Clinical Trial Protocol: PT003008-01

Study Title:	A 28-Week, Multi-Center, Randomized, Double-Blind, Parallel-Group, Active-Controlled Safety Extension Study to Evaluate the Safety and Efficacy of PT003, PT001, and PT005 in Subjects With Moderate to Very Severe COPD, With Spiriva® Handihaler® as an Active Control
Study Number:	PT003008-01
Study Phase:	III
Product Name:	Glycopyrronium and Formoterol Fumarate Inhalation Aerosol; PT003 Formoterol Fumarate Inhalation Aerosol; PT005 Glycopyrronium Inhalation Aerosol; PT001
IND Number:	107739
Indication:	COPD
Investigators:	Multi-center
Sponsor:	[redacted]
Sponsor Contact:	[redacted]

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

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

- Several edits were made to the list of other efficacy endpoints endpoints (Synopsis, Section 3.4, and Section 9.2.2.3). The majority of the changes were made for clarity and consistency with the statistical analysis plan (SAP). Material changes that were made to the other efficacy endpoints include the addition of new other endpoints, time to treatment failure and percentage of days with 'no daytime symptoms'.

- In Section 5.4.2 (Other Prohibited Medications) Table 3 was deleted to remove inactivated and live attenuated vaccines as conditions for study participation.

- In Section 5.7 (Reasons and Procedures for Early Termination), Section 7.1.7 and Section 9.3.4.3 (COPD Exacerbations) classification of severity of exacerbation was updated as follows:

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

- In Sections 9.3.3.1, 9.3.3.3, and 9.9 edits have been made to reflect that the primary analysis of TDI and St. George Respiratory Questionnaire (SGRQ) will be in the Intent-to-Treat (ITT) Population and not the Symptomatic Population as previously specified. This change was in response to a recent article where higher Modified Medical Research Council (MMRC) values indicating greater baseline dyspnea levels did not predict larger differences from placebo in TDI scores for tiotropium or indacaterol (Mahler 2013). If there is not a larger treatment effect in the more symptomatic population, power would be decreased due to the reduction in sample size. Therefore, the ITT Population has been specified as primary. Also related to TDI, in Section 9.3.3.1, a summary of the practice question (tiredness) has been added.

- In Section 9.3.4.3, the analysis approach for chronic obstructive pulmonary disease (COPD) exacerbations was updated to better reflect the underlying distribution of the data. In addition, the text regarding differentiation of exacerbation events and calculation of treatment exposure was changed per recommendations of FDA. Additional changes to model covariates were also made to be consistent with the statistical analysis plan (SAP).

- Additional changes were made for consistency with the SAP. These include:
  - Throughout Section 9.3, the abbreviation MMRM was changed to RM since the variance matrix is being estimated using an unstructured model where subject as a random effect is confounded.

- A margin for evaluating the non-inferiority of GP MDI 14.4 µg to Spiriva for rescue Ventolin HFA use has been added to Section 9.3.3.4.
- In Section 9.3.4.4, the analysis of time to treatment failure was added. Treatment failure due to COPD exacerbation is defined as occurring for a moderate or severe COPD exacerbation rather than for an exacerbation of any severity.
- Covariates for the analyses of COPD exacerbations have been revised to include CAT scores while removing reversibility to Ventolin HFA (Section 9.3.4.3). In addition, text was added to clarify that analyses of COPD exacerbations will be performed with and without imputation of a moderate exacerbation at the time of dropout for subjects withdrawing prematurely from the trial, unless an exacerbation has already been recorded at that time.
- Descriptions of planned analyses of clinical laboratory measurements (Section 9.3.1.4), vital signs (Section 9.3.1.5), and ECG (Section 9.3.1.6) have all been revised to reflect the approach outlined in the SAP.
- The definition of the PP Population has been clarified to match the SAP without materially changing the meaning (Section 9.9).
- Several edits for clarity and consistency with other documents have been made throughout Section 9 that do not change the implementation or meaning of planned analyses.

- In addition, the opportunity was taken to address other minor protocol inconsistencies and typographical errors including updates to the abbreviation and reference lists.

SYNOPSIS

Sponsor:
Pearl Therapeutics

Names of Finished Products:
Glycopyrronium and Formoterol Fumarate Inhalation Aerosol; PT003
Formoterol Fumarate Inhalation Aerosol; PT005
Glycopyrronium Inhalation Aerosol; PT001
Spiriva® Handihaler®; Spiriva

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

Study Title:
A 28-Week, Multi-Center, Randomized, Double-Blind, Parallel-Group, Active-Controlled Safety Extension Study to Evaluate the Safety and Efficacy of PT003, PT001, and PT005 in Subjects With Moderate to Very Severe COPD, With Spiriva® Handihaler® as an Active Control

Study Number: PT003008-00

Study Phase: III

Study Objective(s):

Primary objective:

The primary objective of this Phase III study is to evaluate the long-term safety and tolerability of GFF MDI, GP MDI, FF MDI and Spiriva in subjects with moderate to very severe COPD over 52 weeks.

Secondary Objectives:

The secondary objectives of the study are:

- To compare the efficacy of treatment with GFF MDI to its components on lung function using FEV_1 over 52 weeks
- To compare the effects of GFF MDI to its components on dyspnea using the Transition Dyspnea Index (TDI) focal score over 52 weeks
- To compare the effect of GFF MDI to its components on quality of life using the change in St. George Respiratory Questionnaire (SGRQ) score over 52 weeks
- To compare the effects of GFF MDI to its components on symptoms using the change in rescue Ventolin HFA use as an indirect measure of symptom control over 52 weeks

Healthcare Resource Utilization (HCRU) Objective:

To assess the overall and COPD-specific HCRU between treatment groups

Study Design:

This is a multi-center, randomized, double-blind, parallel group, chronic dosing, active-controlled, 28-week safety extension study of the two pivotal 24-week safety and efficacy studies (Studies PT003006 and PT003007). This study is designed to assess the long-term safety and tolerability of GFF MDI, GP MDI, and FF MDI in subjects with moderate to very severe COPD over a total observation period of 52 weeks. Open-label Spiriva is included as an active control. To be eligible for this study, a subject must complete participation in Study PT003006 or Study PT003007.

All sites from Study PT003006 and Study PT003007 will be eligible to contribute subjects to this study. Across sites from Study PT003006 and Study PT003007, it is planned that approximately 850 subjects with moderate to very severe COPD will be included into the study to provide approximately 700 subjects to complete the study. Approximately 260 subjects will be enrolled into the GFF MDI treatment group, 225 subjects each into the GP MDI and FF MDI treatment groups, and 140 subjects into the Spiriva treatment group. Recruitment will be stopped when the appropriate number of subjects from Study PT003006 and Study PT003007 per treatment group are enrolled (i.e. complete Visit 11b) into the safety extension study (Study PT003008).

During the 28-week safety extension study, subjects who are randomly invited through the centralized IWRS to continue will remain on their treatment assigned from Study PT003006 or Study PT003007. Subjects assigned to Placebo MDI and, in order to maintain the blind, a proportion of subjects assigned to active treatment will not be invited to participate in the extension study (Study PT003008).

The entire study period is scheduled to take a maximum of 30 weeks for each individual subject. The study is anticipated to run for approximately 16 months and should not exceed 24 months.

Study Population:

Approximately 850 subjects with moderate to very severe COPD will be enrolled to provide approximately 700 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	Product Strength	Dosage Form	Comments
GFF MDI 14.4/9.6 µg ex-actuator	GFF MDI 7.2/4.8 µg per actuation	MDI	Taken as 2 inhalations.
GP MDI 14.4 µg ex-actuator	GP MDI 7.2 µg per actuation	MDI	Taken as 2 inhalations.
FF MDI 9.6 µg ex-actuator	FF MDI 4.8 µg per actuation	MDI	Taken as 2 inhalations.
Tiotropium inhalation powder† 18 µg	EU source: Spiriva Handihaler 1 capsule of 18 µg	DPI	Taken as 1 capsule via the Handihaler DPI. Supplies are open-label.
Albuterol Sulfate inhalation aerosol§ 90 µg	US source: Ventolin® HFA Each inhalation contains 108 µg corresponding to 90 µg albuterol base per actuation	MDI	Supplies are open-label.

DPI = dry powder inhaler; FF MDI = Formoterol Fumarate Metered Dose Inhaler; GFF MDI = Glycopyrronium and Formoterol Fumarate Metered Dose Inhaler; GP MDI = Glycopyrronium Metered Dose Inhaler; MDI = Metered Dose Inhaler.

† Active control

§ Rescue medication during the study.

Note: -All study drugs will be administered by oral inhalation. Glycopyrronium 14.4 µg in GFF MDI and GP MDI is equivalent to 18 µg of glycopyrronium bromide.

Duration of Treatment:

Each subject will receive study treatment for 28 weeks. The entire study is scheduled to take a maximum of 30 weeks for each individual subject from the time of enrollment (see Figure 1).

Assessments:

The data from this 28-week study will be combined with the 24 weeks of data obtained from the lead-in studies (Study PT003006 and Study PT003007) to provide safety and efficacy data over 52 weeks of treatment. Baseline for all subjects will remain the original baseline from PT003006 or PT003007.

Safety Endpoints

The primary objective of this study is to assess the safety and tolerability of treatment with GFF MDI (14.4/9.6 µg ex-actuator, BID), FF MDI (9.6 µg ex-actuator, BID), and GP MDI (14.4 µg ex-actuator, BID) over 52 weeks in subjects with moderate to very severe COPD. Safety and tolerability will be evaluated using adverse events (AE), vital sign measurements,

12-lead ECG parameters, and clinical laboratory parameters.

Primary Efficacy Endpoint

- Change from baseline in morning pre-dose trough FEV_1 over 52 weeks

Secondary Efficacy Endpoints (over 52 weeks)

- Transition Dyspnea Index (TDI) focal score
- Peak change from baseline in FEV_1 within 2 hours post-dosing
- Change from baseline in St. George Respiratory Questionnaire (SGRQ) total score
- Change from baseline in average daily rescue Ventolin HFA use

Other Efficacy Endpoints (over 52 weeks unless otherwise stated)

- Rate of all COPD exacerbations
- Time to the first COPD exacerbation of any severity
- Rate of moderate or severe COPD exacerbations
- Time to the first moderate or severe COPD exacerbation
- Time to treatment failure
- Additional spirometry assessments over 52 weeks and at each visit:
  - Change from baseline in morning pre-dose trough for FEV_1, forced vital capacity (FVC), peak expiratory flow rate (PEFR), and forced expiratory flow between 25% to 75% of FVC (FEF_{25-75})
  - Peak change from baseline within 2 hours in FEV_1, FVC, PEFR, and FEF_{25-75}
  - FEV_1 AUC_{0-2}, FVC AUC_{0-2}, PEFR AUC_{0-2}, and FEF_{25-75} AUC_{0-2}
- Percentage of days with 'no rescue Ventolin HFA use'
- Percentage of nights with 'no nighttime awakenings'
- Percentage of nights with fewer than 3 nighttime awakenings
- Percentage of days with 'no daytime symptoms'
- Change from baseline in mean daily total symptom score as well as each individual symptom (cough, shortness of breath, sputum volume, nighttime awakenings, and rescue Ventolin HFA use), the mean daytime total and individual symptom scores, and the mean nighttime total and individual symptom scores over 52 weeks and over each 4 week interval of the 52 weeks of treatment
- TDI focal score at each post-randomization visit
- Individual components of the TDI: functional impairment, magnitude of task, and magnitude of effort over 52-weeks and at each post-randomization visit
- Percentage of subjects achieving a minimal clinically important difference (MCID) threshold of $\geq$1 unit in TDI focal score

- Changes from baseline at each post-randomization visit for SGRQ total score
- Change in individual domain of SGRQ: Symptoms, Activity and Impacts over 52-weeks and at each post-randomization visit
- Percentage of subjects achieving a MCID threshold of $\geq$ 4 units in SGRQ total score

Statistical Methods:

Sample Size Determination: The sample size has been chosen to ensure that a sufficient number of subjects (as recommended on the International Conference on Harmonisation Guidance E1A guidance) will have been exposed to GFF MDI (14.4/9.6 µg, BID), FF MDI (9.6 µg, BID), and GP MDI (14.4 µg, BID) for 52 weeks for long-term safety assessments. Approximately 850 subjects with a clinical diagnosis of moderate to very severe COPD will be enrolled in the study. It is expected that approximately 260 subjects will be enrolled into GFF MDI (14.4/9.6 µg), 225 subjects to GP MDI (14.4 µg), 225 subjects to FF MDI (9.6 µg), and 140 subjects to the Spiriva group (18 µg, open-label). The target enrollment allows for well over 20% of subjects to discontinue treatment while ensuring that at least 100 subjects complete 52 weeks of treatment in all blinded treatment groups. This sample size provides approximately 80% power to detect (i.e., observe at least one) an AE providing that the AE has an underlying incidence rate of 1.1% in the smallest treatment arm (Spiriva) or 0.6% in the largest treatment arm (GFF MDI) during the 28 weeks of this trial.

With regards to the primary efficacy endpoint, changes from baseline in morning pre-dose trough FEV_1 over 52 weeks, this sample size combined with the data from PT003006 and PT003007 will provide approximately 99% power to demonstrate that GFF MDI is superior to its components if the true differences from GP MDI and FF MDI in morning pre-dose trough FEV_1 over 52 weeks are 50 and 60mL, respectively.

Safety Analysis

The number and percent of AEs, SAEs, AEs leading to withdrawal, suspected drug-related AEs, and AEs by length of exposure to study drug will be summarized by treatment group for all events together, by primary system organ class, and by preferred term. No statistical hypothesis testing will be done on adverse events. In addition, to control for possible differences in exposure between the treatment groups, AEs and SAEs will also be presented with the total number of events per patient-years of exposure for all events together, by primary system organ class, and by preferred term. Survival analysis will be used to compare of time to death and time to first Major Adverse Cardiovascular Event (MACE) between treatment groups.

Changes from baseline in vital sign measurements, 12-lead ECG parameters, and clinical laboratory parameters will be summarized by treatment group. Frequency counts for notable values will also be tabulated.

Date of Original Approved Protocol: [redacted]
Date of Amendment 1: [redacted]
Prepared in: Microsoft Word 2007

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	Adverse event
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AR (1)	First order autoregressive
AST	Aspartate aminotransferase
ATS	American Thoracic Society
BDI	Baseline Dyspnea Index
BID	bis in die, Twice Daily
BP	Blood Pressure
BTPS	Body Temperature and Pressure Saturated
CAT	COPD Assessment Test
CCU	Coronary Care Unit
CCV	Cardio- and Cerebro-vascular
CFR	Code of Federal Regulations
CHMP	Committee for Medicinal Products for Human Use
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
COPD	Chronic Obstructive Pulmonary Disease
CTCAE	Common Terminology Criteria for Adverse Events
DMC	Data Monitoring Committee
DPI	Dry Powder Inhaler
e.g.	Exempli gratia, for example
eCRF	Electronic Case Report Form
ECG	Electrocardiogram
eDiary	Electronic Diary
ER	Emergency Room
ERS	European Respiratory Society
EU	European Union
EV	Back Extrapolation Volume

ex-actuator	Dose Delivered From The Actuator (i.e., mouthpiece) Of The MDI
FDA	Food and Drug Administration
FEF_{25-75}	Forced Expiratory Flow from 25% to 75% of FVC
FEV_1	Forced Expiratory Volume In 1 Second
FF MDI	Formoterol Fumarate MDI
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GFF MDI	Glycopyrronium and Formoterol Fumarate MDI
GP MDI	Glycopyrronium MDI
HCG	Human Chorionic Gonadotropin
HCRU	Healthcare Resource Utilization
HFA	Hydrofluroalkane
i.e.	*Id est,* that is
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ICMJE	International Committee of Medical Journal Editors
ICS	Inhaled Corticosteroid
ICU	Intensive Care Unit
IEC	Independent Ethics Committee
IPF	Interstitial Pulmonary Fibrosis
IRB	Institutional Review Board
ITT	Intention-to-treat
IWRS	Interactive Web Response System
L	Liter
LABA	Long-acting Beta Agonist
LAMA	Long-acting Muscarinic Antagonist
MAR	Missing At Random
MACE	Major Cardiovascular Adverse Event
MCAR	Missing Completely At Random
MCH	Mean Corpuscular Hemoglobin

MCHC	Mean Corpuscular Hemoglobin Concentration
MCID	Minimal clinically important difference
MCV	Mean Corpuscular Volume
MDI	Metered Dose Inhaler
MedDRA	Medical Dictionary for Regulatory Activities
mL	Milliliter
NMAR	Not Missing At Random
OTC	Over the counter
PEFR	Peak Expiratory Flow Rate
PFT	Pulmonary Function Test
PI	Primary Investigator
PIN	Personal identification number
PP	Per Protocol
PRN	pro re nata, As Needed
QD	quaque die, Once Daily
QTcF	QT corrected using Fridericia's formula ($QT/(RR^{1/3})$)
RM	Repeated Measures
SABA	Short-acting Beta Agonist
SAC	Self-administered computerized
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure
SGRQ	St. George Respiratory Questionnaire
SOP	Standard Operating Procedure
SMQ	Standard MedDRA Query
TC	Telephone call
TDI	Transition Dyspnea Index
TNF α	Anti-tumor Necrosis Factor α
TURP	Trans-urethral Resection Of Prostate
US	United States

WAVE	Weighted average

TRADEMARK INFORMATION

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Aerolizer
Atrovent
Breezhaler
Combivent
Elkira
Foradil
Handihaler
Robinul
Robinul Forte
Seebri
Spiriva
Tudorza
Ventolin

1 INTRODUCTION AND STUDY RATIONALE

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

COPD is a disease of the lungs characterized by airflow limitation that is not fully reversible. The chronic airflow limitation characteristic of COPD is caused by a mixture of small airways disease (obstructive bronchiolitis) and parenchymal destruction (emphysema) the relative contributions of which vary from person to person. The airflow limitation is progressive in nature and associated with abnormal inflammatory response of the lung to noxious particles or gases. This disease is characterized by premature loss of ventilatory function as determined by a decline in forced expiratory volume in the first second of exhalation (FEV_1). Pathological inflammatory changes are characterized by elevations in activated macrophages, neutrophils, elastases, and CD8 lymphocytes. These molecular and cellular changes cause the destruction of small airways and surrounding alveoli. As expiratory airflow (FEV_1 or forced vital capacity [FVC]) is a function of pressure against resistance, airflow in COPD is diminished due to a loss of elastic recoil and airway constriction.

