and larger time scales are preferred ($\geq$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 $\pm$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 $\geq$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 $\pm$3.5% of the reading or 65 mL, whichever is greater. This limit includes the 0.5% accuracy limit for a 3-L syringe. The linearity check procedure provided by the manufacturer can be used if it is equivalent to one of the following procedures: 1) consecutive injections of 1-L volume increments while comparing observed volume with the corresponding cumulative measured volume, e.g., 0–1,1–2, 2–3,…6–7 and 7–8 L, for an 8-L spirometer; and 2) injection of a 3-L volume starting at a minimal spirometer volume, then repeating this with a 1-L increment in the start position, e.g., 0–3, 1–4, 2–5, 3–6, 4–7 and 5–8 L, for an 8-L spirometer. The linearity check is considered acceptable if the spirometer meets the volume accuracy requirements for all volumes tested.

Quality Control for Flow-Measuring Devices

With regards to volume accuracy, calibration checks must be undertaken at least daily, using a 3-L syringe discharged at least three times to give a range of flows varying between 0.5 and 12 $L\text{-}s^{-1}$ (with 3-L injection times of 6 s and 0.5 s). The volume at each flow should meet the accuracy requirement of $\pm$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 $\pm$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 $\geq$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 $mm\text{-}s^{-1}$.

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

FEVt: forced expiratory volume in t seconds

BTPS correction

All spirometry values should be reported at BTPS by any method (measuring temperature and barometric pressure) proven effective by the manufacturer. For volume-type spirometers, the temperature inside the spirometer should be measured for each breathing maneuver. Regardless of the BTPS correction technique used, the ambient temperature must always be recorded with an accuracy of $\pm$1°C. In situations where the ambient air temperature is changing rapidly (>3°C in <30 min), continuous temperature corrections may be necessary. Spirometer users should be aware of potential problems with testing performed at lower ambient temperatures: 17°C is the

lower limit for ambient temperature, unless a manufacturer states that their spirometer will operate accurately at lower ambient temperatures. If barometric pressure is not used in calculating the BTPS correction factor, the range of barometric pressures over which the BTPS correction factor is valid must be published.

Appendix 2 Spirometry Assessment Criteria

Acceptable Versus Usable Tests

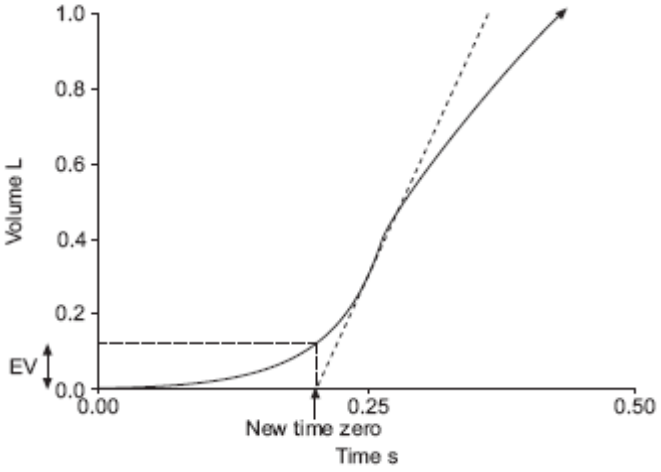
***Acceptable* Tests must meet the following 7 Criteria:**

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

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

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

Figure A2-1. Example of a Usable Spirogram



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

Between-Maneuver Reproducibility Criteria

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

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

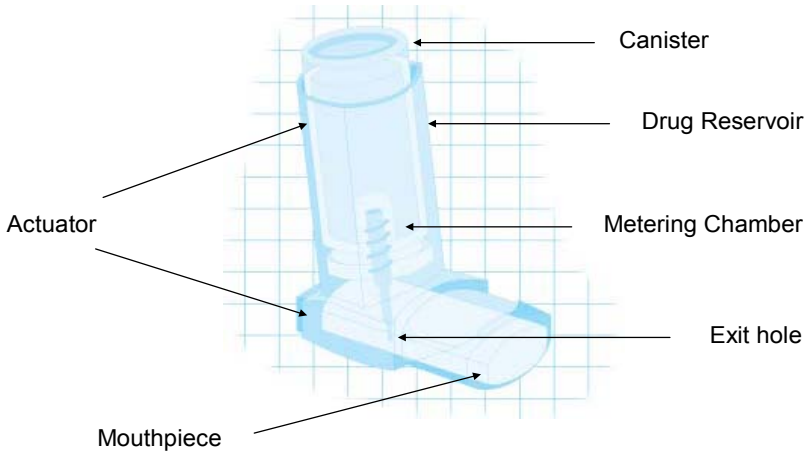
If these criteria are met, the spirometry testing for that time-point may conclude. The highest FEV_1 and the highest FVC obtained at each testing time-point (even if from different reproducible tracings), will be collected.