Pharmacologic therapy for COPD is used to reduce symptoms, reduce the frequency and severity of exacerbations, and improve health status and exercise tolerance. Bronchodilators are the mainstay of pharmacologic treatment of COPD. The principal bronchodilator treatments are short-acting beta agonists (SABAs), long-acting beta agonists (LABAs), short acting muscarinic antagonists, long-acting muscarinic antagonists (LAMAs) and methylxanthines used as monotherapy or in combination. In subjects with significant symptoms but low risk of exacerbations regular treatment with LABAs is more effective in the management of COPD than SABAs. In subjects with a high risk of exacerbations regardless of the number of symptoms, a fixed combination of an inhaled corticosteroid/LABA or a LAMA is recommended (GOLD, 2011).

Currently, no fixed-dose combination of a LABA and a LAMA is available. Combivent® [salbutamol sulfate and ipratropium bromide] is a short-acting fixed dose combination of a SABA and short acting muscarinic antagonist indicated for the treatment of COPD and is administered as two inhalations four times daily. Published studies (van Noord, 2005; van Noord, 2006; Vogelmeier, 2006) have shown that the complementary mechanisms of action of a LABA (formoterol fumarate) and a LAMA (tiotropium bromide) significantly improved bronchodilation in COPD subjects compared to the individual agents.

Pearl Therapeutics is developing a combination product, Glycopyrronium and Formoterol Fumarate Inhalation Aerosol (hereafter referred to as GFF MDI), as a maintenance bronchodilator treatment in patients with COPD. Pearl Therapeutics is also developing the individual products, Glycopyrronium Inhalation Aerosol (hereafter referred to as GP MDI) and Formoterol Fumarate Inhalation Aerosol (hereafter referred to as FF MDI) as maintenance bronchodilator treatments in patients with COPD.

Pearl Therapeutics has recently changed the naming convention for GFF MDI and GP MDI to make reference to the active moiety – glycopyrronium – instead of the bromide salt form previously used (glycopyrronium bromide, also known as glycopyrrolate). There have been no changes made to formulation of GFF MDI or GP MDI, just a change in how the strength/dose is expressed. All references to strengths/doses of GFF MDI and GP MDI in this protocol are based on the mass of glycopyrronium. In all prior clinical studies, Pearl Therapeutics expressed the strengths/doses of GFF MDI and GP MDI based on the mass of glycopyrrolate (glycopyrronium bromide), which is the bromide salt form of the active material. In this study, GFF MDI 14.4/9.6 µg contains 14.4 µg of glycopyrronium and 9.6 µg of formoterol fumarate and GP MDI 14.4 µg contains 14.4 µg of glycopyrronium. Both GFF MDI and GP MDI are administered twice daily (BID). The dose of glycopyrronium (14.4 µg) in GFF MDI and GP MDI is equivalent to 18 µg of glycopyrrolate (glycopyrronium bromide).

Glycopyrronium is a LAMA which exerts its bronchodilatory effect via muscarinic receptors located on smooth muscle cells within the trachea and bronchi. Glycopyrronium is approved in many countries in multiple formulations for different indications, including COPD.

An inhaled formulation of glycopyrronium (Seebri® Breezehaler® Inhalation Powder, glycopyrronium bromide) was recently approved throughout the European Union (EU), Australia and Cananda for the management of adult patients with COPD. The recommended dose is 44 µg (delivered dose of 55 µg of glycopyrronium bromide equivalent to 44 µg of glycopyrronium) administered once daily (QD) using the Seebri Breezhaler inhaler. The clinical development program for Seebri Breezehaler included 12 clinical studies, five Phase I studies, four Phase II clinical studies and three Phase III clinical studies. Overall, the clinical development program included a total of 1,361 patients with COPD exposed to Seebri Breezhaler 44 µg QD with a total of 842 and 428 patients with COPD exposed to Seebri Breezhaler 44 µg QD for ≥26 weeks and ≥38 weeks, respectively [Committee for Medicinal Products for Human Use (CHMP) Assessment Report for Seebri Breezehaler, 2012]. In addition to the published data with Seebri Breezehaler (also referred to as NVA 237), there is also large body of published data evaluating the safety and efficacy of inhaled glycopyrronium in healthy volunteers, patients with COPD, and patients with asthma.

Ten clinical studies have been conducted to support the dose selection of GFF MDI, GP MDI, and FF MDI. Efficacy and safety data are available from three studies conducted with GP MDI, and two studies with FF MDI. In addition, four studies conducted in subjects with COPD and one study conducted in healthy volunteers has been completed with GFF MDI, GP MDI, and FF MDI across a wide range of doses. Please note that the doses of GFF MDI

and GP MDI are expressed in terms of glycopyrronium bromide (glycopyrrolate) for the previously completed studies described below.

GP MDI has been evaluated in eight studies conducted by Pearl Therapeutics, including a single dose, single center, healthy volunteer study in Australia and seven multi-center studies in subjects with COPD conducted in the United States (US), Australia, and New Zealand. This program has assessed the safety and efficacy of GP MDI across a wide range of doses from 144 µg down to 0.6 µg. Across these eight studies, approximately 350 subjects with moderate to severe COPD were exposed to one or more doses of GP MDI. The lower end of the dose-response curve has been adequately characterized in two chronic-dose, dose-ranging studies (Studies PT001002 and PT001003), and the findings from these two studies and the previous Phase II studies support GP MDI 18 µg BID as the most appropriate dose to be evaluated in Phase III clinical studies.

Formoterol fumarate is a potent and selective LABA approved in many countries worldwide for use in asthma and COPD. When inhaled, formoterol fumarate acts locally in the lung as a bronchodilator. Formoterol fumarate stimulates β_2 adrenoreceptors in the airways, inducing airway smooth muscle relaxation and reducing or preventing bronchoconstriction.

In patients with COPD, formoterol fumarate 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. Although formoterol fumarate is classified as a LABA, it has a rapid onset of action similar to SABAs. Formoterol fumarate is highly potent, displays high intrinsic activity, and can result in greater than 80% relaxation even under induced tone (Anderson, 1993). Five large, placebo controlled clinical studies of up to 12 months in duration in nearly 2,500 patients demonstrated that formoterol fumarate is effective and well tolerated in patients with COPD (Dahl, 2001; Rossi, 2002; Aalbers, 2002; Campbell, 2005; Campbell, 2007).

Pearl Therapeutics is developing its combination product GFF MDI in parallel with the individual agents. Eight different doses of GFF MDI have been evaluated in five studies conducted by Pearl Therapeutics, including a single dose, single center, healthy volunteer study in Australia, and four multi-center studies in subjects with COPD conducted in the United States, Australia, and New Zealand. The studies in subjects with COPD included three phase IIb studies of 1-week duration and one cardiovascular safety study of 2-week duration. The GFF MDI doses that have been studied include the following dosing combinations: 72/9.6 µg, 36/9.6 µg, 36/7.2 µg, 18/9.6 µg, 9/9.6 µg, 4.6/9.6 µg, 2.4/9.6 µg, and 1.2/9.6 µg. Throughout this Phase IIb program, over 300 subjects with COPD have been exposed to one or more doses of GFF MDI. A brief summary of the data supporting dose selection is addressed below.

In Study PT0031002, GFF MDI 72/9.6 µg was comparable to GFF MDI 36/9.6 µg and Pearl Therapeutics determined that GFF MDI 36/9.6 µg would be the highest dose for further evaluation. Study PT003003 evaluated the overall cardiovascular safety of GFF MDI 36/9.6 compared to its components and open label Foradil. In this study, 24-hour Holter monitoring data obtained on Day 1 and Day 14 of dosing were comparable across all treatments and comparable to 24-hour Holter monitoring data obtained during the screening period on

Atrovent HFA MDI. Study PT003004 evaluated the safety and efficacy of GFF MDI 36/9.6 µg, GFF MDI 36/7.2 µg, GFF MDI 18/9.6 µg, and GFF MDI 9/9.6 µg compared to GP MDI 36 µg and FF MDI 9.6 µg. In this study, all GFF MDI doses provided roughly comparable bronchodilation as assessed by FEV_1 AUC_{0-12} on Day 7 with a similar safety profile. These results are aligned with those of the earlier GP MDI dose ranging study (Study PT001002) and supported a relatively flat dose response to glycopyrrolate whether administered alone or as a fixed combination with formoterol fumarate. Based on these results, even lower doses of GFF MDI were evaluated in Study PT003005. Study PT003005 was a randomized, double-blind, chronic-dosing (7 days), four-period, eight-treatment, incomplete block, crossover, 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 administered BID) compared with FF MDI (9.6 µg administered BID), GP MDI (18 µg administered BID), and Spiriva® Handihaler® (Spiriva, 18 µg open-label, QD) in subjects with moderate to severe COPD. All doses of GFF MDI demonstrated statistically significant improvements compared to FF MDI 9.6 µg and GP MDI 18 µg in FEV_1 AUC_{0-12} with the exception of GFF MDI 1.2/9.6 µg relative to FF MDI 9.6 µg, which just missed a statistically significant difference. In addition, all doses of GFF MDI from 2.4/9.6 µg to 18/9.6 µg demonstrated statistically significant improvements compared to Spiriva in FEV_1 AUC_{0-12}. Based on this data the incremental value of GP MDI 18 µg when added to FF MDI 9.6 µg provides a reasonable benefit across all parameters. GFF MDI 18/9.6 µg was safe and well tolerated with an AE profile similar to its components and approved products for the management of COPD (i.e. Spiriva, Atrovent, and Foradil Aerolizer). A more detailed description of the studies design and results can be obtained in the Investigator Brochure.

1.1 Study Rationale

The purpose of this Phase III study is to evaluate the long-term safety and tolerability of GFF MDI, GP MDI, FF MDI and Spiriva in subjects with moderate to very severe COPD over 52 weeks. Data obtained from this study, together with two 6-month pivotal studies (Study PT003006 and Study PT003007), are intended to support the registration of GFF MDI, GP MDI and FF MDI worldwide.

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of this Phase III study is to evaluate the long-term safety and tolerability of GFF MDI, GP MDI, FF MDI and Spiriva in subjects with moderate to very severe COPD over 52 weeks.

2.2 Secondary Objectives

The secondary objectives of the study are:

- To compare the efficacy of treatment with GFF MDI to its components on lung function using FEV_1 over 52 weeks
- To compare the effects of GFF MDI to its components on dyspnea using the Transition Dyspnea Index (TDI) focal score over 52 weeks
- To compare the effect of GFF MDI to its components on quality of life using the change in St. George Respiratory Questionnaire (SGRQ) score over 52 weeks
- To compare the effects of GFF MDI to its components on symptoms using the change in rescue Ventolin HFA use as an indirect measure of symptom control over 52 weeks

2.3 Healthcare Resource Utilization (HCRU) Objective:

To assess the overall and COPD-specific HCRU between treatment groups

3 STUDY ENDPOINTS

The data from this 28-week study will be combined with the 24 weeks of data obtained from the lead-in studies (Study PT003006 and Study PT003007) to provide safety and efficacy data over 52 weeks of treatment. Baseline for all subjects will remain the original baseline from PT003006 or PT003007.

3.1 Safety Endpoints

Overall safety and tolerability will be evaluated using adverse events, vital sign measurements, 12-lead ECG parameters, and clinical laboratory parameters over 52 weeks.

3.2 Primary Efficacy Endpoint

Change from baseline in morning pre-dose trough FEV_1 over 52 weeks

3.3 Secondary Efficacy Endpoints (over 52 weeks)

- Transition Dyspnea Index (TDI) focal score
- Peak change from baseline in FEV_1 within 2 hours post-dosing
- Change from baseline in St. George Respiratory Questionnaire (SGRQ) total score
- Change from baseline in average daily rescue Ventolin HFA use

3.4 Other Efficacy Endpoints (over 52 weeks unless otherwise specified)

- Rate of all COPD exacerbations
- Time to the first COPD exacerbation of any severity
- Rate of moderate or severe COPD exacerbations
- Time to the first moderate or severe COPD exacerbation
- Time to treatment failure
- Additional spirometry assessments over 52 weeks and at each visit:
  - Change from baseline in morning pre-dose trough for FEV_1, forced vital capacity (FVC), peak expiratory flow rate (PEFR), and forced expiratory flow between 25% to 75% of FVC (FEF_{25-75})
  - Peak change from baseline within 2 hours in FEV_1, FVC, PEFR, and FEF_{25-75}
  - FEV_1 AUC_{0-2}, FVC AUC_{0-2}, PEFR AUC_{0-2}, and FEF_{25-75} AUC_{0-2}
- Percentage of days with ‘no rescue Ventolin HFA use’
- Percentage of nights with ‘no nighttime awakenings’
- Percentage of nights with fewer than 3 nighttime awakenings
- Percentage of days with ‘no daytime symptoms’

- Change from baseline in mean daily total symptom score as well as each individual symptom (cough, shortness of breath, sputum volume, nighttime awakenings, and rescue Ventolin HFA use), the mean daytime total and individual symptom scores, and the mean nighttime total and individual symptom scores over 52 weeks and over each 4 week interval of the 52 weeks of treatment
- TDI focal score at each post-randomization visit
- Individual components of the TDI: functional impairment, magnitude of task, and magnitude of effort over 52-weeks and at each post-randomization visit
- Percentage of subjects achieving a MCID threshold of ≥ 1 unit in TDI focal score
- Changes from baseline at each post-randomization visit for SGRQ total score
- Change in individual domain of SGRQ: Symptoms, Activity and Impacts over 52-weeks and at each post-randomization visit
- Percentage of subjects achieving a MCID threshold of ≥ 4 units in SGRQ total score

3.5 Health Care Resource Utilization Endpoints

The number of days missed from work, and COPD-related and non-COPD related telephone calls and visits to healthcare providers, Emergency Room (ER) visits, and hospitalizations including days in hospital, days in Intensive Care Units (ICU), days in Coronary Care Units (CCU), and whether the subject was intubated will be captured and compared between treatment groups.

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

This is a multi-center, randomized, double-blind, parallel group, chronic dosing, active-controlled, 28-week safety extension study of the two pivotal 24-week safety and efficacy studies (PT003006 and PT003007). This study is designed to assess the long-term safety and tolerability of GFF MDI, GP MDI, and FF MDI in patients with moderate to very severe COPD over a total observation period of 52 weeks. Open-label Spiriva is included as an active control. To be eligible for this study, a subject must complete participation in Study PT003006 or Study PT003007.

All sites from Study PT003006 and Study PT003007 will be eligible to contribute subjects to this study. Across sites from Study PT003006 and/or Study PT003007, it is planned that approximately 850 subjects with moderate to very severe COPD will be included into the study to provide approximately 700 subjects to complete the study. Approximately 260 subjects will be enrolled into the GFF MDI treatment group, 225 subjects into the GP MDI and FF MDI groups, and 140 subjects into the Spiriva treatment group. Recruitment will be stopped when the appropriate number of subjects are enrolled (complete visit 11b) into the safety extension study (Study PT003008).

During the 28-week safety extension study, subjects who are randomly invited through the centralized IWRS to continue will remain on their treatment assigned from Study PT003006 or Study PT003007. Subjects assigned to Placebo MDI and, in order to maintain the blind, a proportion of subjects assigned to active treatment will not be invited to participate in the extension study (Study PT003008).

The entire study period is scheduled to take a maximum of 30 weeks for each individual subject. The study is anticipated to run for approximately 16 months and should not exceed 24 months.

There are 11 scheduled visits in the lead-in studies, the eleventh visit is the last visit of the lead-in studies and the first visit of the extension study. In order to differentiate, assessments conducted at the completion of the lead-in studies (Studies PT003006 and PT003007) will be captured in Visit 11a and the initial assessment conducted in the extension study (Study PT003008) will be captured in Visit 11b. Visit 11b will begin immediately following completion of Visit 11a procedures.

At Visit 11b, all subjects who are eligible for participation in and agree to participate in Study PT003008 will sign an informed consent form prior to the conduct of any study assessments specific to Study PT003008. Subjects will be reminded to not use certain prohibited COPD medications and to maintain their maintenance COPD therapy as adjusted for participation in Study PT003006 or Study PT003007 (see Section 5.4).

Subjects who meet all entry criteria will undergo Visit 11b procedures including dispensing of study medication by IWRS. Subjects will then be discharged from the clinic and will continue to administer study medication for 4 weeks at home until Visit 12.

Following enrollment (Visit 11b) into this safety extension study, subjects will be examined at Visit 12 (Week 28), Visit 13 (Week 36), Visit 14 (Week 44), and Visit 15 (Week 52). In total each completed subject will attend 5 scheduled visits in this study. For assessments at each of these visits refer to assessment schedule in Table 8.

Subjects will be required to take their study medication twice a day, except for the Spiriva arm which will be taken once daily in the morning. Those subjects assigned to an MDI will inhale 2 puffs from their MDI in the morning between 06:00 and 10:00 AM (Breakfast time) and in the evening between 06:00 and 10:00 PM (Dinner time).

Treatment Visits 11b through Visit 15:

- At the start of each study visit, prior to any study procedures being performed, site personnel must confirm the subject withheld all COPD medications, including study medication, rescue Ventolin HFA, and maintenance medications (ICS, theophylline or PDE4's) 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. completion of Visit 11a).
- 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.
- Subjects will be required to refrain from smoking (nicotine gums or patches are allowed) for at least 4 hours prior to each study visit and throughout the duration of each study visit.
- In order to minimize diurnal variance, sites should make every effort to assess subjects at the same time throughout the study and to discuss the importance of dosing in a timely manner every 12 hours if on an MDI or every 24 hours if on Spiriva.
    - Subjects will be required to return to the clinic at approximately the same time as Visit 2 of the lead-in studies (Study PT003006 and Study PT003007) 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.
    - Sites should make every effort to ensure that the in-clinic dosing time is before 10:00 AM and within 12±2 hours of the prior at home evening dosing time if the subject is assigned to blinded treatment (GFF MDI, GP MDI or FF MDI) or within 24±2 hours of the prior at home morning dosing time if the subject is assigned to the Spiriva.
- To ensure standardization of dosing times, it is recommended that sites encourage subjects to maintain a dosing schedule consistent with their in-clinic dosing time and that

sites call the subject on the day before a scheduled visit to remind the subject of the following:

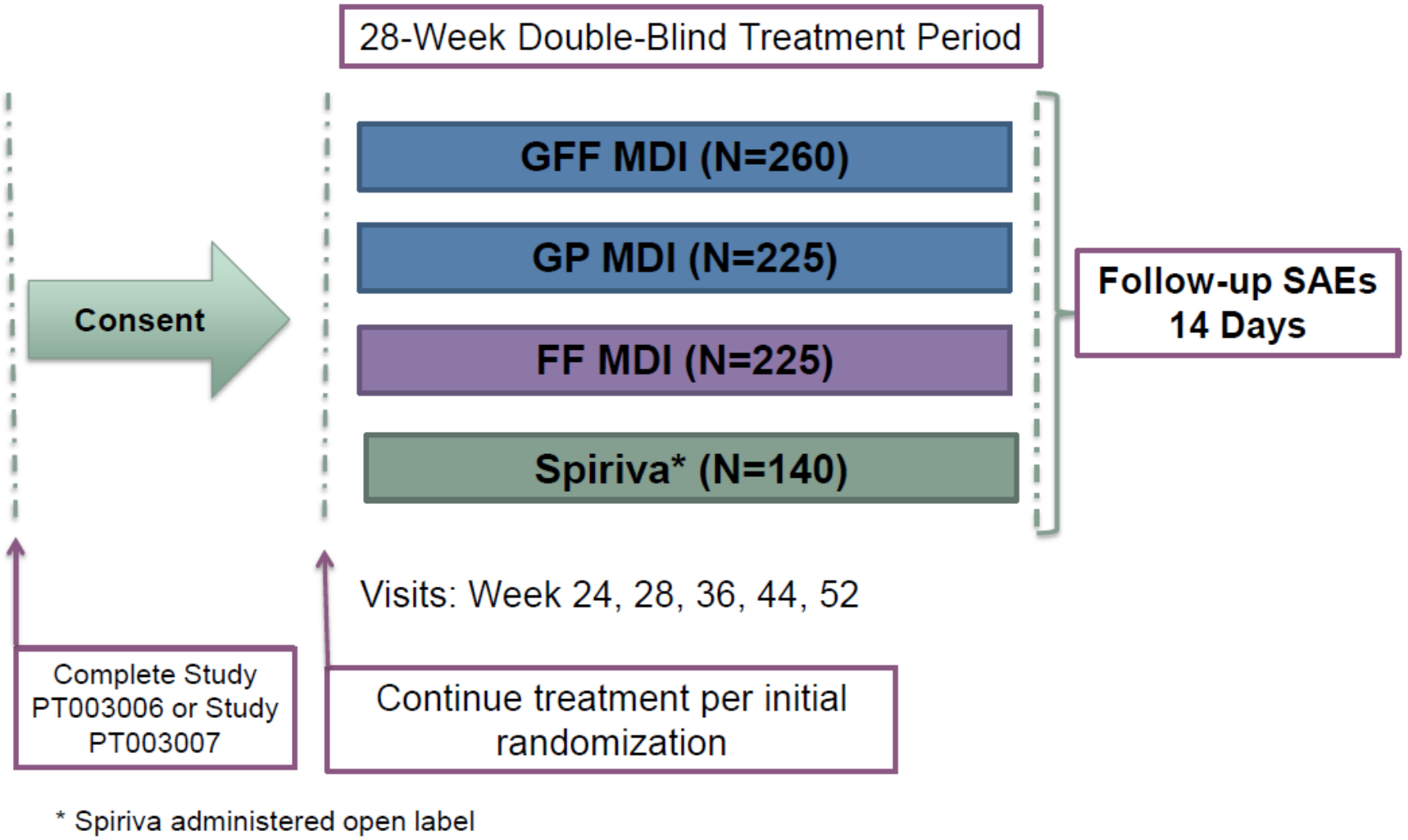
- Subjects assigned to blinded treatment (GFF MDI, GP MDI or FF MDI), should be reminded to take their last dose the evening before the scheduled visit.
- Subjects assigned to Spiriva, should be reminded to take their last dose the morning before the scheduled visit.
- To bring their study medications with them to the clinic and to withhold all COPD medications (including ICS and phosphodiesterase inhibitors) for at least 6 hours prior to PFTs.
- Refrain from ingesting xanthine-containing foods and beverages for at least 6 hours prior to each study visit and for the duration of each study visit.
- Refrain from smoking for at least 4 hours prior to the study visit and throughout the duration of each study visit.

- The in-clinic dosing time for blinded study drug (GFF MDI, GP MDI or FF MDI) will be recorded as the time of administration of the second puff.
- 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 subject use of COPD medications during test day. Site personnel may request the subject to surrender all COPD medications prior to the start of the visit before performing any study procedures and return the COPD medications to the subject at the end of the visit when all study procedures are completed. Subjects will be asked to abstain wherever possible from using rescue Ventolin HFA during study visits. 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 assessments should be continued at the discretion of the Investigator.
- Protocol-adjusted ICS therapy as defined at Visit 1 (Screening) of the lead-in studies (Study PT003006 and Study PT003007) if any, should be continued and remain stable for the duration of the trial (see Section 5.4).
- All visits will be scheduled relative to Visit 4 (Treatment Day 1, Randomization) of Study PT003006 or Study PT003007. Thus Visits 12, 13, 14, and 15, will be scheduled 28, 36, 44, and 52 weeks ± 7 days of Visit 4 of Study PT003006 or PT003007 respectively. Sites should make every effort to maintain subjects within the scheduled visit window (particular attention should be made to schedule the final visit as close to 52 weeks as possible). If a visit falls outside the expected visit window the subsequent visit should still be scheduled as planned relative to visit 4.

Subjects who complete (Visit 15) of this safety extension study will be scheduled for a post-study follow-up telephone call at least 14 days from Visit 15.

A Study Flow Diagram is displayed in Figure 1.

Figure 1. Study Flow Diagram



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. Completion of the treatment phase of the lead-in study either PT003006 or PT003007.
3. Compliance with Study PT003006 or Study PT003007 study procedures and study drug dosing.
4. No medical contraindication as judged by the PI

5.2 Exclusion Criteria

1. Requiring and currently being administered contraindicated medications as listed in Tables 1, 2 and 4.

5.3 Subject Identification

All subjects who participate in this study will maintain the unique screening identification number and unique subject randomization number assigned to them for participation in Study PT003006 or PT003007.

5.4 Prior, Concomitant, and Prohibited Medications

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.

5.4.1 Prohibited COPD Medications

The following medications used for the treatment of COPD are not permitted during this study. These medications must have been discontinued during the Screening Period of Study PT003006 or Study PT003007 and are also not permitted during this extension study (see Table 1).

Table 1. Prohibited COPD Medications

Class of medication
Long-acting anticholinergics
Short-acting anticholinergics
Fixed-combinations of long-acting β_2 agonists and inhaled corticosteroids
Fixed-combinations of short-acting β_2 agonists and short-acting anticholinergics
Long acting β_2 agonists
Short-acting β_2 agonists (other than study rescue Ventolin HFA)
Theophylline (Total daily dose >400 mg/day)*

*Theophylline is allowed if the total daily dose is 400 mg or less. Subjects taking Roflumilast are allowed provided they have been on stable dose of therapy during participation in Study PT003006 or Study PT003007.

Note: During the Treatment Period (Visit 11b to Visit 15), subjects may be treated with corticosteroids if required.

Subjects receiving a maintenance dose of an ICS will be permitted to continue the ICS. Subjects who are steroid dependent and maintained on an equivalent of ≤5 mg oral prednisone per day or ≤10 mg oral prednisone every other day are permitted to enroll in the study provided they have been on a stable dose of therapy during participation in Study PT003006 or Study PT003007.

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

Table 2. Other Respiratory/Nasal Medications:

Class of medication
Leukotriene antagonists (e.g., zafirlukast, montelukast, and zilueton)
Cromoglycate
Nedocromil
Ketotifen *

*Ketotifen eye drops are allowed

5.4.2 Other Prohibited Medications

Subjects requiring the following medications are prohibited from this study (Table 3). These medications are prohibited throughout the course of the study and should a subject require use of any of the listed medications they should be discontinued.

Table 3. Prohibited Medications

Prohibited Medications
Any drug with potential to significantly prolong the QT interval
Other investigational drugs
Non-selective beta-blocking agents
Cardiac antiarrhythmics Class Ia, III
Anticonvulsants for seizure disorder
Anticonvulsants for other indications
Tricyclic antidepressants
Monoamine oxidase inhibitors
Anti-tumor necrosis factor α (TNF α) antibodies (e.g.infliximab and any other members of this class of drugs)
Monoclonal antibodies
Antipsychotic drugs *
Systemic calcineurin inhibitors, systemic antifungal agents, protease inhibitors and cimetidine
Systemic anticholinergics**

*Antipsychotic agents used for other indications may be allowed after consultation with the medical monitor of the trial.

**Systemic anticholinergics are allowed providing the patient was treated with this class of medications during Study PT003006 or PT003007
Note: Benzodiazepines are not exclusionary.

5.5 Other Restrictions, Illicit Drugs or Drugs of Abuse

Illicit drugs or drugs of abuse will not be allowed during the study from Visit 11b to Visit 15 or to whenever the subject discontinues the study. If any illicit drugs or drugs of abuse are used by the subject during the study, the dates of use and the amount will be documented. Medical marijuana is not an exclusionary drug if used for medical purposes, and there is no change in the dose or frequency of consumption.

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

5.6 Smoking Status

Changes in a subject's smoking status (e.g., stopping or re-starting smoking) may have an impact on the efficacy outcome measures. At all visits the subject will be asked about any recent change in their smoking status (i.e. whether a subject's status has changed from smoker to non-smoker or vice versa). Smoking status changes during the 28-week Treatment Period will be captured in the eCRF, but the subject will be permitted to continue in the study. Subjects will be required to refrain from smoking (including medical marijuana and electronic cigarettes) 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 (PRN), in accordance with recommendations from the Investigator during the entire study visit.

Note: Use of electronic cigarettes will be viewed and managed in the same manner as traditional smoking.

5.7 Reasons and Procedures for Early Termination

Subjects may be withdrawn from the study at any time at their own request, upon request of the investigator, or by Pearl Therapeutics at any time or for any reason. 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 enrolled, regardless of the cause, should undergo the assessments outlined in Section 8.4 on the date of discontinuation. If a subject experiences any of the changes of concern listed below, a repeat assessment should be obtained and if confirmed the investigator or designee needs to make a determination as to the suitability of continuing the subject in the study. The changes of concern include:

- Following dosing, a heart rate increase of greater than 40 bpm from the pre-dose value obtained on that specific test day and the measured value is also greater than 120 bpm.
- Following dosing, a systolic BP (SBP) increase of more than 40 mmHg from the pre-dose value obtained on that specific test day and the measured value is also greater than 160 mmHg.
- Decrease in creatinine clearance to a value below 30 mL/min using CKD-EPI formula or a clinically relevant change from baseline as determined by the investigator.
- Hepatic impairment defined as abnormal liver function test of AST, ALT or total bilirubin ≥3 times upper limit of normal on repeat testing
- Calculated QTcF intervals greater than 500 msec, and have increased by 60 msec or more over test day baseline value.
- Subjects who suffer a moderate exacerbation will remain in the study and continue to take their assigned study drug unless the investigator decides that it is in the best interest of the subject to discontinue early from the study. Any subject who suffers a severe exacerbation (requiring hospitalization) will be discontinued. Subjects who suffer more than two moderate COPD exacerbations over the 28-week extension treatment period will be discontinued from the study.

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

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

If a subject requires the following prohibited medications they should be discontinued from the study:

- Initiation of maintenance therapy with any prohibited medications as listed in Table 3.
- Initiation of maintenance therapy with a marketed LABA (e.g., salmeterol, formoterol, indacaterol) administered alone or in combination with an ICS or a marketed LAMA (e.g., tiotropium, aclidinium, glycopyrronium bromide, [Seebri]).

If a female becomes pregnant during the course of the study the subject will be discontinued and the pregnancy will be followed full-term through delivery or final outcome (refer to Section 7.2.7).

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 4.

Table 4. Product Descriptions

Product Name & Potency	Product Strength	Dosage Form	Comments
GFF MDI 14.4/9.6 µg ex-actuator	GFF MDI 7.2/4.8 µg per actuation	MDI	Taken as 2 inhalations.
GP MDI 14.4 µg ex-actuator	GP MDI 7.2 µg per actuation	MDI	Taken as 2 inhalations.
FF MDI 9.6 µg ex-actuator	FF MDI 4.8 µg per actuation	MDI	Taken as 2 inhalations.
Tiotropium inhalation powder[†] 18 µg	EU source: Spiriva Handihaler 1 capsule of 18 µg	DPI	Taken as 1 capsule via the Handihaler DPI. Supplies are open-label.
Albuterol Sulfate inhalation aerosol[§] 90 µg	US source: Ventolin® HFA Each inhalation contains 108 µg corresponding to 90 µg albuterol base per actuation	MDI	Supplies are open-label.

DPI = dry powder inhaler; FF MDI = Formoterol Fumarate Metered Dose Inhaler; GFF MDI = Glycopyrronium and Formoterol Fumarate Metered Dose Inhaler; GP MDI = Glycopyrronium Metered Dose Inhaler; MDI = Metered Dose Inhaler.

[†] Active control

[§] Rescue medication during the study.

Note: All study drugs will be administered by oral inhalation. Glycopyrronium 14.4 µg in GFF MDI and GP MDI is equivalent to 18 µg of glycopyrronium bromide.

Open-label Spiriva and DPIs will be provided from commercial supplies. Manufacturer's instructions for study drug administration will be provided.

Open-label Ventolin HFA MDIs with dose counters will be provided from commercial supplies. 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 5. Spiriva (18 µg, open-label) supplies will be supplied as open-label DPI. Ventolin HFA supplies will be supplied as open-label MDIs.

Table 5. Packaging of Clinical Supplies

Product Name and Potency	Product Strength	Fill Count	Dosing Instructions
GFF MDI 14.4/9.6 µg ex-actuator	GFF MDI 7.2/4.8 µg per actuation	1 MDI 120 inhalations[#]	Take as directed in the morning and evening.
GP MDI 14.4 µg ex-actuator	GP MDI 7.2 µg per actuation	1 MDI 120 inhalations[#]	Take as directed in the morning and evening
FF MDI 9.6 µg ex-actuator	FF MDI 4.8 µg per actuation	1 MDI 120 inhalations[#]	Take 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.
Ventolin HFA Sulfate inhalation aerosol[§] 90 µg ex-actuator	US source: (Ventolin HFA) Each inhalation contains 108 µg corresponding to 90 µg Ventolin HFA base per actuation	1 MDI 60 or 200 actuations	Use only as directed.

[†] Active control
[§] Rescue medication
[#] 120 represents the number of inhalations for subject dosing. The 120 does not include 10 additional actuations available for initial priming and cleaning.

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

Open-label Supplies: Open-label Spiriva will be provided as individually labeled DPIs with bulk commercial blister packs containing individually sealed capsules. The foil pouch will be labeled with a single label.

Open-label Ventolin HFA will be provided as individually labeled MDIs. Each MDI will contain a single label. The MDI actuator will be labeled with a single label. The foil pouch will be labeled with a single label.

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

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

6.4 Secondary Packaging and Labeling Information (Box)

Blinded investigational drug and Open-label (Spiriva and Ventolin HFA) supplies will be packaged in individual boxes as outlined in Table 6. Box configuration is subject to change as a result of packaging constraints.

Table 6. Description of Boxes

Drug Supplies	Individual Box Contents
Blinded	1 MDI
Spiriva Handihaler (tiotropium bromide, 18 µg)	1 DPI Plus Blister Packs
Ventolin HFA	1 MDI

Each box will be labeled with a two-part label printed with black ink and may include the following text:

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

6.5 Emergency Unblinding of treatment assignment

The IWRS should be used in order to unblind subjects and to unmask drug identity. When the investigator contacts the system to unblind a subject, he/she must provide the requested subject identifying information and confirm the necessity to unblind the subject. 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 - 30°C). Do not refrigerate or freeze.

Spiriva Handihaler (tiotropium bromide, 18 µg) supplies: Store at 25ºC (77°F); excursions permitted to 15° - 30°C (59° - 86°F) [see USP Controlled Room Temperature]. The Spiriva capsules should not be exposed to extreme temperature or moisture. Do not store Spiriva capsules in the Handihaler device. Do not store capsules in the HandiHaler device. Spiriva capsules should always be stored in the blister and only removed immediately before use. The drug should be used immediately after the packaging over an individual capsule is opened.

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. Do not use or store near heat or open flame. Exposure to temperatures above 120 °F (49 °C) may cause bursting. Never throw into a fire or incinerator.

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

6.7 Instructions for Preparation of Treatments for Administration and Dispensing

6.7.1 GFF MDI, GP MDI, and FF MDI

Individual GFF MDI, GP MDI, and FF MDI 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 visit treatment box 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 the inhaler is ready to use.

The MDI should be primed in a separate room from the subject treatment area. 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 4 for instructions on the administration of GFF MDI, GP MDI, and FF MDI. Cleaning instructions are provided in Appendix 4.

6.7.2 Spiriva (tiotropium bromide)

Spiriva 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 visit treatment box 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.

Subjects assigned to Spiriva treatment will use one capsule from their newly assigned kit 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 5 for the manufacturer's instructions on the administration of Spiriva.