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

Appendix 3 Subject Instructions for Use of GFF MDI, GP MDI, and FF MDI Devices

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

METERED DOSE INHALER SCHEMA

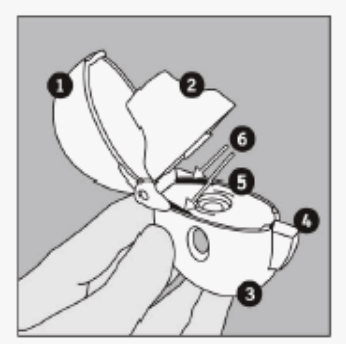


Appendix 4 Instructions for Use of Spiriva Handihaler

Taking your dose of SPIRIVA, requires four main steps: Open the blister and the HandiHaler device, insert the SPIRIVA capsule, press the HandiHaler button, and inhale your medication. (See below for details.)

Become familiar with the components of the HandiHaler inhalation device:

1. dust cap
2. mouthpiece
3. base
4. piercing button
5. center chamber
6. Air intake vents

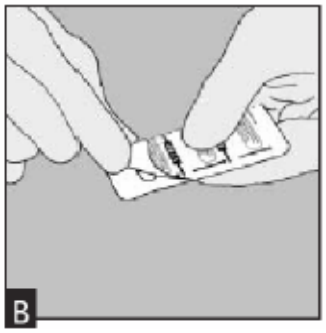


Removing the SPIRIVA capsule from the blister.

A) SPIRIVA capsules are packaged in a blister card. Each blister card consists of one blister strip, containing 5 capsules. Prior to removing the first capsule from the blister card, separate the blister strips by tearing along the perforation.

B) The blister should be carefully opened to expose only one capsule at a time. Immediately before you are ready to use your dose of SPIRIVA, peel back the aluminum foil using the tab at the rounded edge until one capsule is fully visible. The foil lidding should only be peeled back as far as the *STOP* line printed on the blister foil to prevent exposure of more than one capsule. (Figure B) Turn the blister strip upside down and tip the capsule out, tapping the back of the blister pack, if necessary.

DO NOT CUT THE FOIL OR USE SHARP INSTRUMENTS TO REMOVE THE CAPSULE



FROM BLISTER.

Capsules should always be stored in the sealed blisters and only removed immediately before use. The drug should be used immediately after the packaging over an individual capsule is opened, or else its effectiveness may be reduced.

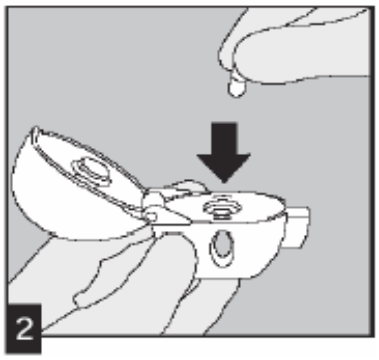
If additional capsules are inadvertently exposed to air, they should not be used and should be discarded.

Do not store capsules in the HandiHaler device.

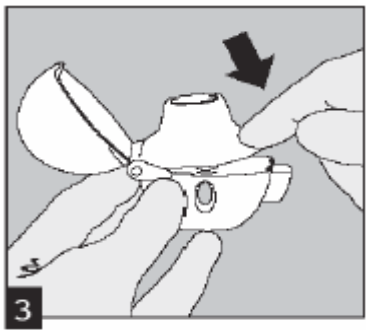
Opening the HandiHaler device and inserting the SPIRIVA capsule.

1) OPEN: Open the dust cap by pulling it upwards. Then open the mouthpiece. (Figure 1)

2) INSERT: Place the capsule in the center chamber. It does not matter which end of the capsule is placed in the chamber. (Figure 2)

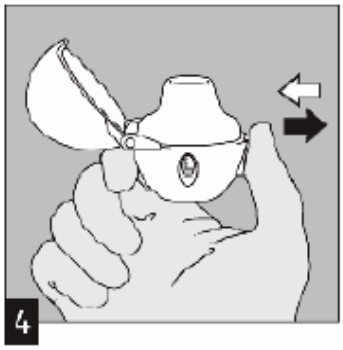


3) Close the mouthpiece firmly until you hear a click, leaving the dust cap open. Check to see that the mouthpiece is completely closed. Be sure that the mouthpiece sits firmly against the gray base so that there is no gap between the mouthpiece and the base. (Figure 3)

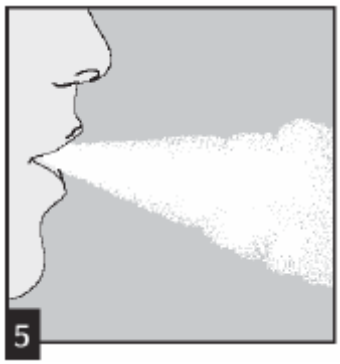


Taking your dose of SPIRIVA.