6.7.3 Ventolin HFA (albuterol sulfate inhalation aerosol)

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 6 for the manufacturer's instructions on the administration of Ventolin HFA. Study personnel will record number on the dose counter at the time of dispensing (following priming) and upon return.

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 secure 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 subject, 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 Therapeutics representative for appropriate documentation that needs to be completed for drug accountability.

The investigator or designated assistant should not open individual clinical supply containers until all pre-dose assessments have been completed and the subject is eligible to 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. 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.

All product complaints (including device malfunctions) must be reported to Pearl Therapeutics using the Product Complaints Form provided in each site's regulatory binder. Pearl Therapeutics will contact the site to evaluate the nature of the complaint and determine what further action is needed.

7 STUDY PROCEDURES

A schedule of events is provided in Table 8. Detailed schedules for pre- and post-dose procedures to be performed on visit days are provided in Table 9.

7.1 Efficacy Assessments

7.1.1 Pulmonary Function Tests

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

All pulmonary function tests including FEV_1, FVC, and PEFR as defined in ATS/ERS guidelines 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 repeatability 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.

Spirometry assessments will be obtained at the conclusion of the lead-in studies (Visit 11a) and will not be obtained during Visit 11b. Spirometry assessments will be conducted at 60 minutes and 30 minutes prior to study drug administration at Visits 12 through Visit 15.

At Visit 13 (Week 36) and Visit 15 (Week 52) only, spirometry will be obtained at 15 and 30 minutes, and 1 and 2 hours post-dosing of study drug.

7.1.2 Subject Electronic Diary (eDiary) Data Collection

Subjects will continue to use their electronic subject diary (eDiary) provided during participation in Study PT003006 or Study PT003007 to continue to record time of study medication administration, morning and evening symptoms, use of rescue albuterol (Ventolin HFA), and dose indicator reading (if assigned to GFF MDI, GP MDI or FF MDI only).

eDiary Compliance Requirement: Subject participation may be terminated at any time during the study for the following reason:

- Chronic failure, in the judgment of the investigator, to comply with diary compliance, despite documentation at the site of repeated efforts to reinforce compliance. As defined for this study, compliance requires >70% subject completion of diary assessments. The sponsor may also instruct a site to discontinue a subject based on consistent noncompliance.

In-clinic dosing times and dose indicator readings will be documented by the site staff and will not be entered by the subject into their eDiary.

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

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 in the electronic diary. 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 consecutive days with worsening symptoms should contact the site.

7.1.4 Medication Compliance

Time of dosing with study medication will be recorded in the subject’s electronic diary for each day of treatment (except the in-clinic dosing time). Study medication compliance will be checked at all visits and any issues identified will be documented in the appropriate study files.

7.1.5 Recording of Dose Indicator Reading

The GFF MDI, GP MDI and FF MDI will be fitted with a dose indicator to track in life use of the MDI.

Subjects will be instructed to record the dose indicator reading from the MDI in their eDiary.

Prior to dosing at Visit 12 to Visit 15, site personnel will observe the dose indicator reading on the study drug returned by the subject and record the dose indicator reading in the source.

Note: The dose indicator reading recorded by the site staff will be dose indicator reading **observed prior to subject dosing. For new MDIs the recorded count will be the count** following the priming of the MDI but before the subject dose.

At each visit, the site staff will compare the dose indicator reading from the prior evening entered in the subject eDiary with the dose indicator reading recorded by the site staff. For major discrepancies (i.e. >20 puff difference) the site staff will review the major discrepancy with the subject and document reason for the major discrepancy. If appropriate, site staff will retrain the subject on the proper recording of dose indicator reading and/or proper use of the MDI.

7.1.6 Subject Questionnaires

The following subject questionnaires will be completed by subjects using the study supplied electronic questionnaire devices at specified visits throughout the study: St. George Respiratory Questionnaire (SGRQ) and Transition (TDI) Dyspnea Index. Whenever possible, it is recommended that the BDI/TDI be collected first followed by the SGRQ.

7.1.6.1 Baseline (BDI) and Transition (TDI) Dyspnea Indices (BDI/ TDI)

Dyspnea is the primary symptom of COPD and its relief is an important goal of therapy. In the evaluation of pharmacotherapy for COPD, several instruments are available to provide a discriminative and evaluative assessment of dyspnea. Among these are the baseline (BDI) and transition (TDI) dyspnea indices, which assess breathlessness in components related to functional impairment, magnitude of task and magnitude of effort. The reliability and validity of the BDI have been reported (Mahler, 1984; Eakin, 1995). The validity of the BDI/ TDI based on its association with other related measures has also been demonstrated (Witek, 2003). The BDI/TDI questionnaire should always be completed before any other assessments are made to avoid influencing the responses. The self-administered computerized (SAC) version will be used. The SAC includes the same questions as the paper version but also includes an initial practice question related to tiredness, which is not included in the overall score. The paper version of the questionnaire can be found in Appendix 8 and is provided for illustrative purposes only. The appropriate language version of the questionnaires will be used. The BDI score ranges from 0 (very severe impairment) to 4 (no impairment) for each component and are summed to determine the BDI focal score (0 to 12) (i.e. the lower the score, the worse the severity of dyspnea). TDI components are: Change in Functional Impairment, Change in Magnitude of Task, and Change in Magnitude of Effort. The TDI score ranges from -3 (major deterioration) to +3 (major improvement) for each component. The sum of all components yields the TDI focal score (-9 to +9) (i.e. the lower the score, the more deterioration in severity of dyspnea). The subject should complete

the questionnaires in a quiet area and be allowed to ask questions; however site staff should take care not to influence the subject's responses. The subject will be instructed to provide the truest and for them best response. The questionnaire will be checked for completeness and collected before the subject leaves the center. At later visits subjects are not allowed to review their previous responses.

TDI will be completed by the subject at all visits and Premature Discontinuation Visit.

Whenever possible, it is recommended that the BDI/TDI be completed prior to study drug administration and before administration of the SGRQ.

7.1.6.2 St George Respiratory Questionnaire (SGRQ)

The St. George Respiratory Questionnaire (SGRQ) will be used to provide the health status/health-related Quality of Life (QoL) measurements in this study (See Appendix 7). For the purposes of this study when TDI and SGRQ are obtained at the same visit, and whenever possible, the TDI questionnaire will be collected first followed by the SGRQ. The appropriate language versions of the questionnaires will be available in each participating country. The subject should complete the questionnaires in a quiet area and be allowed to ask questions; however site staff should take care not to influence the subject's responses. The subject will be instructed to provide the truest and for them best response. The questionnaire will be checked for completeness and collected before the subject leaves the center. At later visits, subjects are not allowed to review their previous responses.

The SGRQ contains 51 items divided into three domains: "Symptoms" concerned with respiratory symptoms, their frequency and severity; "Activity" concerned with activities that cause or are limited by breathlessness; and "Impacts" which covers a range of aspects concerned with social functioning and psychological disturbances resulting from airway disease. A score will be calculated for each component and a "Total" score will also be calculated. In each case the lowest possible value is zero and the highest is 100. Higher values correspond to greater impairment of quality of life. Completed questionnaires will be reviewed and examined by the investigator or designee, before the clinical examination, for responses which may indicate potential AEs or SAEs. The investigator should review not only the responses to the questions in the questionnaire but also for any unsolicited comments written by the subject. Investigators should not encourage the subjects to change the responses reported in the questionnaire.

The SGRQ (See Appendix 7) will be completed by the subject at Visit 13 (Week 36), and Visit 15 (Week 52) or Premature Discontinuation Visit.

If AEs or SAEs are confirmed, then the investigator or designee must record the events as per instructions given in Section 7.2.6 of the protocol.

7.1.7 COPD Exacerbations

Site personnel will evaluate whether the subject has experienced a worsening of their COPD that meets the definition of a COPD exacerbation since their last visit. An exacerbation will

be defined as a change in the subject's baseline dyspnea, cough, and/or sputum (increase in volume or change in color towards purulence) that lasts 3 or more days, is beyond normal day-to-day variations, is acute in onset and may warrant a change in regular medication.

All COPD exacerbations will be captured using a COPD Exacerbation CRF and will not be reported as AEs unless considered an SAE.

The severity of COPD exacerbations will be classified as follows:

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

7.2 Safety Assessments

The safety assessments include physical examination findings, vital signs, ECGs, clinical laboratory tests in addition to recording of AEs and SAEs.

7.2.1 Medical/Surgical History and Physical Examination

Medical history and history of COPD exacerbation will be taken at Screening in Study PT003006 or Study PT003007. A complete physical examination will be performed at the conclusion of the lead-in studies (Visit 11a) and will not be obtained during Visit 11b. A complete physical examination will also be conducted at the Final Visit (Visit 15). A complete physical examination will include the following: general appearance, skin, head, eyes, ears, nose, throat, neck (including thyroid), lymph nodes, chest, heart, abdomen, extremities, and nervous system. Weight, assessed in ordinary indoor clothing with shoes removed, will be recorded at Visit 15.

7.2.2 Vital Sign Measurements

Heart rate and systolic and diastolic blood pressure ('vital signs') will be assessed as outlined below; assessments may be obtained in the supine or seated position.

Vital signs will be obtained at the conclusion of the lead-in studies (Visit 11a) and will not be obtained during Visit 11b.

At all visits:

- Pre-dose vital signs will be obtained within 1 hour prior to study drug dosing.
- Post-dose vital signs will be obtained at 30 minutes post study drug dosing.

Post-dose vital signs will be obtained at 2 hours post study drug dosing at Visit 13 (Week 36) and Visit 15 (Week 52) only.

A single set of vital signs will be obtained at a Premature Discontinuation Visit.

Temperature will be obtained at pre-dose on all test days and will not be repeated at subsequent time points unless clinically indicated.

7.2.3 12-Lead Electrocardiogram (ECG)

ECGs will be obtained at the conclusion of the lead-in studies (Visit 11a) and will not be obtained during Visit 11b.

At Visit 13 (Week 36) and Visit 15 (Week 52) only, an ECG will be obtained within 1 hour prior to study drug dosing and at 30 minutes and two hours post study drug dosing.

An ECG will be obtained at a Premature Discontinuation Visit.

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

QT intervals and calculated QTcF intervals will be reviewed and checked for gross inaccuracies by the investigator or designated ECG reviewer. If the calculated QTcF intervals are greater than 500 msec, and have increased by 60 msec or more over test day baseline value, the investigator will make a determination on the suitability of continuing the subject in the study. If QTcF interval prolongation exceeding these limits is verified during treatment, the subject's medical history should be examined closely for risk factors that may have contributed to the event, including evidence of prior genotyping for hereditary long QT syndromes, if appropriate.

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

7.2.4 Clinical Laboratory Tests

Clinical safety laboratory tests will be analyzed by a central laboratory according to standardized, validated assays. The laboratory will supply detailed instructions and all containers for blood and urine investigations. Blood sample volumes will meet the laboratory's specification. Clinical laboratory tests will be obtained prior to dosing at the final visit of the lead-in studies (Visit 11a), and will not be obtained during Visit 11b. During the course of this study, clinical laboratory tests will be obtained prior to dosing at Visit 13 (Week 36) and Visit 15 (Week 52) only or Premature Discontinuation Visit.

7.2.4.1 Hematology

Hemoglobin, hematocrit, red blood cell count, white blood cell count with differential, and platelet count will be measured prior to dosing at the final visit of the lead-in studies (Visit 11a), and will not be obtained during Visit 11b. During the course of this study, hematology assessments will be obtained at Visit 13 (Week 36) and Visit 15 (Week 52) only or Premature Discontinuation Visit.

7.2.4.2 Clinical Chemistry

Albumin, alkaline phosphatase, total bilirubin, calcium, total cholesterol, magnesium, phosphate, sodium, potassium, chloride, creatinine, γ -GT, blood glucose, total protein, AST and ALT will be measured prior to dosing at the final visit of the lead-in studies (Visit 11a), and will not be obtained during Visit 11b. During the course of this study, clinical chemistry assessments will be obtained at Visit 13 (Week 36) and Visit 15 (Week 52) only or Premature Discontinuation Visit.

The Central Laboratory will supply procedures for the preparation and collection of these samples (Table 7).

Table 7. Lab Parameters

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)	Calcium[a]
Alkaline phosphatase	Chloride[a]
Bilirubin, total	Cholesterol
Gamma-glutamyl transferase	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 Visit 15 only and Urine HCG at Visit 13 (Week 36)	
Creatinine clearance will be estimated by the CKD-EPI formula.	
[a]Parameters included in the Basic Metabolic Panel (BMP).	

7.2.4.3 Urinalysis

Urinalysis will be measured at the final visit of the lead-in studies (Visit 11a), and will not be obtained during Visit 11b. During the course of this study, urinalysis will be obtained prior to dosing at Visit 13 (Week 36) and Visit 15 (Week 52) only or Premature Discontinuation Visit.

7.2.4.4 Pregnancy Test

A serum pregnancy test will be performed at the Central Laboratory in pre-menopausal women who are not surgically sterile at the final visit of the lead-in studies (Visit 11a), and will not be obtained during Visit 11b. A serum pregnancy test will also be obtained at Visit 15 (Week 52) or Premature Discontinuation Visit. A urine pregnancy test will be performed at Visit 13 (Week 36). If any of these tests are positive, the subject must be discontinued from the study. The pregnancy test should be performed prior to ECG, spirometry or blood collection for laboratory assessments.

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, the U.S. Code of Federal Regulations [21 CFR 312.32] and European Union Directive 2001/83/EC and are included herein.

An AE is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An adverse event (also referred to as an adverse drug reaction/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 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.

7.2.5.4 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.

7.2.5.5 COPD Exacerbations

COPD exacerbations are expected events in subjects with moderate to very severe COPD. All COPD exacerbations will be captured using a COPD Exacerbation eCRF and will not be reported as AEs unless considered an SAE.

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 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 jeopordize 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.

Unexpected adverse event means any adverse event, the specificity or severity of which is not consistent with the current Investigator's Brochure.

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 telephone call 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 Overdose

An overdose is defined as a dose greater than the dose levels 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 and Ventolin HFA.

7.2.7 Pregnancy

To ensure subject safety, each pregnancy in a female subject during the study (Visit 11b to Follow-Up telephone call) must be reported to Pearl Therapeutics within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to Pearl Therapeutics. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the Pearl Therapeutics study drug of any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

7.2.8 Use of Steroids during the Trial

At each visit, subjects will be asked whether they have been administered oral, intramuscular or intravenous corticosteroids since last visit. Use of oral, intramuscular or intravenous corticosteroids for the management of COPD exacerbations or other condition is not a reason for early termination. Use of corticosteroids should be documented. Subjects who are being treated for a COPD exacerbation with oral corticosteroids or have been treated for a COPD exacerbation with oral corticosteroids within 14 days of the scheduled visit will be allowed to perform pulmonary function tests under close medical supervision. The investigator can decide to stop pulmonary function tests if subject safety is at risk or symptoms make it difficult for the subject to continue.

Subjects treated with oral, intramuscular, or intravenous corticosteroids for other indications will follow their visit schedule. If a subject requires intraocular corticosteroids this should be

fully documented and the Investigator should make a determination as to the suitability of the subject continuing in the study.

7.2.9 Data Monitoring and Adjudication Committees

Data Safety Monitoring Committee:

An independent, external Data Monitoring Committee (DMC) will be set up to review all serious adverse events (including deaths and all hospitalizations) and cardiovascular events. Members of the DMC will review these data generated externally and independently of Pearl Therapeutics at predetermined intervals. If significant safety issues arise in between scheduled meetings, ad hoc meetings will be scheduled to review the data. Based on the safety implications of the data, the DMC may recommend modification or termination of the study.

Adjudication Committees:

Two external adjudication committees will be established for this study. The committees will consist of independent experts outside of Pearl Therapeutics who are not involved in the study conduct. A mortality adjudication committee will assess the cause of death occurring during the study and for 14 days after completion of the 24-week study treatment. Committee members will be blinded with respect to the subject's study medication. At regular intervals, the Committee will review narratives, discharge summaries and medical records, as available, to determine the most likely cause of death, in particular for cardiovascular and respiratory related deaths.

A cardio- and cerebro-vascular (CCV) external adjudication committee will consist of experts who will review at regular intervals the program-wide selected CCV events to ensure that events are correctly classified. All details of both adjudication processes will be included in the adjudication committee charter.

The Committee will consist of independent experts outside of Pearl Therapeutics who are not involved in the study conduct. Committee members will be blinded with respect to the subject's study medication. At regular intervals, the Committee will review narratives, discharge summaries, and medical records, as available, to determine whether the cases presented were CCV events or not.

Further details are provided in the Adjudication Committee and DMC Charters.

7.3 Health Care Resource Utilization

The number of days missed from work, and COPD-related and non-COPD related telephone calls and visits to healthcare providers, Emergency Room (ER) visits, and hospitalizations including days in hospital, days in Intensive Care Units (ICU), days in Coronary Care Units (CCU), and whether the subject was intubated will be captured at all visits (Visits 12 to Visit 15).

7.4 Termination of the Study

An investigator may choose to discontinue study participation at any time with sufficient notice by the investigator for any reason as per the terms of the contract with 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.

8 STUDY ACTIVITIES

A time and events schedule is provided in Table 8. Detailed schedules for pre- and post-dose procedures to be performed are provided in Table 9

Table 8. Schedule of Events

Procedures	Treatment Period						Follow-Up
	Visit 11b Week 24	**Visit 12 Week 28**	**Visit 13 Week 36**	**Visit 14 Week 44**	**Visit 15 Week 52**	**Discon[§] Visit**	**14 Days Post-Dose**
Study Day/Week[a]	**Wk 24 ±7 Days**	**Wk 28 ±7 Days[a]**	**Wk 36 ±7 Days [a]**	**Wk 44 ±7 Days [a]**	**Wk 52 ±7 Days [a]**		**Wk 54 +7 Days [a]**
Obtain Informed Consent	X						
Review Incl/Excl Criteria	X						
Verify Continued Eligibility		X	X	X	X		
Smoking Status		X	X	X	X		
Prior/Concomitant Medications[b]		X	X	X	X	X	X
Spirometry[c]		X	X	X	X		
Physical Examination					X	X	
Vital Signs[d]		X	X	X	X	X	
12-Lead ECG[e]			X		X	X	
Pregnancy Test[f]			X		X	X	
Clinical Laboratory Testing[f]			X		X	X	
Adjust COPD Medications[g]					X	X	
COPD Exacerbations and Adverse Events		X	X	X	X	X	X
Study Drug Dispensing/Collection	X	X	X	X	X	X	
Study Drug Administration[h]		X	X	X	X		
TDI[i]		X	X	X	X	X	
SGRQ[i]			X		X	X	
Review of Electronic Diary Data[j]		X	X	X	X	X	
Record Dose Indicator Reading[k]	X	X	X	X	X	X	
HCRU[l]		X	X	X	X	X	
Telephone Contact[m]		X	X	X	X		X

a. **Scheduling visits:** All visits will be scheduled relative to Visit 4 (Treatment Day 1, Randomization) of the lead-in studies (Study PT003006 or Study PT003007). Thus Visits 12, 13, 14, and 15, will be scheduled 28, 36, 44, and 52 weeks ± 7 days of Visit 4 of the lead-in studies respectively.

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

c. Refer to Section 7.1.1 for spirometry assessments and specific time points to be performed at each treatment visit.

d. Refer to Section 7.2.2 for vital signs assessments and specific time points to be performed at each treatment visit. Weight will be obtained at Visit 15 only.

e. Refer to Section 7.2.3 for ECG assessments and specific time points to be performed at each treatment visit

f. Refer to Section 7.2.4 for clinical laboratory assessments (hematology, chemistry and urinalysis) and specific time points to be performed at each treatment visit. Serum pregnancy test will be performed at Visit 15 (Week 52) and a urine pregnancy test will be done at Visit 13 (Week 36).

g. At the end of Visit 15, return subject to pre-study or other appropriate inhaled maintenance COPD medications.

h. In-clinic dosing time is recorded as time of the second puff/inhalation. The in-clinic dosing time should be timed to be within 12±2 hours of the prior evening dosing time if assigned to blinded treatment or 24±2 hours of the prior morning dosing time if assigned to Spiriva.

i. When TDI and SGRQ are obtained at the same visit TDI will be collected first followed immediately by SGRQ. These questionnaires must be completed by the subject prior to any other visit procedures.

j. Refer to Section 7.1.2 for details of electronic diary review.

k. Refer to Section 7.1.5 for details and instructions on recording dose indicator readings.

l. Refer to Section 7.3 for details on HCRU collection

m. It is recommended that sites call the subject on the day before a scheduled visit and remind the subject of the expectations for the upcoming visit (e.g. Dosing appropriately the day before the visit, withholding COPD medications the morning of the scheduled visit, bring all study drug and eDiary to the visit, etc).

§ - Illustrates the procedures that may be required at a premature discontinuation visit. **Note:** Premature discontinuation visits will be captured as unscheduled visits (See Section 8.4).

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

Table 9. Timed Assessments during Treatment Period (Visits 12-15)

Clinical Variable[a]	Pre-dosing		Post-dosing			
	-1 hour	-30 minutes	15 minutes	30 minutes	1 hour	2 hours
TDI[b]	X†					
SGRQ[b]	X†					
Review of Electronic Diary Data	X†					
Vital Signs[c]	X†			X		X[c]
12- Lead ECG[d]	X†			X[d]		X[d]
Clinical Laboratory Testing[e]	X†					
Spirometry (FEV_1, FVC, PEFR)[f]	X	X	X[f]	X[f]	X[f]	X[f]
Study Drug Collection[g]	X†					
Record Dose Indicator Reading[h]		X†				
Study Drug Dispensing[i]						X†

a. In-clinic dosing time is recorded as time of the second puff. Safety 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 assessments 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.

b. When TDI and SGRQ are obtained at the same visit TDI will be collected first followed immediately by SGRQ. These questionnaires must be completed by the subject prior to any other visit procedures. TDI and SGRQ will be obtained at Visit 13 (Week 32) and Visit 15 (Week 52) only

c. Post-dose Vital signs will be obtained at two hours post study drug dosing at Visit 13 (Week 36) and Visit 15 (Week 52) only. Temperature will be obtained pre-dose; no further temperature assessments required unless clinically indicated.

d. Pre-dose ECG will be obtained once within one hour prior to dosing and a post-dose ECG will be obtained at 30 minutes and two hours post study drug dosing at Visit 13 (Week 36) and Visit 15 (Week 52) only.

e. Clinical laboratory tests (hematology, chemistry and urinalysis) will be obtained prior to dosing at Visit 13 (Week 36) and Visit 15 (Week 52) only.

f. Spirometry assessments will be obtained at 15 and 30 minutes, and 1 and 2 hours post-dosing of study drug Visit 13 (Week 36) and Visit 15 (Week 52) only.

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

h. Site staff will record the dose indicator reading at each visit. The dose indicator reading recorded by the site staff will be dose indicator count observed prior to subject dosing. For new MDIs the recorded count will be the count following the priming of the device but before the subject dose. Refer to Section 7.1.5 for more details

i. Dispense study drug for home use to subject following completion of all post-dose assessments. See Section 6.7 for Instructions for Preparation of Treatments for Administration and Dispensing.

† This is not a timed assessment. Sites should plan to perform these activities so as not to interfere with collection of timed assessments such as spirometry.

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

8.1 Visit 11b (Safety Extension Entry Visit)

There are 11 scheduled visits in the lead-in studies, the eleventh visit is the last visit of the lead-in studies and the first visit of the extension study. In order to differentiate, assessments conducted at the completion of the lead-in studies will be captured in Visit 11a and procedures conducted in the extension study will be captured in Visit 11b. Visit 11b will be completed **following completion of all Visit 11a study procedures**.

Note: Visit 11b will be completed only in subjects who are randomly invited to participate in Study PT003008 and who consent to participate in the safety extension study.

- Obtain informed consent.
- Review safety extension inclusion/exclusion criteria and confirm subject eligibility to enroll into the safety extension study.
- **Confirm all visit 11a procedures have been completed before proceeding to register subjects in IWRS.**
- Register subject in IWRS to confirm participation in the safety extension study and obtain safety extension study drug assignment.
- Return electronic diary to subjects and provide retraining if appropriate.
- When assigned blinded study drug site personnel will complete priming in the clinic before dispensing to the subject for at home use.
    - 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.
    - Record/document the dose indicator reading. The dose indicator count recorded by the site staff will be dose indicator count observed after priming but prior to subject dosing. For new MDIs the recorded count will be the count following the priming of the device but before the subject dose. Refer to Section 7.1.5 for more details.
- Subject will administer first dose of safety extension study drug at home in the evening (excluding subjects participating in the Spiriva arm, who will dose on schedule the following morning). **Note:** During the extension study subjects will continue on the same treatment that they were assigned in the lead-in studies.
- Subjects will be instructed to bring their eDiary and all study medication (including used study drug, replacement MDI kit if assigned to blinded study drug and sponsor-provided rescue Ventolin HFA) to the next scheduled clinic visit.
- Schedule next visit and ensure subject has adequate supply of study drug including a replacement MDI kit if assigned to blinded study drug and sponsor-provided rescue Ventolin HFA.

8.2 Visit 12 to Visit 14

- Review subject diary for data collection compliance.
- Determine time of last dose of short-acting bronchodilator and other COPD medications (if <6 hours, the visit must be rescheduled).
- Confirm the subject took their last dose of randomized study medication as scheduled (prior evening if on blinded study medication or prior morning if on Spiriva). If the time of dosing was not in accordance with the protocol, then the visit must be rescheduled.
- Confirm subject eligibility to continue.
- Have subject complete TDI questionnaire before any other study procedures are performed.
  - **Note:** At Visit 13 (Week 36) have subject complete TDI questionnaire first followed by SGRQ questionnaire before any other study procedures are performed.
- Collect HCRU information.
- Record COPD exacerbations and adverse events (if any).
- Review all concomitant medications and ensure adherence to COPD regimen.
- Perform all pre-dose assessments (refer to Table 9).
- Return electronic diary to subjects and provide retraining if appropriate.
- Prior to dosing, site personnel will use IWRS to assign subjects a new kit of study drug for in-clinic dosing and to continue dosing at home until the next scheduled visit.
  - 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.
  - If assigned to blinded study drug, record/document the dose indicator readings of the used device and the replacement device.
  - For new MDIs, the recorded count will be the count following the priming of the device but before the subject doses. Refer to Section 7.1.5 for more details.
- **Administer in-clinic study drug dosing from the new kit assigned at the visit**.
- Perform post-dose assessments (refer to Table 9) if applicable.
- Subjects will be instructed to track study drug dosing in their electronic diary between study clinic visits.
- Subject assigned to blinded study drug will be instructed to dose while at home from the site-primed MDI **only**, unless all of the following **replacement conditions** are met:
  - Dose indicator is in the red zone (See Appendix 9 for dose indicator reading instructions),
  - The dose indicator registers ≤10 puffs remaining, and

- Their next scheduled study clinic visit is not the following day.

- If these replacement conditions are met, subjects will be instructed to open one of their replacement kits, prime the MDI and start using for at home dosing until the next scheduled study clinic visit.
- Subjects will be instructed to bring their eDiary and all study medication (including used study drug, replacement MDI kit if assigned to blinded study drug and sponsor-provided rescue Ventolin HFA) to the next scheduled clinic visit.
- Schedule next visit and ensure subject has adequate supply of study drug including **two** replacement MDI kits if assigned to blinded study drug and sponsor-provided rescue Ventolin HFA.

Visit Reminders:
At Visit 13 (Week 36) only, the following additional assessments will be performed:

- SGRQ
- Post-dose vital signs will be obtained at 30 minutes and two hours post study drug dosing.
- A pre-dose ECG will be obtained once within one hour prior to dosing.
- A post-dose ECG will be obtained at 30 minutes and two hours post study drug dosing.
- Clinical laboratory tests.
- Spirometry assessments will be obtained at 15 and 30 minutes, and 1 and 2 hours post-dosing of study drug Visit 13 (Week 36) only.

8.3 Final Visit (Visit 15)

- Review subject diary for data collection compliance.
- Determine time of last dose of short-acting bronchodilator and other COPD medications (if <6 hours, the visit must be rescheduled).
- Confirm the subject took their last dose of randomized study medication as scheduled (prior evening if on blinded study medication or prior morning if on Spiriva). If the time of dosing was not in accordance with the protocol, then the visit must be rescheduled.
- Have subject complete TDI questionnaire followed by SGRQ questionnaire before any other study procedures are performed.
- Collect HCRU information.
- Record COPD exacerbations and adverse events (if any).
- Review all concomitant medications and ensure adherence to COPD regimen.
- Confirm subject eligibility to continue.

- Perform all pre-dose assessments (refer to Table 9) including clinical laboratory assessment, physical examination and serum pregnancy test for women of child bearing potential.
  - **Reminder:** A pre-dose ECG will be obtained within one hour prior to study drug dosing
- Prior to dosing, site personnel will use IWRS to assign subjects a new kit of study drug for in-clinic dosing.
  - 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.
  - If assigned to blinded study drug, record/document the dose indicator readings of the used device and the replacement device.
  - For the new MDI, the recorded count will be the count following the priming of the device but before the subject doses. Refer to Section 7.1.5 for more details.
- **Administer in-clinic study drug dose from the new kit assigned at the visit**.
- Perform all post-dose assessments (refer to Table 9) including:
  - Post-dose vital signs at 30 minutes and two hours post study drug dosing
  - Post-dose ECGs at 30 minutes and two hours post study drug dosing.
  - Post-dose spirometry assessments at 15 and 30 minutes, and 1 and 2 hours post-dosing of study drug.
- Collect subject eDiary.
- Collect all study medication including sponsor-provided Ventolin HFA.
- At completion of all Visit 15 assessments, return subject to pre-study or appropriate inhaled maintenance COPD medications.
- Inform subject about reporting all SAEs up to 14 days following the last dose of study drug.
- Schedule the follow-up telephone call at least 14 days from Visit 15.

8.4 Unscheduled Visit/Premature Discontinuation Visit

Repeat assessments, if needed, will be captured in unscheduled visits.

Premature discontinuations visits will be captured as unscheduled visits. The following minimum procedures should be completed at the Premature Discontinuation Visit:

- Have subject complete TDI questionnaire first followed by SGRQ questionnaire second before any other study procedures are performed.

- Collect HCRU information.
- Record COPD exacerbations and adverse events (if any).
- Review concomitant medications.
- Conduct a physical examination, including vital signs.
- Perform ECG and collect blood samples for hematology and chemistry.
- Collect a blood sample for pregnancy test for women of child bearing potential.
- Collect subject eDiary.
- Collect all study drug.
- Inform subject about reporting all SAEs up to 14 days following the last dose of study drug.
- Return subject to pre-study or appropriate maintenance COPD medications.
- Capture the subject discontinuation reason.
- Schedule a follow-up telephone call (TC) 14 days post last study drug dosing. If the discontinuation visit is performed > 14 days post last study drug dosing a follow-up TC will not be required.

8.5 Follow-Up Telephone Call

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

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

8.6 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
- Lack of efficacy
- Major protocol violation
- Death
- Completion of the study
- Protocol specified criteria such as heart rate, systolic or diastolic blood pressure, or use of prohibited medications (see Section 5.7).

9 PLANNED STATISTICAL METHODS

9.1 Introduction

This study will be conducted as a double-blind active-control (open label) parallel-group study evaluating the following treatments in approximately 850 subjects:

- GFF MDI (14.4/9.6 μg BID)
- GP MDI (14.4 μg BID)
- FF MDI (9.6 μg BID)
- Spiriva (18 μg QD, open-label)

The primary objective of this study is to assess the long-term safety of the fixed dose combination GFF MDI versus its components (GP MDI and FF MDI). In addition, as primary objectives, the study will assess the long-term safety of the monotherapies (GP MDI and FF MDI). This study will also assess the effects of the fixed dose combination and the monotherapies in terms of pulmonary function testing, COPD symptoms, and disease related health status. This study will include a 28-week treatment period that will immediately follow an initial 24-week treatment period from Study PT003006 or Study PT003007. Analyses will include all non-placebo data from Study PT003006 or Study PT003007 in order to minimize the impact of bias caused by dropout and in order to allow inferences to be made over 52 weeks. Baseline for all subjects will remain the original baseline from PT003006 or PT003007. For clinic measured values, the baseline is the assessment obtained prior to initial dosing at Visit 4. Specifically for the primary efficacy measure, baseline is the average of the -60 min and -30 min assessments. For diary data, the baseline is the average of the values obtained during the seven days prior to Visit 4 including the morning of Visit 4 prior to initial dosing.

9.2 Protocol Variables

The data from this 28-week study will be combined with the 24 weeks of data obtained from the lead-in studies (Study PT003006 and Study PT003007) to provide safety and efficacy data over 52 weeks of treatment.

9.2.1 Safety Endpoints

Overall safety and tolerability will be evaluated using adverse events, vital sign measurements, 12-lead ECG parameters, and clinical laboratory parameters over 52 weeks.

9.2.2 Efficacy Endpoints

9.2.2.1 Primary Efficacy Endpoint

Change from baseline in morning pre-dose trough FEV_1 over 52 weeks

9.2.2.2 Secondary Efficacy Endpoints (over 52 weeks)

- Transition Dyspnea Index (TDI) focal score
- Peak change from baseline in FEV_1 within 2 hours post-dosing
- Change from baseline in St George Respiratory Questionnaire (SGRQ) total score
- Change from baseline in average daily rescue Ventolin HFA use

9.2.2.3 Other Efficacy Endpoints (over 52 weeks unless otherwise specified)

- Rate of all COPD exacerbations
- Time to the first COPD exacerbation of any severity
- Rate of moderate or severe COPD exacerbations
- Time to the first moderate or severe COPD exacerbation
- Time to treatment failure
- Additional spirometry assessments over 52 weeks and at each visit:
  - Change from baseline in morning pre-dose trough for FEV_1, forced vital capacity (FVC), peak expiratory flow rate (PEFR), and forced expiratory flow between 25% to 75% of FVC (FEF_{25-75})
  - Peak change from baseline within 2 hours in FEV_1, FVC, PEFR, and FEF_{25-75}
  - FEV_1 AUC_{0-2}, FVC AUC_{0-2}, PEFR AUC_{0-2}, and FEF_{25-75} AUC_{0-2}
- Percentage of days with 'no rescue Ventolin HFA use'
- Percentage of nights with 'no nighttime awakenings'
- Percentage of nights with fewer than 3 nighttime awakenings
- Percentage of days with 'no daytime symptoms'
- Percentage of days with 'no limitation of daily activities'
- Change from baseline in mean daily total symptom score as well as each individual symptom (cough, shortness of breath, sputum volume, nighttime awakenings, and rescue Ventolin HFA use), the mean daytime total and individual symptom scores, and the mean nighttime total and individual symptom scores over 52 weeks and over each 4 week interval of the 52 weeks of treatment.
- TDI focal score at each post-randomization visit
- Individual components of the TDI: functional impairment, magnitude of task, and magnitude of effort over 52-weeks and at each post-randomization visit
- Percentage of subjects achieving a MCID threshold of ≥ 1 unit in TDI focal score
- Changes from baseline at each post-randomization visit for SGRQ total score
- Change in individual domain scores of SGRQ: Symptoms, Activity and Impacts over 52-weeks and at each post-randomization visit
- Percentage of subjects achieving a MCID threshold of ≥ 4 units or more on average in SGRQ total score

9.2.3 Health Care Resource Utilization Endpoints

The number of days missed from work, and COPD-related and non-COPD related telephone calls and visits to healthcare providers, Emergency Room (ER) visits, and hospitalizations including days in hospital, days in Intensive Care Units (ICU), days in Coronary Care Units (CCU), and whether the subject was intubated will be captured and compared between treatment groups.