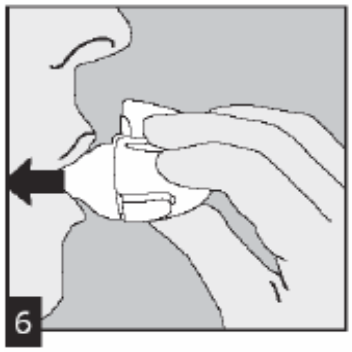
4) PRESS: Hold the HandiHaler device with the mouthpiece upwards and press the piercing button completely in once until it is flush against the base, and release. This makes holes in the capsule and allows the medication to be released when you breathe in. (Figure 4)



5) Breathe out completely. (Figure 5) Important: Do not breathe (exhale) into the HandiHaler mouthpiece at any time.



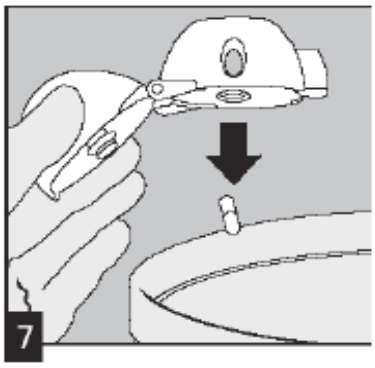
6) INHALE: Holding the HandiHaler by only the gray base and without blocking the air intake vents, raise the HandiHaler device to your mouth and close your lips tightly around the mouthpiece. Keep your head in an upright position and breathe in slowly and deeply but at a rate sufficient to hear or feel the capsule vibrate. Breathe in until your lungs are full; then hold your breath as long as is comfortable and at the same time take the HandiHaler device out of your mouth. Resume normal breathing. (Figure 6)



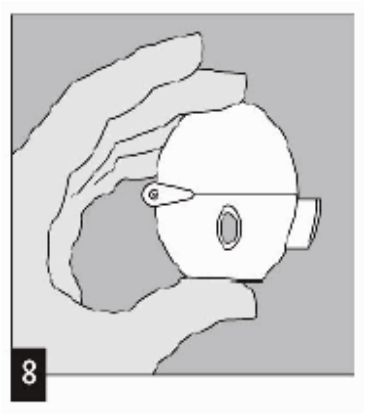
To ensure you get the full dose of SPIRIVA, you must repeat steps 5 and 6 once again.

If you do not hear or feel the capsule vibrate, DO NOT PRESS THE GREEN BUTTON AGAIN, but instead tap the HandiHaler gently on a table, holding it in an upright position. Check to see that the mouthpiece is completely closed. Then breathe in again – slowly and deeply. If you still do not hear or feel the capsule vibrate after repeating the above steps please consult your physician.

7) After you have finished taking your daily dose of SPIRIVA, open the mouthpiece again. Tip out the used capsule and discard. (Figure 7)



8) Close the mouthpiece and dust cap for storage of your HandiHaler device. (Figure 8)



Appendix 5 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.

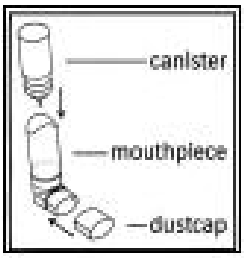


Figure 1

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.

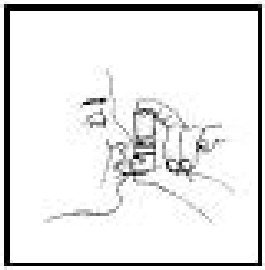


Figure 2

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.

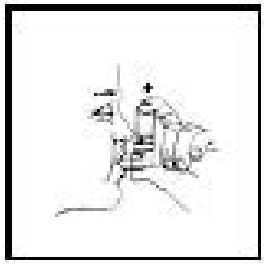


Figure 3

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.**

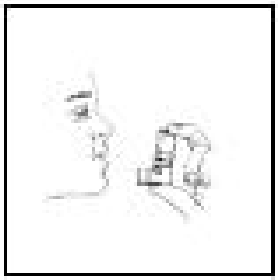


Figure 4

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.