9.3 Analyses

9.3.1 Safety Analyses

9.3.1.1 Adverse Events

All treatment-emergent AEs (TEAEs) will be recorded. AEs and serious adverse events (SAEs) starting on or after the time of the first inhalation of study drug will be classified as treatment emergent. All AEs will be summarized for two sets of data. One set will contain all non-placebo data from PT003006, PT003007, and this trial. The second set will contain only the subjects who participate in this trial and only including AEs that started during this trial. The following TEAE summaries will be produced: overall by system organ class and preferred term, overall by system organ class and by Standard MedDRA Queries (SMQs) as appropriate, preferred term and maximum severity, suspected drug-related adverse events by system organ class and preferred term, SAEs by system organ class and preferred term, and AEs leading to permanent discontinuation of study drug by system organ class and preferred term. The assessment of safety will comprise all safety measurements including all AEs. AEs of special interest related to known class effects of LAMAs and LABAs will be described in the SAP.

Additional analyses of AEs will be conducted that adjust for variable amounts of exposure between groups by reporting the incidence of AEs per 1000 years of patient exposure.

9.3.1.2 Major Adverse Cardiovascular Event (MACE)

MACEs will be summarized by treatment group. Treatment groups will be compared for time to first MACE using a Cox proportional hazards model with adjustment for age and disease severity.

9.3.1.3 Cause of Death

Causes of death will be listed by patient and summarized by treatment groups for (1) all cause mortality, (2) mortality of probable cardiovascular cause, (3) mortality of probable respiratory cause and (4) mortality of probable other causes using the Safety Population based on (A) cases reported during the active treatment period and (B) cases reported during the active treatment period plus the following 14 days. Treatment groups will be compared for time to death for each of the four cases using a Cox proportional hazards model with adjustment for age and baseline percent predicted FEV_1.

9.3.1.4 Clinical Laboratory Measurements

Summary statistics (n, mean, median, standard deviation, minimum, and maximum) for the baseline assessment (Day 1) and for the pre-dose value and change from baseline at pre-dose value of post-baseline visits with scheduled lab assessments of continuous laboratory variables, including serum potassium and glucose, will be tabulated.

Shift tables relative to the normal reference ranges will be produced using the categories defined by the CTCAE Version 4.03 grades. For these shift tables, for each treatment, the subject's pre-dose grade will be cross-tabulated by the subject's maximum post-baseline grade during the treatment; also, the subject's maximum post-baseline grade during treatment will be tabulated for all baseline grades combined.

The number and percent of subjects with potentially clinically significant (PCS) lab values will be summarized. PCS values for serum potassium are < 3.0 mmol/L or > 6.0 mmol/L and for blood glucose < 2.2 mmol/L or > 13.9 mmol/L. PCS values for additional labs will be defined in the SAP. No hypothesis tests will be performed.

9.3.1.5 Vital Signs

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 vital signs, baseline values will be defined as the average of the values prior to dosing at the randomization visit (Visit 4). PCS values for vital signs will be defined in the SAP and the percentage of subjects with PCS values will be summarized. No hypothesis tests will be performed.

9.3.1.6 ECGs

Summary statistics (mean, median, standard deviation and range) for raw values and change from baseline values in Heart Rate, PR Interval, QRS Axis, QRS Interval, QT Interval and QTcF interval will be calculated, where baseline is defined as the average of the pre-dose measurements taken prior to the start of treatment at the randomization visit (Visit 4). The QTcF (Fridericia Corrected QT) is defined as $(QT/(RR^{1/3}))$ **.** HR (bpm) is estimated as 60,000/RR. These assessments will be tabulated for each treatment and assessment time. PCS values for ECG parameters will be defined in the SAP, and the percentage and number of subjects with PCS ECG values will be tabulated. No hypothesis tests will be performed.

9.3.2 Primary Efficacy Analysis

<u>Morning Pre-dose Trough FEV_1</u>

The change from baseline in pre-dose trough FEV_1 will be analyzed using a repeated measures (RM) linear model. The analysis of covariance (ANCOVA) model will include baseline FEV_1 and reversibility to Ventolin HFA as continuous covariates and visit, treatment, treatment by visit, smoking status at baseline, ICS use at baseline, and lead-in

study as categorical covariates. An unstructured correlation model will be used to model additional autocorrelation within subject. If this model fit fails to converge, an AR (1) structure will be used to model correlation between time points from the same subject; for this model, subject will be included as a random effect. Two-sided p-values and point estimates with two-sided 95% confidence intervals will be produced for each treatment difference. The primary analysis will be conducted using the ITT Population and will assess the treatment effects over the entire 52 weeks of treatment, i.e. subject data from the first 24 weeks of the lead-in studies, PT003006 and PT003007, will be included in the analyses. The comparison of GP MDI to Spiriva will be for non-inferiority rather than superiority and will use a margin of 85 mL.

Additional supportive analyses of morning pre-dose trough FEV_1 will include the change from baseline over 52 weeks in the PP Population, treatment differences at individual time points estimated by the RM model, comparisons to open-label tiotropium also estimated from the RM model, and the analysis of weighted average (WAVE). WAVE will be calculated as the weighted average change from baseline using the exposure time represented by each clinic visit as the weights. It will be analyzed using an ANCOVA. The ANCOVA will evaluate treatment differences and include baseline and reversibility to Ventolin HFA as continuous covariates and smoking status at baseline, ICS use at baseline, and lead-in study as categorical covariates.

9.3.3 Secondary Efficacy Analyses

9.3.3.1 TDI

Assessments of dyspnea will be obtained using the Baseline and Transition Dyspnea Index (BDI/TDI) which is an interviewer based instrument. The BDI/TDI questionnaire can be found in Appendix 8 of the protocol. In addition, there is a practice question included in the self-administered computerized (SAC) version of the BDI/TDI related to tiredness. This question is not included in the focal score, but will be summarized separately.

At Visit 4 of the lead-in studies, the severity of dyspnea at baseline will be assessed using the BDI. At subsequent visits (as per schedule of events table) change from baseline will be assessed using the TDI. The difference between treatment groups in TDI focal score over 52 weeks will be evaluated using a similar RM approach as for morning pre-dose trough FEV_1 (Section 9.3.2). BDI will be included as a continuous covariate replacing baseline in the model. Scoring and handling of missing items will be conducted in accordance with the user's guide for the TDI score. Two-sided p-values and point estimates with two-sided 95% confidence intervals will be produced for each treatment difference. The comparison of GP MDI to Spiriva will be for non-inferiority rather than superiority and will use a margin of 1.0.

The primary analysis will be conducted using the ITT Population. Supportive analyses of the TDI will use the Symptomatic Population, a population possessing sufficient levels of dyspnea at the time of randomization to allow for a treatment benefit. See Section 9.9 for further details. Analyses in the PP Population will also be conducted as supportive.

As additional supportive analyses, the difference between treatments at each of the individual visits will also be evaluated and summarized as well as the individual components of the TDI: functional impairment, magnitude of task, and magnitude of effort. Furthermore as supportive analyses, responder analyses will be performed where responders are defined as a response of 1.0 points or more on average over the treatment period. Logistic regression will be used to compare the treatment groups with BDI and reversibility to Ventolin HFA as continuous covariates and treatment, smoking status at baseline, ICS use at baseline, and lead-in study as categorical covariates. P-values and odds ratios with 95% CI will be produced for each treatment comparison.

9.3.3.2 Peak FEV_1

The peak change from baseline in FEV_1 within 2 hours post-dosing over 52 weeks will be analyzed in a similar way to morning pre-dose trough FEV_1.

9.3.3.3 St George Respiratory Questionnaire (SGRQ)

The difference between treatment groups in the change from baseline in SGRQ over 52 weeks will be evaluated using a similar RM approach as for the primary endpoint. Scoring and handling of missing items will be conducted in accordance with the user's guide for the SGRQ. Each response is to be given a unique empirically derived weight between 0 and 100, the weighted responses are then summed up and divided by the maximum possible score and expressed as a percentage. Missing data of the SGRQ total score will not be imputed. Two-sided p-values and point estimates with two-sided 95% confidence intervals will be produced for each treatment difference. The comparison of GP MDI to Spiriva will be for non-inferiority rather than superiority and will use a margin of 4.0.

The primary analysis will be conducted using the ITT Population. Supportive analysis of the SGRQ will use the Symptomatic Population, a population possessing sufficiently diminished levels of quality of life at the time of randomization to allow for a treatment benefit. See Section 9.9 for further details. Analyses in the PP Population will be conducted as supportive.

As additional supportive analyses, the difference between treatments at each of the individual visits will also be evaluated and summarized. Individual domains of the SGRQ will also be analyzed in a similar fashion as the overall score. Furthermore as supportive analyses, responder analyses will be performed where responders are defined as an improvement of 4.0 points or more on average over the treatment period. Logistic regression will be used to compare the treatment groups with baseline SGRQ and reversibility to Ventolin HFA as continuous covariates and treatment, smoking status at baseline, ICS use at baseline, and lead-in study as categorical covariates. P-values and odds ratios with 95% CI will be produced for each treatment comparison.

9.3.3.4 Rescue Ventolin HFA Use

The number of puffs of rescue Ventolin HFA taken in the previous 12 hours will be recorded in the subject diary in the morning and evening. For every period of time for which the mean

number of puffs of rescue will be calculated, missing values will be ignored in both the numerator and denominator. As such, the denominator will be adjusted based on the number of days (including half days) with non-missing values.

The mean daily number of puffs of rescue Ventolin HFA will be calculated overall and for each of the 4 week intervals during the treatment period. Diary data recorded during the last 7 days of the 10-14 day screening period of the lead-in study will be used to calculate the baseline. The difference between treatment groups in the change from baseline in mean daily rescue Ventolin HFA use over 52 weeks will be evaluated using a similar RM approach as for morning pre-dose trough FEV_1. Instead of visit, the number of the relevant 4 week interval (1-6) will be used as a categorical covariate in the model. As supportive analyses, the treatment difference for each 4-week interval will be evaluated and summarized. Additionally as supportive analyses, daytime rescue Ventolin HFA use and nighttime rescue Ventolin HFA use will be evaluated and summarized in a similar fashion.

Two-sided p-values and point estimates with two-sided 95% confidence intervals will be produced for each treatment difference.

The comparison of GP MDI to Spiriva will be for non-inferiority rather than superiority and will use a margin of 1.0 puff per day.

9.3.4 Other Efficacy Analyses

9.3.4.1 Other Spirometry Endpoints

The analysis of the other comparisons of changes in morning pre-dose trough FEV_1 over 52 weeks has already been described in Section 9.3.1. Treatment differences in the change from baseline in FEV_1 AUC_{0-2}, FVC, PEFR, and FEF_{25-75} will be evaluated in a similar manner to morning pre-dose trough FEV_1.

9.3.4.2 Percentage of days with “no rescue Ventolin HFA use” over the treatment period

As a supportive analysis, percentage of days with ‘no rescue Ventolin HFA use’ over 52 weeks will be analyzed. A ‘day with no rescue use’ is defined using rescue Ventolin HFA usage data from days where rescue Ventolin HFA usage data is non-missing as any day where the subject reported no puffs of rescue Ventolin HFA. The percentage of days with ‘no rescue use’ will be summarized by treatment and analyzed using ANCOVA as for the pre-dose FEV_1 WAVE described in Section 9.3.2, but with baseline average daily rescue Ventolin HFA use instead of baseline FEV_1 as a covariate.

9.3.4.3 COPD Exacerbations

The severity of exacerbations will be classified as follows:

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

The rate of all COPD exacerbations of any severity will be analyzed using negative binomial regression. COPD exacerbations will be considered separate events provided that 7 or more days are between the recorded stop date of the earlier event and start date of the later. Exposure to randomized medication will be used as an offset variable. Time during an exacerbation or in the 7 days following an exacerbation will not be included in the calculation of exposure. Treatments will be compared adjusting for baseline percent predicted FEV_1, baseline CAT score, baseline COPD exacerbation history, smoking status at baseline, ICS use at baseline and lead-in study.

The time to first COPD exacerbation of any severity will be analyzed using Cox regression model for the ITT population. The model will include treatment, baseline percent predicted FEV_1, baseline COPD exacerbation history, baseline CAT score, smoking status at baseline, ICS use at baseline and lead-in study. Estimated adjusted hazard ratios for all treatment comparisons will be displayed along with the associated Wald two-sided 95% confidence interval and p-values. Time to first moderate or severe COPD exacerbation as well as the time to first COPD exacerbation will be displayed graphically for each treatment group using a Kaplan-Meier curve. Subjects who did not experience a COPD exacerbation will be censored at the Week 52visit. Subjects who withdrew from the study without experiencing a COPD exacerbation will be censored at the date of withdrawal.

The rate of moderate and severe COPD exacerbations and the time to first moderate or severe COPD exacerbation will be analyzed similarly to the rate of COPD exacerbations of any severity and the time to first COPD exacerbation of any severity.

Additional analyses of the rate of COPD exacerbations will be performed with imputation of a moderate exacerbation at the time of dropout for subjects withdrawing prematurely from the study, unless an exacerbation has already been recorded at that time.

9.3.4.4 Time to Treatment Failure

Treatment failure will be defined as a moderate or severe COPD exacerbation or discontinuation from the study for any reason. The time to treatment failure will be analyzed using a Cox regression model for the ITT Population. The model will include treatment, baseline percent predicted FEV_1, baseline COPD exacerbation history, baseline CAT score, smoking status at baseline, ICS use at baseline and lead-in study. Estimated adjusted hazard ratios will be displayed along with associated 95% confidence interval and p-values. Time to treatment failure will be displayed graphically for each treatment group using a Kaplan-Meier curve. Subjects who did not experience a treatment failure will be censored at Week 52.

9.3.4.5 Symptom Scores (Daily, Morning and Evening Symptom Scores)

All subjects will be provided with an electronic subject diary to record daytime and nighttime clinical symptoms; cough, shortness of breath, sputum volume, nighttime awakenings and rescue Ventolin HFA use.

The mean daily total symptom score, the mean daytime symptom score and the mean nighttime symptom score will be calculated for each subject over each 4 week interval of the 52 week treatment period. The last seven days of the 10-14 day Screening period from the lead-in studies (Study PT003006 and Study PT003007) will be used to calculate the baseline. The mean change from baseline in the daily, daytime and nighttime symptom scores will be analyzed using a similar model as for morning pre-dose trough FEV_1. In addition, summaries of the daily, daytime and nighttime symptom scores will be provided for each 4-week period. The above summaries will be repeated for each individual symptom score.

Percentage of Nights With 'No Night-time Awakenings' Over 52 Weeks

A night with 'no night-time awakenings' is defined from diary data as any night where the subject did not report waking up. The percentage of nights with 'no night-time awakenings' will be analyzed as for the pre-dose FEV_1 WAVE, but use baseline average daily nighttime awakenings instead of baseline FEV_1 as a covariate.

Percentage of Nights With 'Fewer than Three Night-time Awakenings' Over 52 Weeks

A night with 'fewer than three night-time awakenings' is defined from diary data as any night where the subject reported two or less awakenings. The percentage of nights with 'fewer than three night-time awakenings' will be analyzed as for the pre-dose FEV_1 WAVE, but use baseline average daily night-time awakenings instead of baseline FEV_1 as a covariate.

Percentage of Days With 'No Daytime Symptoms' Over 52 Weeks

A day with 'no daytime symptoms' is defined from the diary data as any day where the subject has recorded in the evening no symptoms for all symptom questions during the past 12 hours (approximately 8 am to 8 pm). The percentage of days with 'no daytime symptoms' will be analyzed as for the pre-dose FEV_1 WAVE but use baseline average daily total symptom score instead of baseline FEV_1 as a covariate.

9.3.5 Type I Error Control

Type I error is controlled by the specification of a primary efficacy measure and a limited set of secondary efficacy measures. Since the primary objective of the trial is the evaluation of safety, no additional controls of type I error are planned.

9.3.6 Health Care Resource Utilization

COPD-related and non-COPD-related HCRU will be summarized by treatment group.

9.4 Randomization

Until the targets for enrollment into the trial are met, 90% of subjects in the GFF MDI, FF MDI, and GP MDI arms meeting the inclusion criteria will be randomly selected for invitation into the trial. The random exclusion of 10% of these subjects is done to preserve the blind of PT003006 and PT003007 as subjects in the placebo arm will not be invited into the trial. Until the targets for enrollment into the trial are met, all subjects in the Spiriva arm meeting the inclusion criteria will be invited into the trial. Subjects will be maintained on the same treatment as they received during the lead-in study (Study PT003006 or PT003007). Treatment will remain double-blinded unless the treatment is open-label Spiriva. An IWRS will be used to maintain the blinding.

9.5 Experimental Design

This study is a multi-center, double-blind, parallel-group, active-controlled (open-label) design. All study treatments are given in addition to permitted COPD background therapy.

9.6 Sample Size Consideration

The sample size has been chosen to ensure that a sufficient number of subjects (as recommended on the International Conference on Harmonisation Guidance E1A guidance) will have been exposed to GFF MDI (14.4/9.6 µg, BID), FF MDI (9.6 µg, BID), and GP MDI (14.4 µg, BID) for 52 weeks for long-term safety assessments. Approximately 850 subjects with a clinical diagnosis of moderate to very severe COPD will be allowed in the study. It is expected that around 260 will belong to GFF MDI (14.4/9.6 µg), another 225 to GP MDI (14.4 µg), 225 to FF MDI (9.6 µg), and 140 to the Spiriva group (18 µg, open-label). The target enrollment allows for well over 20% of subjects to discontinue treatment while ensuring that at least 100 complete 52 weeks of treatment in all blinded treatment groups. This sample size provides approximately 80% power to detect (i.e., observe at least one) an AE providing that AE has an underlying incidence rate of 1.1% in the smallest treatment arm Spiriva (18 µg, open-label) or 0.6% in the largest treatment arm (GFF MDI) during the 28 weeks of this trial.

With regards to the primary efficacy endpoint, changes from baseline in morning pre-dose trough FEV_1 over 52 weeks, this sample size combined with the data from PT003006 and PT003007 will provide approximately 99% power to demonstrate that GFF MDI is superior to its components if the true differences from GP MDI and FF MDI in morning pre-dose trough FEV_1 over 52 weeks are 50 and 60mL, 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 and potential influence of outliers will be evaluated and

additional sensitivity analyses will be conducted if warranted to demonstrate the robustness of the primary and secondary results.

9.8 Analysis Plan

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

9.9 Study Populations

The following analysis populations are defined in this study:

- The **Intent-To-Treat (ITT) Population** is defined as all subjects who are randomized to active (non-placebo) treatment and receive at least one dose of the study treatment regardless of whether or not they participated in PT003008. Subjects will be analyzed according to the treatment they were assigned to at randomization. (Note that a subject who used a study treatment, but took less than one full dose of treatment will qualify for this population).
- The **PT003008 Intent-To-Treat (ITT) Population** is defined as only those ITT subjects who enrolled in Study PT003008. Subjects will be analyzed according to the active treatment they were assigned to at randomization. (Note that a subject who used a study treatment, but took less than one full dose of treatment will qualify for this population). Data from both lead-in studies and data from Study PT003008 will be included.
- The **Per-Protocol (PP) Population** is a subset of the ITT Population defined as all subjects with post-randomization data obtained prior to any major protocol deviations. Data obtained after any major protocol deviation will be excluded. Since receiving the wrong treatment will be a major protocol deviation, subjects in the PP population will be analyzed as randomized (which for this population if identical to analysis by the actual treatment received). Any evaluability criteria with a potential impact on efficacy results will be identified in a blinded fashion from review of data listings prior to unblinding. Major protocol deviations (protocol violations), therefore, can result in exclusion of all data from a particular subject from the PP population or require exclusion of data from a specific timepoint and/or subsequent timepoints for an endpoint.
- The **Safety Population** is similar to the ITT Population (all subjects who are randomized to treatment and receive at least one dose of the study treatment). However, subjects will be analyzed according to treatment received rather than randomized. If a subject received more than one randomized treatment, they will be analyzed and included in summaries according to the treatment they received the most. (Note that a subject who used a study treatment, but took less than one full dose of treatment will qualify for this population). Of note, the statement that a subject had no adverse events also constitutes a safety assessment.
- The **PT003008 Safety Population** is defined as the subset of the Safety Population who were enrolled into Study PT003008. Only data obtained during Study PT003008 and baseline data obtained prior to randomization in Study PT003006 or PT003007 are included.

- The **Symptomatic Population** is defined as all subjects in the ITT Population with CAT scores of ≥10 at Visit 4.

Population membership for each subject depends on the data obtained in both the lead-in study and this study. 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 PP population or require exclusion of data from a specific treatment period or from a particular time point within a treatment period. Data already adjudicated for Studies PT003006 and PT003007 do not need to be reassessed.

Analyses will be performed as follows:

Demographics will be summarized for the ITT, PT003008 ITT, PP, Safety, and PT003008 Safety Populations. Extent of exposure will be summarized for the ITT, Safety, and PT003008 Safety Populations. The Safety and PT003008 Safety Population will be used to summarize safety. Efficacy Analyses will be performed for the ITT and PP Populations, with the ITT Population being considered the primary population. Trough FEV_1 will also be evaluated using the PT003008 ITT Population as supportive. Supportive analyses for the TDI and SGRQ will be performed using the Symptomatic Population.

9.10 Handling of Missing Data

All observed values from active treatment groups will be included in the ITT population and the primary and secondary analyses. As a maximum likelihood method, RM is valid for missing-at-random (MAR) missingness (Little, 2002). If the nature and magnitude of the missing data leads to concerns about potential biases in the evaluation of treatment effects, additional sensitivity analyses will be performed using multiple imputation under varying assumptions about treatment effects in the unobserved data. Missing data will be classified as missing completely at random (MCAR), MAR, or not MAR (NMAR) based on the reason for the missing value captured in the CRF. This determination will be specified in detail in the SAP as well as further details about this analysis. MNAR data will be imputed using varying assumptions about the treatment effects in the unobserved data whereas missing data classified as MCAR or MAR will be imputed using the observed data model.

Change from baseline in morning pre-dose trough FEV_1 at each visit is defined as the average of the 60 and 30 minute pre-dose values 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, morning pre-dose trough FEV_1 at that visit will not be calculated.

Peak FEV_1 will be included in ITT analyses as long as there is at least 1 non-missing post-dose value during the first 2 hours post-dose. For the PP Population analyses, the peak change from baseline in FEV_1 within 2 hours post-dosing will be included in analyses as long as there are at least 2 non-missing FEV_1 data points during the first 2 hours post-dose.

9.11 Statistical Software

Data processing, statistical screening, descriptive reporting and analysis of the efficacy and safety data will be performed using 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 in conjunction 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. **Reporting of Clinical Trials Results:** To provide transparency in the conduct and reporting of randomized clinical trials, Pearl reports clinical findings based on the guidance of The CONSORT (CONsolidated Standards of Reporting Trials) Statement [CONSORT, 2010] and a 25-item checklist which is intended to improve the reporting of a randomized controlled trial, and to facilitate reader understanding of the trial design, conduct, analysis and interpretation, and to support their ability to assess the validity of its results.

7. **Internet Clinical Trial Listing:** In addition, also consistent with the recommendations of the ICMJE, Pearl Therapeutics will make available appropriate information regarding the study via the internet. This will include registration and listing of the study on www.clinicaltrials.gov, the US National Institutes of Health listing of clinical trials.

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Appendix 1 Spirometry Performance Recommendations

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

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

FEV_1 AND FVC MANEUVERS

Equipment Requirements

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

Display

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

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

When a volume–time curve is plotted as hardcopy, the volume scale must be $\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 ±3.5% is appropriate.

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

Volume-type spirometer systems must be evaluated for leaks every day. The importance of undertaking this daily test cannot be overstressed. Leaks can be detected by applying a constant positive pressure of ≥3.0 cmH2O (0.3 kPa) with the spirometer outlet occluded (preferably at or including the mouthpiece). Any observed volume loss of .30 mL after 1 minute indicates a leak and needs to be corrected.

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

Quality Control for Flow-Measuring Devices

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

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

VC AND IC MANEUVERS

Equipment

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

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

TECHNICAL CONSIDERATIONS

Minimal recommendations for spirometry systems

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

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

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

FEVt: forced expiratory volume in t seconds

BTPS correction

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

Appendix 2 Spirometry Assessment Criteria

Acceptable Versus Usable Tests

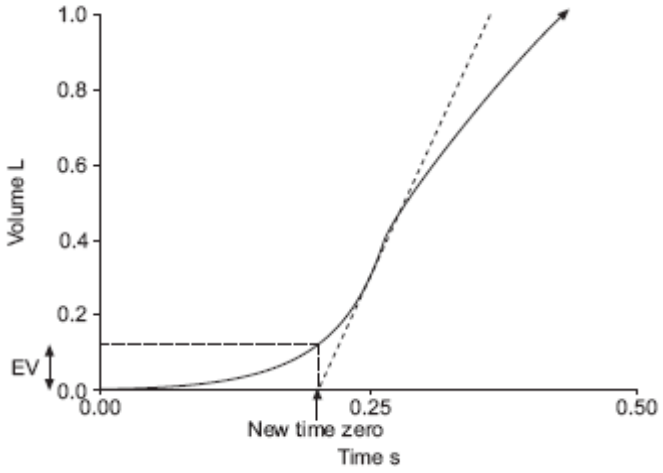
***Acceptable* Tests must meet the following 7 Criteria:**

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

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

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

Figure A2-1.Example of a Usable Spirogram



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

Between-Maneuver Reproducibility Criteria

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

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

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

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

Appendix 3 Classification of Severity - GOLD Guidelines (2013)

The GOLD staging system classifies people with COPD based on their degree of airflow limitation (obstruction). The airflow limitation is measured during pulmonary function tests (PFTs).

Because of lung damage, people with COPD take longer to blow air out. This impairment is called obstruction or airflow limitation. An FEV_1 less than 70% of FVC can make the diagnosis of COPD in someone with compatible symptoms and history.

In GOLD COPD, classifications are then used to describe the severity of the obstruction or airflow limitation.

Table A3-1.Classification of Severity of Airflow Limitation in COPD (Based on Post-Bronchodilator FEV_1)

Stage I	Mild COPD	FEV1/FVC<0.70	$FEV_1 \geq$ 80% normal
Stage II	Moderate COPD	FEV1/FVC<0.70	FEV_1 50-79% normal
Stage III	Severe COPD	FEV1/FVC<0.70	FEV_1 30-49% normal
Stage IV	Very Severe COPD	FEV1/FVC<0.70	FEV_1 <30% normal,

Appendix 4 Subject Instructions for Use of GFF,GP, and FF MDI Devices

Before using GFF MDI, GP MDI and FF MDI

1. Take the inhaler out of the foil pouch. Safely throw away the pouch and the drying packet that comes inside the pouch. Check the indicator at the top of the canister; the indicator should read as shown in Figure 2.

Figure 2. Indicator at Top of Canister

2. Take the cap off the inhaler and 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.
3. The inhaler should be stored at room temperature.

How to prime GFF MDI, GP MDI and FF MDI

1. The inhaler 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 the inhaler is ready to use.
2. Take the cap off the mouthpiece of the actuator.
3. To prime the inhaler, gently shake the inhaler for 5-10 seconds and then spray once into the air away from yourself and others.
4. Wait approximately 5-10 seconds and repeat the process three more times.

How to take a dose from GFF MDI, GP MDI and FF MDI

Steps 3-6 below should be done one after the other.

1. Take the cap off the mouthpiece of the actuator.
2. Hold the inhaler with the mouthpiece down.
3. Shake the canister for 5-10 seconds.
4. Breathe out fully through mouth, expelling as much air from the lungs as possible.
5. Tilt head back slightly, place the mouthpiece into mouth, and close lips around it. To allow the medication to enter the lungs, keep tongue flat on the floor of your mouth. Keep the mouthpiece at the bottom and the dose indicator at the top.

6. While breathing in deeply and slowly, press down on the center of the dose indicator with finger. Fully depress the canister until it stops moving in the actuator while delivering the dose. Note: It is normal to hear a soft click from the indicator as it counts down during use.
7. Hold breath as long as possible, up to 10 seconds, and then breathe normally.
8. Repeat steps 3 to 7, with gentle shaking for 5-10 seconds before the second spray.
9. Put the cap back on the mouthpiece after every time the inhaler is used, and make sure it is firmly seated in place.

How to clean GFF MDI, GP MDI and FF MDI

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

Wash the actuator once a week for the first three weeks as directed below.

1. Take the canister out of the actuator, and take the cap off the mouthpiece.
2. Wash the actuator through the top of the actuator with warm running water for 30 seconds (see Figure 3).

Figure 3. Wash Actuator through Top of Actuator

3. Then wash the actuator again through the mouthpiece (see Figure 4).

Figure 4. Wash Actuator through Mouthpiece

4. 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 visible build-up, repeat steps 2 and 3.
5. Let the actuator air dry completely, such as overnight.
6. When the actuator is dry, put the canister in the actuator, making sure the canister is fully and firmly fitted into the actuator. Shake the inhaler gently for 5-10 seconds and spray it 2 times into the air away from your face, shaking gently 5-10 seconds before each spray. Put the cap back on the mouthpiece.

If the actuator becomes blocked

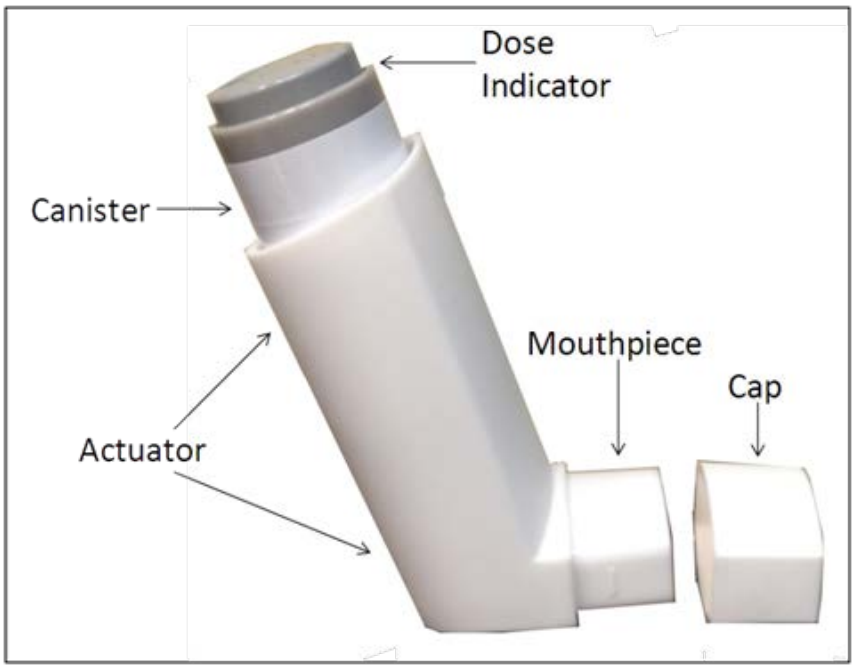
Blockage from medicine build-up is more likely to happen if the actuator is not routinely cleaned and the actuator is not air-dried completely. If the actuator gets blocked so that little or no medicine comes out of the mouthpiece, wash the actuator as described in cleaning steps 1-6.

If the inhaler is needed before the actuator is completely dry, shake as much water off the actuator as possible. Put the canister in the actuator and make sure it fits firmly. Shake the inhaler gently for 5-10 seconds and spray it 2 times into the air away from your face, shaking gently 5-10 seconds before each spray. Then take the dose as prescribed and described above. Then clean and air-dry it completely.

How to read the inhaler dose indicator

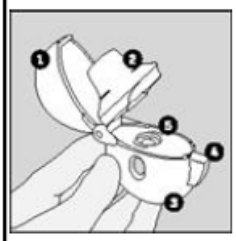
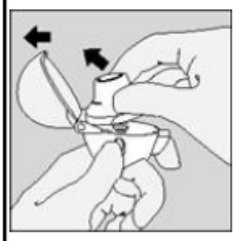
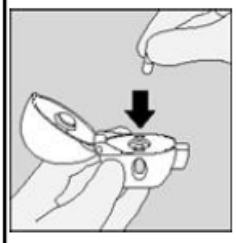
The inhaler is fitted with a dose indicator which shows how much medicine is left during use. The dose indicator display will move after every tenth puff. The dose indicator pointer will start to point to the red area when there are 20 puffs remaining. This means that the inhaler needs to be replaced soon.

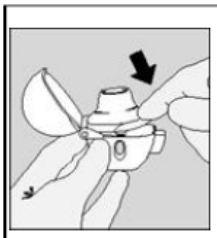
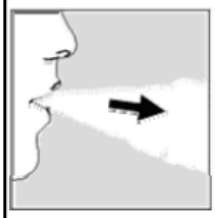
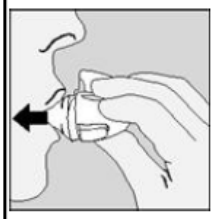
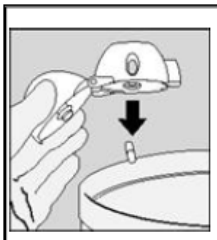
Figure 5. Metered Dose Inhaler Parts



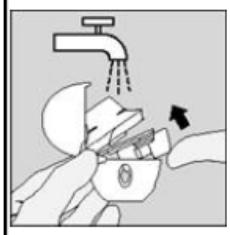
Appendix 5 Instructions for Use of Spiriva Handihaler

Instructions for handling and use:

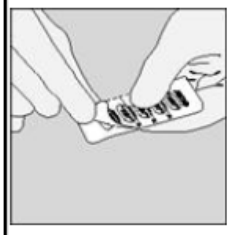
	Remember to carefully follow your doctor's instructions for using SPIRIVA. The HandiHaler is especially designed for SPIRIVA. You must not use it to take any other medication. You can use your HandiHaler for up to one year to take your medication.
	The HandiHaler 1 Dust cap 2 Mouthpiece 3 Base 4 Piercing button 5 Centre chamber
	1. To release the dust cap press the piercing button completely in and let go.
	2. Open the dust cap completely by pulling it upwards. Then open the mouthpiece by pulling it upwards.
	3. Remove a SPIRIVA capsule from the blister (only immediately before use) and place it in the centre chamber (5), as illustrated. It does not matter which way the capsule is placed in the chamber.

	4. Close the mouthpiece firmly until you hear a click, leaving the dust cap open.
	5. Hold the HandiHaler device with the mouthpiece upwards and press the piercing button completely in only once, and release. This makes holes in the capsule and allows the medication to be released when you breathe in.
	6. Breathe out completely. Important: Please avoid breathing into the mouthpiece at any time.
	7. Raise the HandiHaler 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 comfortable and at the same time take the HandiHaler out of your mouth. Resume normal breathing. Repeat steps 6 and 7 once, in order to empty the capsule completely.
	8. Open the mouthpiece again. Tip out the used capsule and dispose. Close the mouthpiece and dust cap for storage of your HandiHaler device.

Cleaning your HandiHaler

	Clean the HandiHaler once a month. Open the dust cap and mouthpiece. Then open the base by lifting the piercing button. Rinse the complete inhaler with warm water to remove any powder. Dry the HandiHaler thoroughly by tipping excess of water out on a paper towel and air-dry afterwards, leaving the dust cap, mouthpiece and base open. It takes 24 hours to air dry, so clean it right after you used it and it will be ready for your next dose. If needed, the outside of the mouthpiece may be cleaned with a moist but not wet tissue.

Blister handling

	A. Separate the blister strips by tearing along the perforation.
	B. Peel back foil (only immediately before use) using the tab until one capsule is fully visible. In case a second capsule is exposed to air inadvertently this capsule has to be discarded.
	C. Remove capsule.

SPIRIVA® capsules contain only a small amount of powder so that the capsule is only partially filled.