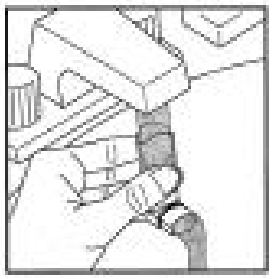


Figure 5

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 6 Instructions for Use of Ventolin HFA Inhaler

The Parts of Your VENTOLIN HFA Inhaler

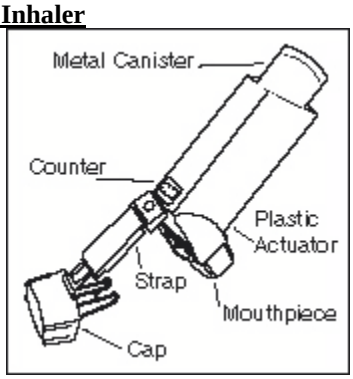


Figure 1

There are 2 main parts to your VENTOLIN HFA inhaler:

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

The counter starts at 204, the number will count down by 1 each time you spray the inhaler. The counter will stop counting at 000.

Never try to change the numbers or take the counter off the metal canister. The counter cannot be reset, and it is permanently attached to the canister.

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

How to Use Your VENTOLIN HFA

Before using your VENTOLIN HFA:

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.

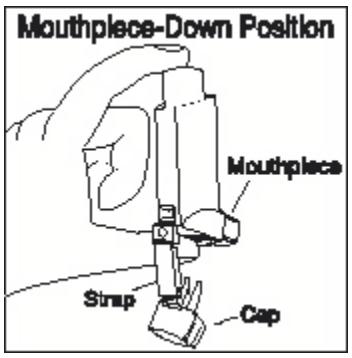


Figure 2

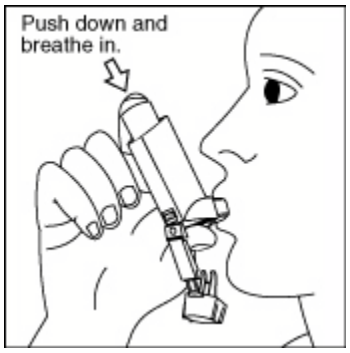


Figure 3

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).

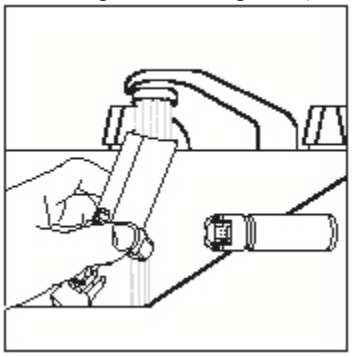


Figure 4

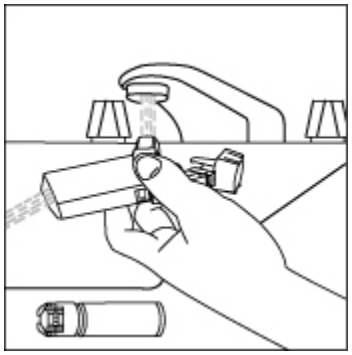


Figure 5

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).

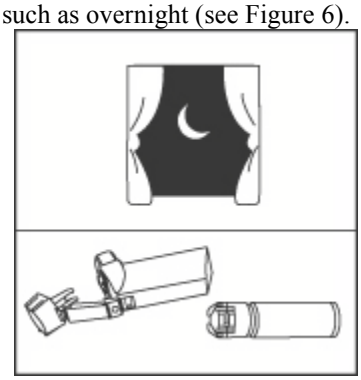


Figure 6

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.

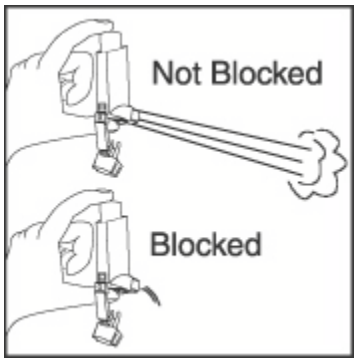


Figure 7

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 7 COPD Assessment Test

Your name:	Today's date:

CAT
COPD Assessment Test

How is your COPD? Take the COPD Assessment Test™ (CAT)

This questionnaire will help you and your healthcare professional measure the impact COPD (Chronic Obstructive Pulmonary Disease) is having on your wellbeing and daily life. Your answers, and test score, can be used by you and your healthcare professional to help improve the management of your COPD and get the greatest benefit from treatment.

For each item below, place a mark (X) in the box that best describes you currently. Be sure to only select one response for each question.

Example: I am very happy 0 X 2 3 4 5 I am very sad

			SCORE
I never cough	0 1 2 3 4 5	I cough all the time	
I have no phlegm (mucus) in my chest at all	0 1 2 3 4 5	My chest is completely full of phlegm (mucus)	
My chest does not feel tight at all	0 1 2 3 4 5	My chest feels very tight	
When I walk up a hill or one flight of stairs I am not breathless	0 1 2 3 4 5	When I walk up a hill or one flight of stairs I am very breathless	
I am not limited doing any activities at home	0 1 2 3 4 5	I am very limited doing activities at home	
I am confident leaving my home despite my lung condition	0 1 2 3 4 5	I am not at all confident leaving my home because of my lung condition	
I sleep soundly	0 1 2 3 4 5	I don't sleep soundly because of my lung condition	
I have lots of energy	0 1 2 3 4 5	I have no energy at all	
		TOTAL SCORE	

Appendix 8 Treatment Sequences

The 160 planned Treatment sequences are shown in Table B1-1. A further 8 sequences, for use if more than 160 patients are randomized are shown in Table B1-2.

Table B1-1. Planned Treatment Sequences

	Period:			
Sequence	A	B	C	D
1	GFF 18/9.6	GFF4.6/9.6	Tiotropium 18	GFF9/9.6
2	GFF2.3/9.6	FF 9.6	GFF1.2/9.6	GP 18
3	GFF9/9.6	GFF1.2/9.6	Tiotropium 18	GFF2.3/9.6
4	GFF2.3/9.6	Tiotropium 18	GFF1.2/9.6	GFF4.6/9.6
5	Tiotropium 18	GFF4.6/9.6	GFF2.3/9.6	GFF1.2/9.6
6	GFF1.2/9.6	GFF2.3/9.6	GFF9/9.6	Tiotropium 18
7	GFF1.2/9.6	GFF2.3/9.6	GFF9/9.6	Tiotropium 18
8	GFF 18/9.6	GP 18	GFF2.3/9.6	GFF4.6/9.6
9	GFF9/9.6	GFF2.3/9.6	GFF 18/9.6	FF 9.6
10	Tiotropium 18	FF 9.6	GFF2.3/9.6	GFF 18/9.6
11	GFF 18/9.6	GFF2.3/9.6	FF 9.6	Tiotropium 18
12	GP 18	GFF1.2/9.6	GFF 18/9.6	Tiotropium 18
13	FF 9.6	GFF 18/9.6	GFF1.2/9.6	GFF4.6/9.6
14	GFF1.2/9.6	GFF2.3/9.6	GFF4.6/9.6	Tiotropium 18
15	GFF1.2/9.6	FF 9.6	GFF4.6/9.6	GFF 18/9.6
16	GP 18	GFF4.6/9.6	GFF2.3/9.6	GFF9/9.6
17	GFF9/9.6	GFF1.2/9.6	GFF4.6/9.6	FF 9.6
18	GFF2.3/9.6	GFF 18/9.6	GFF4.6/9.6	GP 18
19	FF 9.6	GFF4.6/9.6	GFF1.2/9.6	GFF9/9.6
20	GFF4.6/9.6	GFF2.3/9.6	GP 18	GFF 18/9.6
21	GFF2.3/9.6	Tiotropium 18	GFF1.2/9.6	GFF4.6/9.6
22	GP 18	GFF4.6/9.6	FF 9.6	Tiotropium 18
23	GFF9/9.6	GFF2.3/9.6	GFF4.6/9.6	GP 18
24	FF 9.6	GFF 18/9.6	GFF2.3/9.6	GFF9/9.6
25	Tiotropium 18	GFF 18/9.6	GFF9/9.6	GFF4.6/9.6
26	FF 9.6	GP 18	GFF2.3/9.6	GFF1.2/9.6
27	GFF9/9.6	GFF2.3/9.6	GFF 18/9.6	FF 9.6
28	GFF4.6/9.6	GFF9/9.6	GP 18	GFF2.3/9.6
29	GFF9/9.6	Tiotropium 18	GFF4.6/9.6	GFF 18/9.6
30	GFF4.6/9.6	GFF9/9.6	FF 9.6	GFF1.2/9.6
31	FF 9.6	GFF 18/9.6	GFF1.2/9.6	GFF4.6/9.6
32	GFF1.2/9.6	GFF2.3/9.6	GP 18	FF 9.6