Appendix 6 Instructions for Use of Ventolin HFA Inhaler

The Parts of Your VENTOLIN HFA Inhaler

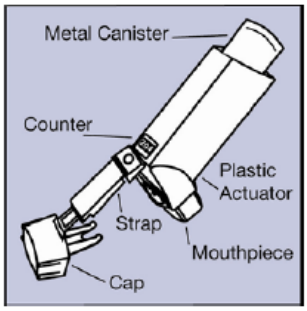


Figure A

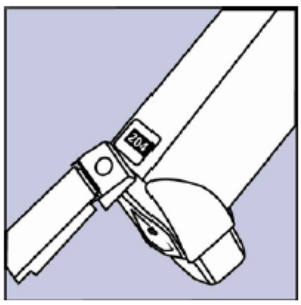


Figure B

There are 2 main parts of your VENTOLIN HFA inhaler:

- the blue plastic actuator that sprays the medicine into your mouth. See Figure A.
- the metal canister that holds the medicine. See Figure A.

The actuator has a protective cap that covers the mouthpiece. The strap on the cap will stay attached to the actuator.

Do not use this actuator with a canister of medicine from any other inhaler.

Do not use this canister of medicine with an actuator from any other inhaler.

The canister has a counter that shows you how many sprays of medicine you have left. The number shows through a window in the back of the actuator. The counter starts at either 204 or 64, depending on which size inhaler you have. See Figure B.

Priming your VENTOLIN HFA inhaler:

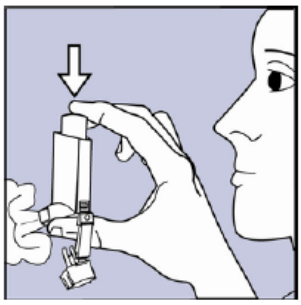


Figure C

Your VENTOLIN HFA inhaler must be primed before you use it for the first time, when it has not been used for more than 14 days in a row, or if it has been dropped. Do not prime your VENTOLIN HFA every day.

- Remove your VENTOLIN HFA inhaler from its packaging.
- Throw away the pouch and the drying packet that comes inside the pouch.
- Remove the protective cap from the mouthpiece.
- Shake the inhaler well, and spray it into the air away from your face. See Figure C.

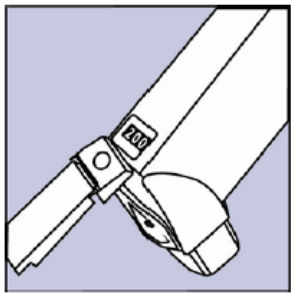


Figure D

- Shake and spray the inhaler like this 3 more times to finish priming it. After you prime the actuator for the first time, the dose counter in the window on the back of the actuator should show the number 200 or 60, depending on which size inhaler you have. See Figure D.

Each time you use your VENTOLIN HFA inhaler:

- Make sure the canister fits firmly in the plastic actuator.
- 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 the cap has not been used to cover the mouthpiece.

Reading the dose counter on your VENTOLIN HFA actuator:

- The dose counter will count down by 1 number each time you spray the inhaler.
- The dose counter stops counting when it reaches **000.** It will continue to show **000**.
- The dose counter cannot be reset, and it is permanently attached to the metal canister. **Never** try to change the numbers for the dose counter or take the counter off the metal canister.
- **Do not** remove the canister from the plastic actuator except during cleaning to prevent accidently spraying a dose of VENTOLIN HFA into the air.

Using your VENTOLIN HFA inhaler:

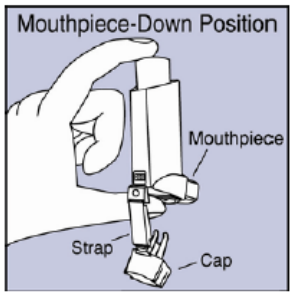


Figure E

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

Step 2. Hold the inhaler with the mouthpiece down. See Figure E.

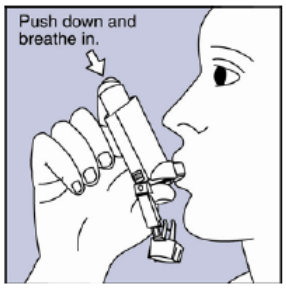


Figure F

Step 3. 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. See Figure F.

Step 4. Push the top of the canister all the way down while you breathe in deeply and slowly through your mouth. See Figure F.

Step 5. 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.

Step 6. **Hold your breath as long as you can**, up to 10 seconds, then breathe normally.

If your healthcare provider has told you to use more sprays, wait 1 minute and shake the inhaler again. Repeat Steps 2 through Step 6.

Step 7. Put the cap back on the mouthpiece after every time you use the inhaler. Make sure the cap snaps firmly into place.

Cleaning your VENTOLIN HFA actuator:

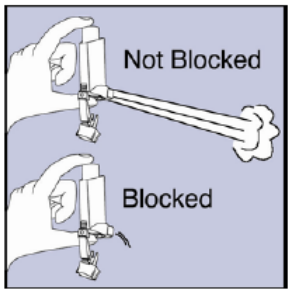


Figure G

It is very important to keep the plastic actuator clean so the medicine will not build-up and block the spray. See Figure G.

- **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 as follows:

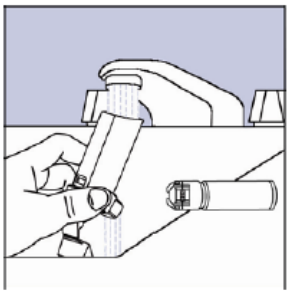


Figure H

Step 8. 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.

Step 9. Hold the actuator under the faucet and run warm water through it for about 30 seconds. See Figure H.

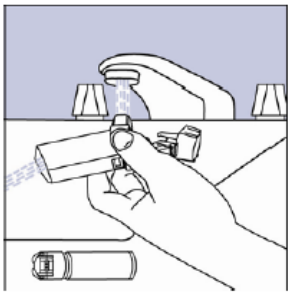


Figure I

Step 10. Turn the actuator upside down and run warm water through the mouthpiece for about 30 seconds. See Figure I.

Step 11. 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 Steps 9 and 10.

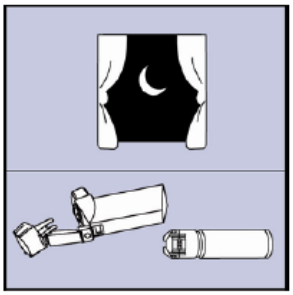


Figure J

Step 12. Let the actuator air-dry completely, such as overnight. See Figure J.

Step 13. 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 number.) Put the cap back on the mouthpiece.

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.
- Take your VENTOLIN HFA dose as prescribed.
- Follow cleaning Steps 8 through 13 above.

Replacing your VENTOLIN HFA inhaler:

- **When the dose counter on the actuator shows the number 020**, you need to refill your prescription or ask your doctor for another prescription for VENTOLIN HFA.
- **Throw the VENTOLIN HFA inhaler away** as soon as the dose counter shows **000**, after the expiration date on the VENTOLIN HFA packaging, or 12 months after you open the foil pouch, whichever comes first. You should not keep using the inhaler after the dose counter shows **000** even though the canister may not be completely empty. You cannot be sure you will receive the right amount of medicine.

Appendix 7 St. George Respiratory Questionnaire (SGRQ)

(*The samples provided here is for illustrative purposes only*)

HRN Health Respiratory Network of the FRSQ

Pulmonary Rehabilitation Research Infrastructure
COPD Research Axis

ST-GEORGE RESPIRATORY QUESTIONNAIRE (SGRQ)

Centre ☐☐☐ Project ☐☐☐ Subject ☐☐☐☐☐☐ Visit ☐

Pre-rehabilitation evaluation (visit 1) ☐ Post-rehabilitation evaluation < 1 month (visit 2) ☐

Post-rehabilitation evaluation : 1 yr (visit 3) ☐ 2 yrs (visit 4) ☐ 3 yrs (visit 5) ☐

Date ☐☐☐☐☐☐☐☐ yyyy-mmm-dd Time at the beginning of the questionnaire ☐☐:☐☐ on 24:00

Current or recent exacerbation

The subject currently has or had an exacerbation in the past 4 weeks? No ☐ Yes ☐

This questionnaire is designed to help us learn much more about how your breathing is troubling you and how it affects your life. We are using it to find out which aspects of your illness cause you the most problem.

Please read the instructions carefully and ask if you do not understand something. Do not spend too long deciding about your answer.

Part 1

Questions about how much chest trouble you had over the last year. Please fill in the relevant number next to each activity.

1- Over the last year, I have coughed : ☐

1- Most days a week
2- Several days a week
3- A few days a week
4- Only with chest infections
5- Not at all

2- Over the last year, I have brought up phlegm (sputum) : ☐

1- Most days a week
2- Several days a week
3- A few days a week
4- Only with chest infections
5- Not at all

3- Over the last year, I have had shortness of breath : ☐

1- Most days a week
2- Several days a week
3- A few days a week
4- Only with chest infections
5- Not at all

[redacted] 1/5

HRN Health Respiratory Network of the FRSQ

Pulmonary Rehabilitation Research Infrastructure
COPD Research Axis

ST-GEORGE RESPIRATORY QUESTIONNAIRE (SGRQ)

Centre |_|_|_| Project |_|_|_| Subject |_|_|_|_|_|_| Visit |_|

4- ***Over the last year, I have had attacks of wheezing :*** ☐

1- Most days a week
2- Several days a week
3- A few days a week
4- Only with chest infections
5- Not at all

5- ***During the last year, how many severe unpleasant attacks of chest trouble have you had :*** ☐

1- More than 3 attacks
2- 3 attacks
3- 2 attacks
4- 1 attack
5- No attack

GO TO QUESTION 7 IF YOU HAD NO SEVERE ATTACKS.

6- ***How long did the worst attack of chest trouble last :*** ☐

1- A week or more
2- 3 or more days
3- 1 or 2 days
4- Less than a day

7- ***Over the last year, in an average week, how many good days (with little chest trouble) have you had :*** ☐

1- No good days
2- 1 or 2 good days
3- 3 or 4 good days
4- Nearly every day is good
5- Every day is good

	No	*Yes*	*Not applicable**
8- ***If you have a wheeze, is it worse in the morning :***	☐	☐	☐

* CHECK « NOT APPLICABLE » IF ANSWERED 5-NOT AT ALL TO QUESTION 4.

Part 2

SECTION 1

9- ***How would you describe your chest condition :*** ☐

1- The most important problem I have.
2- Causes me quite a lot of problems.
3- Causes me quite a few problems.
4- Causes me no problem.

[redacted]

HRN Health Respiratory Network of the FRSQ

Pulmonary Rehabilitation Research Infrastructure
COPD Research Axis

ST-GEORGE RESPIRATORY QUESTIONNAIRE (SGRQ)

Centre ____ Project ____ Subject ____ Visit ____

10- If you have ever had paid employment, please choose one of these answers : ☐

1- My chest trouble made me stop work.
2- My chest trouble interferes with my work or made me change my work.
3- My chest trouble does not affect my work.

SECTION 2

Questions about what activities usually make you feel breathless these days. For each item, please answer either true or false as it applies to you.

		True	False
11-	*Sitting or lying still.*	☐	☐
12-	*Getting washed or dressed.*	☐	☐
13-	*Walking around the house.*	☐	☐
14-	*Walking outside on level ground.*	☐	☐
15-	*Walking up a flight of stairs.*	☐	☐
16-	*Walking hills.*	☐	☐
17-	*Playing sports or games.*	☐	☐

SECTION 3

Some more questions about your cough and breathlessness these days. For each item, please answer either true or false as it applies to you.

		True	False
18-	*My cough hurts.*	☐	☐
19-	*My cough makes me tired.*	☐	☐
20-	*I am breathless when I talk.*	☐	☐
21-	*I am breathless when I bend over.*	☐	☐
22-	*My cough or breathing disturbs my sleep.*	☐	☐
23-	*I get exhausted easily.*	☐	☐

SECTION 4

Questions about other effects that your chest trouble may have on you these days. For each item, please answer true or false as it applies to you.

		True	False
24-	*My cough or breathing is embarrassing in public.*	☐	☐
25-	*My chest trouble is a nuisance to my family, friends or neighbours.*	☐	☐
26-	*I get afraid or panic when I cannot get my breath.*	☐	☐
27-	**I feel that I am not in control of my chest problems.**	☐	☐
28-	*I do not expect my chest to get any better.*	☐	☐
29-	*I have become frail or an invalid because of my chest.*	☐	☐
30-	*Exercise is not safe for me.*	☐	☐
31-	*Everything seems too much of an effort.*	☐	☐

[redacted]

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HRN Health Respiratory Network of the FRQS

Pulmonary Rehabilitation Research Infrastructure
COPD Research Axis

ST-GEORGE RESPIRATORY QUESTIONNAIRE (SGRQ)

Centre ☐☐☐ Project ☐☐☐ Subject ☐☐☐☐☐ Visit ☐

SECTION 5

Questions about your medication. If you are receiving no medication go straight to **section 6**. For each item, please answer either « true » or « false » as it applies to you.

		True	*False*
32-	***My medication does not help me very much.***	☐	☐
33-	***I get embarrassed using my medication in public.***	☐	☐
34-	***I have unpleasant side effects from my medication.***	☐	☐
35-	***My medication interferes with my life a lot.***	☐	☐

SECTION 6

These are questions about how your activities might be affected by you breathing. For each question, please answer « true » if one or more parts applies to you because or you breathing. Otherwise, answer « false ».

		True	*False*
36-	***I take a long time to get washed or dressed.***	☐	☐
37-	***I cannot take a bath or shower, or I take a long time.***	☐	☐
38-	***I walk slower than other people, or else I stop for rests.***	☐	☐
39-	***Jobs such as housework take a long time, or I have to stop for rests.***	☐	☐
40-	***If I walk up one flight of stairs, I have to go slowly or stop.***	☐	☐
41-	***If I hurry or walk fast, I have to stop or slow down.***	☐	☐
42-	***My breathing makes it difficult to do things such as walking up hills, carrying things up stairs, light gardening such as weeding, dance, play bowling or play golf.***	☐	☐
43-	***My breathing makes it difficult to do things such as carry heavy loads, dig the garden or shovel snow, jog or walk at 5 miles (8 km) per hour, play tennis or swim.***	☐	☐
44-	***My breathing makes it difficult to do things such as carry heavy manual work, run, cycle, swim fast or play competitive sports.***	☐	☐

SECTION 7

We would like to know how your chest trouble usually affects your daily life. Please answer either « true » or « false » as it applies to you because of your chest trouble. (remember that « **true** » only applies to you if you cannot do something **because of your breathing**.)

		True	*False*
45-	***I cannot play sports or games.***	☐	☐
46-	***I cannot go out for entertainment or recreation.***	☐	☐
47-	***I cannot go out of the house to do the shopping.***	☐	☐
48-	***I cannot do the housework.***	☐	☐
49-	***I cannot move far from my bed or chair.***	☐	☐

[redacted]

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HRN Health Respiratory Network of the FRSQ

Pulmonary Rehabilitation Research Infrastructure
COPD Research Axis

ST-GEORGE RESPIRATORY QUESTIONNAIRE (SGRQ)

Centre ____ Project ____ Subject ____ ____ Visit ____

Here is a list of other activities that your chest trouble may prevent you doing. (You do not have to choose; they are just to remind you of ways in which your breathlessness may affect you):

Going for walks or walking the dog.
Doing things at home or in the garden.
Sexual intercourse.
Going out to church, or a place of entertainment.
Going out in bad weather or into smoky rooms.
Visiting family or friends or playing with grandchildren.

50- Please mention any other important activities that your chest trouble may stop you doing :

_____

_____

_____

_____

51- Now, would you choose (one only) which you think best describes how your chest trouble affects you: ☐

1- It does not stop me doing anything I would like to do.
2- It stops me doing one or two things I would like to do.
3- It stops me doing most of the things I would like to do.
4- It stops me doing everything I would like to do.

Time at the end of the questionnaire ____ : ____ on 24:00

[redacted]

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Appendix 8 BDI/TDI Questionnaire

(The samples provided here is for illustrative purposes only)

Baseline/Transition Dyspnea Index (BDI/TDI)

BASELINE DYSPNEA INDEX

Baseline Functional Impairment

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

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

Baseline Magnitude of Task

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

Baseline Magnitude of Effort

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

TRANSITION DYSPNEA INDEX

Change in Functional Impairment

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

Change in Magnitude of Task

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

Change in Magnitude of Effort

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

Appendix 9 Dose Indicator Display Reading Instructions

For the purposes of this study, when recording the dose indicator display value, review the indicator display at the top of the MDI and record the number of inhalations remaining that matches the chart below:

130 Count (Actuation) Version Shown				
 If your dose indicator display looks like this record **120+**	 If your dose indicator display looks like this record **120**	 If your dose indicator display looks like this record **110**	 If your dose indicator display looks like this record **100**	 If your dose indicator display looks like this record **90**
 If your dose indicator display looks like this record **80**	 If your dose indicator display looks like this record **70**	 If your dose indicator display looks like this record **60**	 If your dose indicator display looks like this record **50**	 If your dose indicator display looks like this record **40**
 If your dose indicator display looks like this record **30**	 If your dose indicator display looks like this record **20**	 If your dose indicator display looks like this record **10**	 If your dose indicator display looks like this record **0**	

Appendix 10 Sponsor Signatory

Study Title: A 28-Week, Multi-Center, Randomized, Double-Blind, Parallel-Group, Active-Controlled Safety Extension Study to Evaluate the Safety and Efficacy of PT003, PT001, and PT005 in Subjects With Moderate to Very Severe COPD, With Spiriva® Handihaler® as an Active Control

Study Number: PT003008-01

Final Date: [redacted]

Signature: [redacted]

Name [redacted]

[redacted]

Appendix 11 Investigator's Agreement and Signature Page

Study Title: A 28-Week, Multi-Center, Randomized, Double-Blind, Parallel-Group, Active-Controlled Safety Extension Study to Evaluate the Safety and Efficacy of PT003, PT001, and PT005 in Subjects With Moderate to Very Severe COPD, With Spiriva® Handihaler® as an Active Control

Study Number: PT003008-01

Final Date: [redacted]

I agree:

- To assume responsibility for the proper conduct of the study at this site.
- To conduct the study in compliance with the protocol and with any other study conduct procedures provided by Pearl Therapeutics.
- 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:_____