	Period:			
Sequence	A	B	C	D
33	FF 9.6	GP 18	Tiotropium 18	GFF4.6/9.6
34	Tiotropium 18	GFF4.6/9.6	GFF2.3/9.6	GFF1.2/9.6
35	GFF2.3/9.6	Tiotropium 18	GFF 18/9.6	FF 9.6
36	Tiotropium 18	FF 9.6	GFF4.6/9.6	GP 18
37	GFF4.6/9.6	Tiotropium 18	GP 18	FF 9.6
38	FF 9.6	GP 18	Tiotropium 18	GFF9/9.6
39	Tiotropium 18	GFF 18/9.6	GFF1.2/9.6	GP 18
40	GFF1.2/9.6	GFF2.3/9.6	GFF4.6/9.6	Tiotropium 18
41	GFF1.2/9.6	Tiotropium 18	GP 18	GFF 18/9.6
42	GFF 18/9.6	GFF4.6/9.6	Tiotropium 18	GFF9/9.6
43	Tiotropium 18	GFF 18/9.6	GFF9/9.6	GFF4.6/9.6
44	GFF9/9.6	GFF1.2/9.6	Tiotropium 18	GFF2.3/9.6
45	Tiotropium 18	GFF9/9.6	GFF2.3/9.6	GFF1.2/9.6
46	GFF1.2/9.6	FF 9.6	GFF9/9.6	GFF4.6/9.6
47	GFF9/9.6	Tiotropium 18	GFF4.6/9.6	GFF 18/9.6
48	GFF4.6/9.6	GFF1.2/9.6	Tiotropium 18	GFF2.3/9.6
49	GFF4.6/9.6	GFF1.2/9.6	GFF 18/9.6	FF 9.6
50	GFF 18/9.6	GP 18	GFF1.2/9.6	GFF9/9.6
51	GFF1.2/9.6	FF 9.6	GFF4.6/9.6	GFF 18/9.6
52	FF 9.6	GFF 18/9.6	GFF2.3/9.6	GFF9/9.6
53	GFF2.3/9.6	FF 9.6	GFF9/9.6	GFF 18/9.6
54	GFF9/9.6	Tiotropium 18	GP 18	FF 9.6
55	GFF1.2/9.6	GFF 18/9.6	GFF9/9.6	GP 18
56	GP 18	GFF1.2/9.6	FF 9.6	GFF2.3/9.6
57	Tiotropium 18	FF 9.6	GFF4.6/9.6	GP 18
58	GFF 18/9.6	GP 18	Tiotropium 18	GFF1.2/9.6
59	GFF1.2/9.6	FF 9.6	GFF9/9.6	GFF4.6/9.6
60	FF 9.6	GFF 18/9.6	Tiotropium 18	GFF2.3/9.6
61	GFF2.3/9.6	Tiotropium 18	GFF1.2/9.6	GFF9/9.6
62	Tiotropium 18	GFF 18/9.6	GFF1.2/9.6	GP 18
63	GFF4.6/9.6	GFF2.3/9.6	GP 18	GFF 18/9.6
64	GFF4.6/9.6	GFF9/9.6	GP 18	GFF2.3/9.6
65	Tiotropium 18	FF 9.6	GFF9/9.6	GP 18
66	GFF 18/9.6	GP 18	GFF1.2/9.6	GFF9/9.6
67	FF 9.6	GP 18	GFF2.3/9.6	GFF1.2/9.6
68	GFF 18/9.6	GFF4.6/9.6	FF 9.6	GFF1.2/9.6
69	GFF4.6/9.6	GFF9/9.6	GFF 18/9.6	Tiotropium 18
70	GP 18	GFF1.2/9.6	GFF 18/9.6	Tiotropium 18

	Period:			
Sequence	A	B	C	D
71	Tiotropium 18	FF 9.6	GFF9/9.6	GP 18
72	GFF 18/9.6	GFF4.6/9.6	FF 9.6	GFF1.2/9.6
73	GFF4.6/9.6	Tiotropium 18	GP 18	FF 9.6
74	GFF9/9.6	GFF1.2/9.6	GP 18	GFF 18/9.6
75	GFF2.3/9.6	GFF 18/9.6	GFF4.6/9.6	GP 18
76	GFF9/9.6	GFF1.2/9.6	GP 18	GFF 18/9.6
77	GFF4.6/9.6	GFF9/9.6	GFF 18/9.6	Tiotropium 18
78	GFF 18/9.6	GP 18	Tiotropium 18	GFF1.2/9.6
79	GFF2.3/9.6	GP 18	GFF9/9.6	GFF4.6/9.6
80	GP 18	GFF9/9.6	GFF 18/9.6	GFF1.2/9.6
81	GP 18	GFF4.6/9.6	FF 9.6	Tiotropium 18
82	FF 9.6	GFF 18/9.6	Tiotropium 18	GFF2.3/9.6
83	GP 18	GFF4.6/9.6	GFF 18/9.6	GFF2.3/9.6
84	FF 9.6	GP 18	Tiotropium 18	GFF9/9.6
85	GFF9/9.6	Tiotropium 18	GP 18	FF 9.6
86	GFF9/9.6	GFF2.3/9.6	GFF4.6/9.6	GP 18
87	GFF 18/9.6	GFF9/9.6	FF 9.6	GFF2.3/9.6
88	GFF2.3/9.6	FF 9.6	GFF9/9.6	GFF 18/9.6
89	FF 9.6	GP 18	Tiotropium 18	GFF4.6/9.6
90	GP 18	GFF1.2/9.6	FF 9.6	GFF2.3/9.6
91	GFF 18/9.6	GP 18	GFF2.3/9.6	GFF4.6/9.6
92	FF 9.6	GFF4.6/9.6	GFF1.2/9.6	GFF9/9.6
93	GP 18	GFF4.6/9.6	GFF 18/9.6	GFF2.3/9.6
94	GFF2.3/9.6	Tiotropium 18	GFF 18/9.6	FF 9.6
95	GFF4.6/9.6	GFF1.2/9.6	Tiotropium 18	GFF2.3/9.6
96	GP 18	GFF9/9.6	GFF 18/9.6	GFF1.2/9.6
97	GFF2.3/9.6	FF 9.6	GFF1.2/9.6	GP 18
98	Tiotropium 18	FF 9.6	GFF2.3/9.6	GFF 18/9.6
99	GFF1.2/9.6	GFF 18/9.6	GFF9/9.6	GP 18
100	GP 18	GFF4.6/9.6	GFF2.3/9.6	GFF9/9.6
101	Tiotropium 18	GFF9/9.6	GFF2.3/9.6	GFF1.2/9.6
102	GFF4.6/9.6	GFF1.2/9.6	GFF 18/9.6	FF 9.6
103	GFF2.3/9.6	Tiotropium 18	GFF1.2/9.6	GFF9/9.6
104	GFF1.2/9.6	Tiotropium 18	GP 18	GFF 18/9.6
105	GP 18	GFF9/9.6	FF 9.6	Tiotropium 18
106	GFF1.2/9.6	GFF2.3/9.6	GP 18	FF 9.6
107	GFF 18/9.6	GFF2.3/9.6	FF 9.6	Tiotropium 18
108	GFF9/9.6	GFF1.2/9.6	GFF4.6/9.6	FF 9.6

	Period:			
Sequence	A	B	C	D
109	GFF4.6/9.6	GFF9/9.6	FF 9.6	GFF1.2/9.6
110	GFF 18/9.6	GFF9/9.6	FF 9.6	GFF2.3/9.6
111	GFF2.3/9.6	GP 18	GFF9/9.6	GFF4.6/9.6
112	GP 18	GFF9/9.6	FF 9.6	Tiotropium 18
113	GFF9/9.6	GFF1.2/9.6	GFF2.3/9.6	GFF4.6/9.6
114	GP 18	GFF4.6/9.6	FF 9.6	GFF2.3/9.6
115	GFF2.3/9.6	FF 9.6	GFF4.6/9.6	GFF 18/9.6
116	GFF4.6/9.6	GFF2.3/9.6	GP 18	FF 9.6
117	GFF1.2/9.6	GFF4.6/9.6	GFF9/9.6	GFF2.3/9.6
118	GFF9/9.6	GP 18	Tiotropium 18	GFF4.6/9.6
119	GFF4.6/9.6	GFF2.3/9.6	GFF1.2/9.6	GFF9/9.6
120	GFF1.2/9.6	FF 9.6	GFF9/9.6	GFF 18/9.6
121	Tiotropium 18	GFF9/9.6	FF 9.6	GFF2.3/9.6
122	GFF 18/9.6	GFF9/9.6	FF 9.6	GP 18
123	FF 9.6	GFF 18/9.6	GP 18	GFF9/9.6
124	GFF2.3/9.6	GFF9/9.6	GFF4.6/9.6	GFF1.2/9.6
125	Tiotropium 18	GFF1.2/9.6	FF 9.6	GFF4.6/9.6
126	Tiotropium 18	GFF1.2/9.6	GFF 18/9.6	GFF2.3/9.6
127	FF 9.6	Tiotropium 18	GFF2.3/9.6	GFF9/9.6
128	GFF2.3/9.6	GFF 18/9.6	GP 18	Tiotropium 18
129	GP 18	GFF4.6/9.6	GFF9/9.6	Tiotropium 18
130	GFF 18/9.6	Tiotropium 18	GFF2.3/9.6	GFF1.2/9.6
131	GFF1.2/9.6	GFF4.6/9.6	Tiotropium 18	FF 9.6
132	GFF 18/9.6	GP 18	GFF4.6/9.6	GFF1.2/9.6
133	FF 9.6	Tiotropium 18	GFF4.6/9.6	GFF1.2/9.6
134	GFF1.2/9.6	GFF4.6/9.6	GP 18	GFF 18/9.6
135	Tiotropium 18	GFF9/9.6	GFF4.6/9.6	GP 18
136	GFF1.2/9.6	GFF2.3/9.6	Tiotropium 18	GFF 18/9.6
137	FF 9.6	GP 18	GFF2.3/9.6	GFF4.6/9.6
138	GFF2.3/9.6	GFF 18/9.6	GFF1.2/9.6	Tiotropium 18
139	Tiotropium 18	GP 18	GFF 18/9.6	GFF2.3/9.6
140	GFF2.3/9.6	FF 9.6	GFF4.6/9.6	GP 18
141	GFF9/9.6	GP 18	GFF 18/9.6	FF 9.6
142	GFF4.6/9.6	FF 9.6	GFF1.2/9.6	Tiotropium 18
143	GFF 18/9.6	GFF4.6/9.6	FF 9.6	GFF2.3/9.6
144	GFF4.6/9.6	GFF 18/9.6	GFF1.2/9.6	GP 18
145	FF 9.6	Tiotropium 18	GFF1.2/9.6	GP 18
146	GP 18	GFF2.3/9.6	Tiotropium 18	GFF 18/9.6

	Period:			
Sequence	A	B	C	D
147	GP 18	FF 9.6	GFF9/9.6	GFF 18/9.6
148	GFF9/9.6	GFF1.2/9.6	GFF 18/9.6	FF 9.6
149	GFF 18/9.6	Tiotropium 18	GFF2.3/9.6	GP 18
150	GFF1.2/9.6	GFF2.3/9.6	GP 18	GFF9/9.6
151	GFF9/9.6	GP 18	GFF2.3/9.6	GFF1.2/9.6
152	GP 18	GFF1.2/9.6	Tiotropium 18	FF 9.6
153	GP 18	GFF1.2/9.6	GFF 18/9.6	GFF4.6/9.6
154	FF 9.6	GFF 18/9.6	GFF1.2/9.6	GFF9/9.6
155	GFF4.6/9.6	Tiotropium 18	GP 18	GFF9/9.6
156	GFF4.6/9.6	GFF 18/9.6	GFF9/9.6	Tiotropium 18
157	GFF9/9.6	GFF2.3/9.6	Tiotropium 18	FF 9.6
158	Tiotropium 18	GFF9/9.6	GFF 18/9.6	GFF4.6/9.6
159	GFF 18/9.6	GFF9/9.6	FF 9.6	GFF1.2/9.6
160	GFF2.3/9.6	FF 9.6	GFF9/9.6	Tiotropium 18

Table B1-2. Extra Sequences

	Period:			
Extra Sequence	A	B	C	D
1	GFF9/9.6	GFF2.3/9.6	Tiotropium 18	GP 18
2	GFF2.3/9.6	GP 18	GFF9/9.6	Tiotropium 18
3	GP 18	Tiotropium 18	GFF2.3/9.6	GFF9/9.6
4	Tiotropium 18	GFF9/9.6	GP 18	GFF2.3/9.6
5	GFF 18/9.6	GFF4.6/9.6	FF 9.6	GFF1.2/9.6
6	GFF4.6/9.6	GFF1.2/9.6	GFF 18/9.6	FF 9.6
7	GFF1.2/9.6	FF 9.6	GFF4.6/9.6	GFF 18/9.6
8	FF 9.6	GFF 18/9.6	GFF1.2/9.6	GFF4.6/9.6

Appendix 9 Sponsor Signatory

Study Title: A Randomized, Double-Blind, (Test Products), Chronic Dosing (7 Days), Four-Period, Eight-Treatment , Incomplete Block, Cross-Over, Multi-Center Study to Assess Efficacy and Safety of Five Doses of PT003, One Dose of PT001 and One Dose of PT005 in Patients With Moderate to Severe COPD, Compared With Spiriva® Handihaler® (Tiotropium Bromide 18 µg, Open-Label) as Active Control

Study Number: PT003005-00

Final Date: [redacted]

Signature: [redacted] Date: [redacted]

Name: [redacted]

Title: [redacted]

Appendix 10 Investigator's Agreement and Signature Page

Study Title: A Randomized, Double-Blind, (Test Products), Chronic Dosing (7 Days), Four-Period, Eight-Treatment , Incomplete Block, Cross-Over, Multi-Center Study to Assess Efficacy and Safety of Five Doses of PT003, One Dose of PT001 and One Dose of PT005 in Patients With Moderate to Severe COPD, Compared With Spiriva® Handihaler® (Tiotropium Bromide 18 µg, Open-Label) as Active Control

Study Number: PT003005-00

Final Date: [redacted]

I agree:

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

Signature:_____ Date:_____

Name:_____

Affiliation: _____

_____